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—Original Article—

SERUM THYROID HORMONE LEVELS IN PATIENTS WITH FULMINANT HEPATITIS: USEFULNESS OF rT3 AND THE rT3/T3 RATIO AS PROGNOSTIC INDICES

Takashi KANO, M.D., Takao KOJIMA, M.D., Takeshi TAKAHASHI, M.D. and Yasutoshi MUTO, M.D.

First Department of Internal Medicine, Gifu University School of Medicine, Gifu 500, Japan

Summary

To evaluate thyroid function in 19 patients with fulminant hepatitis (FH), we have measured total and free 3,5,3′-triiodothyronine (T3) and thyroxine (T4), 3,3′,5′-triiodothyronine (reverse T3, rT3), thyroid-stimulating hormone (TSH) and thyroxin-binding globulin (TBG) in patients with FH, compared with those of 80 patients with other various liver diseases and of 10 healthy controls. Patients with FH showed the lowest values of serum T3 and the highest levels of rT3 among all patients with liver diseases studied. Furthermore, patients with FH showed a significant increase of rT3 in comparison with subacute hepatitis (SAH), "acute-on-chronic" (AOC) type of hepatic failure, ordinary and severe forms of acute hepatitis (AHo and AHs) and decompensated liver cirrhosis (LC-D). In addition, serum T3 and rT3 and the rT3/T3 ratio significantly correlated with prothrombin time (PT) and plasma methionine level. We also found that serum T3 and rT3 concentrations and the rT3/T3 ratio showed early and rapid normalization in cases of FH that survived, but they did not improve in patients with fatal outcome. These results suggest that serum T3, particularly rT3 concentrations and the rT3/T3 ratio may be useful indicators for assessing the severity and prognosis of patients with FH and can be considered to the sensitive indices for functioning hepatic microsomal reserve as well.

Key Words: *Fulminant hepatitis, Hepatic microrosomal function, T3, T4, rT3.*

Introduction

The existence of the so-called low T3 syndrome-that is, low total T3 with normal total T4 and TSH concentrations and increased rT3 levels in the absence of clinical hypothyroidism, has been frequently reported in patients with liver diseases[1–6], and it has been shown to be due to the impaired conversion of T4 to T3 and reduced degradation of rT3 in the liver[7–9]. In addition, it is well known that both formation of T3 from T4 and catabolism of rT3 are effected by iodothyronine 5′-deiodinase, found predominantly in the microsomal and plasma membranes of the liver[9–11]. Furthermore, previous studies have reported that serum T3 and rT3 concentrations may be useful indicators for assessing the severity and prognosis of patients with liver diseases[2,3,6,12]. Recently, Itoh et al.[13] have reported that the T3/T4 ratio in patients with

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Address for correspondence: Takashi Kano, M.D., First Department of Internal Medicine, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu City 500, Japan.

FH was significantly less than in controls and patients with other liver diseases. However, no report regarding serum rT3 levels in patients with FH has yet been made. The usefulness of serum thyroid hormones as a prognostic index remains to be established in patients with FH. Gershon et al.[2] have also reported that the aminopyrine breath test (ABT), which is a semiquantitative method for assessing hepatic microsomal drug-metabolizing capacity, correlated significantly with serum T3 and rT3 values and the rT3/T3 ratio. In this context, we have determined serum thyroid hormone levels in patients with FH to elucidate whether or not these are sensitive indicators reflecting the hepatic functioning mass (i.e. microsomal function) in FH and indicating the severity and prognosis of the disease.

Patients and Methods

The patients consisted of 19 cases of fulminant hepatitis (FH), 5 cases of the "acute-on-chronic" (AOC) type of hepatic failure, 13 cases of subacute hepatitis (SAH), 5 cases of the severe form of acute hepatitis (AHs), 10 cases of the ordinary form of AH (AHo), 14 cases of chronic hepatitis (CH), 12 cases of compensated liver cirrhosis (LC-C), 14 cases of decompensated liver cirrhosis (LC-D), 17 cases of hepatocellular carcinoma (HCC) with LC and 10 healthy controls. Diagnosis of these liver diseases was made on the basis of the clinical, biochemical and serological investigations and was histologically confirmed in all cases by laparoscopy and liver biopsy or autopsy. According to the criteria of the 12th

Table 1. Age, sex and liver function tests in patients with various hepatic diseases

Diseases	Age	Sex		T.P.	Alb.	GPT	T.B.	D.B.	Ch-E	PT
		M	F	(g/dl)	(g/dl)	(IU/l)	(mg/dl)	(mg/dl)	(ΔpH)	(%)
FH (n=19)	46±20	9	10	6.0±0.6	3.3±0.5	1692±1925	15.7± 7.8	10.0±5.7	0.6±0.3	27±15
SAH (n=13)	45±15	7	6	5.7±0.8	3.1±0.5	284± 171	24.4±12.0	16.7±8.7	0.4±0.1	46±28
AOC (n= 5)	51± 9	5	0	6.2±0.2	2.7±0.4	679±1137	18.0±11.8	11.4±7.4	0.3±0.1	34±15
AHs (n= 5)	39±10	2	3	5.8±0.8	3.3±0.5	2138±1807	10.4± 7.2	7.2±5.7	0.4±0.2	50±15
AHs (n=10)	35±10	4	6	7.1±0.6	4.0±0.3	1282±1056	4.4± 3.0	3.2±2.4	0.7±0.1	89±12
CH (n=14)	41±14	10	4	7.0±0.7	3.7±0.3	147± 132	1.6± 1.2	1.0±0.9	0.6±0.2	87±15
LC-C (n=12)	53± 9	8	4	7.0±0.7	3.3±0.3	77± 68	1.3± 0.4	0.8±0.2	0.4±0.1	69±17
LC-D (n=14)	55± 8	8	6	6.0±0.8	2.8±0.3	38± 14	5.0±10.0	3.1±6.5	0.3±0.1	53±13
HCC (n=17)	57±11	14	3	6.9±0.7	3.3±0.5	57± 36	2.5± 5.0	2.7±5.4	0.4±0.2	71±18
Control (n=10)	39±12	3	7	7.6±0.5	4.3±0.2	15± 5	0.6± 0.2	0.4±0.1	0.9±0.2	90± 5

