

Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution

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Abstract

This study was carried out to investigate the clinical and biochemical factors which might be of importance in predicting the outcome of patients with myxoedema coma. Eleven patients (ten female) aged 68.1 ± 19.5 years attended our institution over a period of 18 years.

Glasgow and APACHE II scores and serum free thyroxine and TSH were measured in all the patients on entry. Patients were selected at random to be treated with two different regimens of L-thyroxine.

Four patients died with the mortality rate being 36.4%. The patients in coma at entry had significantly higher mortality rates than those with minor degrees of consciousness (75% vs 14.3% respectively, $P=0.04$). The

surviving patients had significantly higher Glasgow scores than those who died (11.85 ± 2.3 vs 5.25 ± 2.2 respectively, $P<0.001$). Comparison of the mean values of APACHE II scores between the surviving group and those who died was significantly different (18.0 ± 2.08 vs 31.5 ± 2.08 respectively, $P<0.0001$).

The degree of consciousness, the Glasgow score and the severity of the illness measured by APACHE II score on entry were the main factors that determined the post-treatment outcome of patients with myxoedema coma.

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Introduction

Myxoedema coma is a rarely occurring extreme expression of hypothyroidism. Recognition of this entity is hampered by its insidious onset and rarity. The incidence rate of this condition in our area is 0.22 per 1 000 000 per year (Galofré & García-Mayor 1997). In the past, the overall mortality rate for myxoedema was 60–70%. Early recognition and advances in intensive supportive care have reduced the mortality rate to 20–25% (Jordan 1995).

The aim of the present study was to prospectively collect all cases of myxoedema coma which presented at our institution and investigate factors which might be of importance in predicting the outcome of these patients.

Materials and Methods

This prospective study includes all cases of myxoedema coma who presented at our institution from January 1985 to December 2002. Diagnosis of myxoedema coma was established by the following criteria: altered mental status, hyperthermia ($\leq 35^\circ\text{C}$), a precipitating illness associated

with low serum levels of thyroid hormones and increased levels of thyrotrophin (TSH), or depressed/normal levels of TSH associated with other pituitary damage or tumours. Eleven patients (ten female and one male) aged 68.1 ± 19.5 years, range 20–84 years, were included in the present study. No patients had been previously diagnosed as having hypothyroidism. Eight had primary hypothyroidism (chronic autoimmune thyroiditis was diagnosed in cases 3, 5, 6, 7, 9 and 11, idiopathic hypothyroidism in case 1 and sublingual ectopic thyroid gland in case 8) and three had secondary hypothyroidism due to a non-functional pituitary macroadenoma (Table 1). Patients 1, 3, 4, 5 and 9 were diagnosed in winter. They were treated at the Intensive Care Unit of the University Hospital of Vigo.

Impaired consciousness was graded as obtundation, stupor or coma and by the Glasgow score (Wilson *et al.* 1998). The severity of the patients' illness was assessed by the APACHE II score, in which an increasing score is associated with an increasing risk of hospital death (Knaus *et al.* 1985).

The patients were treated with L-thyroxine (L-T4) following two regimens: six received an initial dose of 500 μg i.v. ('high' dose) followed by a 100 μg daily dose

Table 1 Clinical and laboratory findings in eleven patients with myxoedema coma

Patient	Age (years)	Sex	Type of hypothyroidism	Precipitating factors	Degree of consciousness at entry	Concomitant disorders	Free thyroxine (mmol/l)	TSH (μ U/ml)	L-thyroxine dose	Outcome
1	84	M	Primary	Urinary infection	Obtundation	Pleural effusion	0.46	51.3	High	Alive
2	75	F	Secondary	Pneumonia, sepsis	Coma	Anaemia DIC, ARDS Septic shock	0.25	0.43	High	Dead
3	70	F	Primary	Abdominal surgery	Coma	Respiratory failure Shock	0.18	71	Low	Dead
4	65	F	Secondary	Urinary infection	Obtundation	Pericardial effusion	0.23	2.54	High	Alive
5	20	F	Primary	Typhoid fever	Obtundation	Anaemia Pneumonia	0.28	76.04	Low	Alive
6	81	F	Primary	Ileus	Coma	Respiratory failure Pleural effusion Shock	0.17	28	Low	Dead
7	63	F	Primary	Urinary infection	Obtundation	Anaemia Respiratory failure	0.15	38	High	Alive
8	83	F	Primary	Urinary infection	Coma	None	0.15	60.6	High	Alive
9	79	F	Primary	Respiratory infection	Obtundation	None	0.15	153	Low	Alive
10	47	F	Secondary	Urinary infection	Obtundation	Anaemia Respiratory failure	0.37	9.85	High	Alive
11	82	F	Primary	Pneumonia	Obtundation	Respiratory failure Shock	0.5	78.2	Low	Dead

DIC, Disseminated Intravascular coagulation; ARDS, adult respiratory distress syndrome.

via the i.v. route until they regained their vital functions, the serum free thyroxine (T₄) values were normalized and they were able to take oral medication; and the other five patients were treated similarly but without the initial high dose of L-T₄ ('low' dose) (Table 1). The selection of patients who received either one or the other L-T₄ regimen was at random with the aid of a table of random numbers. In addition, since starting the treatment all subjects had been given hydrocortisone acetate (200–400 mg/day) until the possibility of coexisting adrenal insufficiency had been excluded. Before starting the treatment, serum samples for the determination of thyroid hormone and TSH levels were obtained and kept frozen – 40 °C until assayed in the same run.

The patients' relatives gave their informed consent before the participation of the patients in this protocol of treatment, which was approved by the Hospital Ethical Committee.

The mortality rate of myxoedema coma was determined. We also studied the mortality rates in the group of patients with primary hypothyroidism compared with the group with secondary hypothyroidism. To assess the role of improved equipment and the skill of the members of the Intensive Care Unit over the period of this study, we compared the mortality rates over two periods arbitrarily divided between 1985–1993 and 1994–2002.

We studied the clinical (age, body temperature, heart rate, degree of consciousness, Glasgow score and APACHE II score) and biochemical (free T₄ and TSH)

data at entry between the group of patients who survived and those who died. To assess the role of the dose of L-T₄ used in the treatment, we compared the mortality rates and survival curves between the 'high' and the 'low' L-T₄ dose groups.

Serum TSH (normal range 0.3–4.5 mU/l) and serum free T₄ concentrations (normal range 0.7–1.9 mmol/l) were measured by competitive chemiluminiscent enzyme immunoassay, using commercial kits (Diagnostic Products Corporation, Los Angeles, CA, USA).

Statistical analysis

Quantitative data are expressed as means \pm S.D. and their 95% confidence intervals (CI). Differences between mean values were tested by Student's *t*-test with a previous verification of normality by the Kolmogorov–Smirnov test, whereas differences between percent values were assessed by the Chi-square test or exact Fisher's test when required. Treatment response was assayed for survival curves over 40 days using the Kaplan–Meier method whilst comparison of survival curves was assessed by the log-rank test.

Results

Four out of eleven patients died, with the mortality rate being 36.4% (Table 1). The time until the patient died was

Table 2 Variables used for APACHE II score calculations

Patient	RT (°C)	Mean AP (mmHg)	HR	RR	PaO ₂	Arterial pH	Serum Na	Serum K	Serum Cr	Hct. (%)	WBC (× 10 ³)	Glasgow score	APACHE II score
1	34.5	110	39	24	68	7.32	133	4.4	1.2	40.7	3.6	13	18
2	34.4	108	124	25	54	7.30	122	5.5	2.4	31.0	5.4	4	32
3	33.9	115	38	15	204*	7.31	144	3.9	1.4	39.3	6.2	3	29
4	34.9	74	104	14	76	7.35	124	2.8	1.1	44.0	4.6	8	17
5	34.2	72	114	11	64	7.34	128	3.5	1.1	19.0	22.0	14	14
6	34.8	68	38	10	505*	7.30	126	6.0	1.4	29.0	4.0	8	34
7	35.0	88	124	20	68	7.42	110	4.1	1.5	29.0	16.0	13	18
8	35.0	95	65	22	58	7.48	122	3.5	1.4	31.4	8.0	9	20
9	34.8	128	52	18	58	7.41	120	3.9	1.2	35.6	9.5	13	19
10	34.9	112	144	23	60	7.31	126	4.6	0.9	29.0	15.4	13	20
11	33.6	80	38	10	360*	7.30	120	2.7	1.3	33.0	14.0	6	31

AP, arterial pressure; RT, rectal temperature; HR, heart rate in beats/min; RR, respiratory rate in breaths/min; Hct, haematocrit; WBC, white blood cells; FIO₂ fraction of inspired oxygen; *alveolar-arterial difference O₂ when FIO₂ >0.05; Na and K in mEq/l; Cr in mg/dl.

4–15 days after the start of treatment. One patient died of septic shock (case 2) and three of circulatory failure (cases 3, 6 and 11). One out of three patients with secondary hypothyroidism and three out of eight patients with primary hypothyroidism died ($P=0.56$ for the difference in rates). On observing the mortality rates over the periods 1985–93 and 1994–2002, rates of three out of six (50%) and one out of five (20%) for the former and latter groups were observed respectively ($P=0.54$).

The mean age of surviving patients was lower but not significantly different from the mean age of patients who died (63.0 ± 23.1 and 77.0 ± 5.6 years respectively, $P=0.27$).

Neither the body temperature and the heart rates (Table 2) nor the mean values of free T4 (0.27 ± 0.15 vs 0.24 ± 0.10 mmol/l, $P=0.71$) and TSH levels (55.90 ± 50.27 vs 44.40 ± 36.75 mU/l) were different between the patients who survived and those who died.

With regard to the state of consciousness, three out of four patients who were in coma on admission died, whereas only one of seven patients with minor degrees of consciousness died, with the two mortality rates being significantly different ($P=0.044$). The patients in coma on entry had a mean survival of 16 ± 7 days (95% CI, 2.14–29.86) while those with minor degrees of consciousness had a mean survival of 36.4 ± 3.3 days (95% CI, 29.95–42.91), log-rank analyses revealed significant differences between both cumulative survival rates ($P=0.019$). Comparison of the mean values of Glasgow scores between the patients who survived and those who died was seen to be significantly different (11.85 ± 3.24 vs 5.25 ± 2.21 respectively, $P<0.001$).

Comparison of the mean values of APACHE II scores between the patients who survived and those who died was significantly different (18.0 ± 2.08 vs 31.5 ± 2.08 respectively, $P<0.0001$) (Table 2). Furthermore, com-

parison of the survival curves for patients who had >20 with those who had ≤ 20 on the APACHE II score revealed significantly lower cumulative survival rates in the former group than in the latter (19.83 ± 5.98 (95% CI, 8.11–31.56) vs 40 days respectively, log-rank $P=0.031$).

Comparison of the mortality rates between the 'high' L-T4 dose and the 'low' L-T4 dose groups revealed that the former group had a lower mortality rate than the latter (16.7% vs 60% respectively) but the difference did not reach statistical significance. Likewise, comparison of the cumulative survival rates between both groups showed that the former group had a survival rate of 35.33 ± 4.26 days (95% CI, 26.98–43.68) and the latter group of 21.4 ± 6.9 (95% CI, 7.73–35.06) ($P=0.13$).

Discussion

The main flaw of the present investigation was the small sample of patients. However, it had the advantage of being a prospective study, having a homogeneous sample of patients treated in a single institution with a previously established protocol, which made the comparison between the subgroups easier.

The mortality rate of myxoedema coma in the present investigation was similar to most recent reports (Jordan 1995, Yamamoto *et al.* 1999).

Ageing has been associated with a fatal outcome of myxoedema coma (Hylander & Rosenquist 1985, Jordan 1995); in line with this, the mean age of our surviving patients was lower than those who died, although this difference was not statistically significant.

The clinical features of thyroid insufficiency resulting from TSH deficiency are similar to those of primary hypothyroidism. They are, however, generally less

pronounced. In this study the mortality rates for both kinds of hypothyroidism were similar.

The term myxoedema coma is used more broadly and includes patients who, although not yet in coma, demonstrate a clear deterioration of their mental status, exhibiting lethargy, psychotic symptomatology or even more subtle signs, such as confusion and disorientation (Tsitouras 1995, Reinhardt & Mann 1997). In the present study, the analyses of mortality rates and survival curves between the surviving and non-surviving groups of patients clearly demonstrated that the risks of mortality in these patients were related to the degrees of consciousness and to the Glasgow scores. Furthermore, the outcomes of these patients were also related to the severity of the patients' illness on entry determined by the APACHE II score. In this sense, the patients with an APACHE II score of more than 20 had high mortality risks, in agreement with previous data for other clinical conditions (Olalla Gallo *et al.* 1999). However, these data are in conflict with data reported by Yamamoto *et al.* (1999) who did not find any differences by simple inspection of APACHE II score between two patients who died and their other six surviving patients. However, these authors did not indicate at what moment during the patient's treatment the score was determined and statistical analysis was not performed.

Intravenous bolus administration of 300–500 µg L-T₄ at the beginning of treatment followed by 50–100 µg daily is considered to be safe and has remained a standard thyroid hormone replacement for the past three decades (Holvey *et al.* 1964, Ridgway *et al.* 1972). However, some investigators have reported a better treatment response using a low dose of L-T₄ than with classical recommendations (Khaleeli 1978, Pereira *et al.* 1982, Yamamoto *et al.* 1999). Our results suggested that the patients treated with a high initial dose of L-T₄ had a tendency towards better prognoses than those treated without that dose of levothyroxine which is in line with the aforementioned reports.

In conclusion, the results of the present investigation indicate that the degree of consciousness, the Glasgow score and the severity of the illness measured by the APACHE II score on entry are the main factors that determine the post-treatment outcome of patients with myxoedema coma. Furthermore, it also suggests that those patients who received an initial i.v. high dose of L-T₄ had better prognoses than those who received less vigorous regimens.

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