Values are the means ± SD. FH, fulminant hepatitis; SAH, subacute hepatitis; AOC, "acute-on-chronic"; AHs, acute hepatitis (severe); AHo, acute hepatitis (ordinary); CH, chronic hepatitis; LC-C, liver cirrhosis (compensated); LC-D, liver cirrhosis (decompensated); HCC, hepatocellular carcinoma.

Inuyama Symposium (1981) in Japan[14], FH was defined as a hepatitis which manifests encephalopathy greater than Grade II within 8 weeks after onset of initial symptoms and shows a prothrombin time (PT) lower than 40%. The "acute-on-chronic" (AOC) type of hepatic failure was diagnosed according to the modified definition of Sherlock (1981)[15]. We included not only heavy drinking but also viral infection and drugs as aggravating factors, which add to the underlying compensated chronic liver diseases. The distinction between AHo and AHs was determined according to the activity of PT, over or below 40%, respectively. The age, sex and laboratory data of the various groups of patients are shown in **Table 1**. Samples of blood were collected in the morning before breakfast. Serum was stored at −20°C until further use. T3, T4, rT3, free T3 and T4 (FT3 and FT4), TSH and TBG were determined by respective radioimmunoassay systems (T3 and T4 RIA kit Eiken, rT3 kit Dainabot, Amerlex free T3 and T4 RIA kit Amersham, TSH kit Daichi and TBG kit Eiken). Three patients with FH were followed up, and thyroid hormone measurements were also repeated during hospitalization. The data were expressed as means ± standard deviations (M ± SD) and evaluated by Student's t test. P value less than 0.05 was considered to be statistically significant.

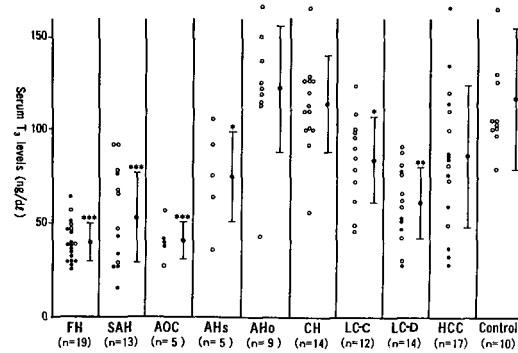

Fig. 1. Serum T3 levels in patients with various hepatic diseases. ⊢●⊣ represents the means ± SD. Open and closed circles show surviving and fatal outcome cases, respectively. *P<0.05; **P<0.01; ***P<0.001, compared with healthy controls.

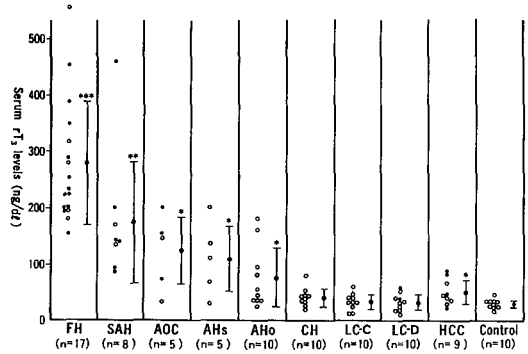

Fig. 2. Serum rT3 levels in patients with various hepatic diseases. Open and closed circles show surviving and fatal outcome cases, respectively. *P<0.05; **P<0.01; ***P<0.001, compared with healthy controls.

Results

The levels of serum T3 and rT3 in patients studied are shown in **Figs. 1** and **2**. The serum T3 levels were significantly lower in FH cases (40 ± 10 ng/dl, P<0.001), in SAH (53 ± 24, P<0.001), in AOC (41 ± 10, P<0.001), in AHs (75 ± 24, P<0.05), in LC-C (84 ± 23, P<0.05) and in LC-D (61 ± 19, P<0.01) compared with healthy controls (117 ± 38). The serum rT3 was 30 ± 7 ng/dl in healthy controls and significantly higher in patients with FH (278 ± 109, P<0.001), in SAH (178 ± 112, P<0.01), in AOC (123 ± 59, P<0.05), in AHs (109 ± 58, P<0.05), in AHo (75 ± 52, P<0.05) and in HCC (50 ± 21, P<0.05). Furthermore, patients with FH showed significantly reduced serum levels of T3, as compared with AHo (P<0.001), AHs (P<0.05) and LC-C (P<0.01) and LC-D (P<0.01) and significantly increased levels of rT3 as compared with SAH (P<0.05), AOC (P<0.001), AHo (P<0.001), AHs (P<0.001) and LC-D (P<0.001). Therefore, as shown in **Fig. 3**, the rT3/T3 ratio was significantly higher in

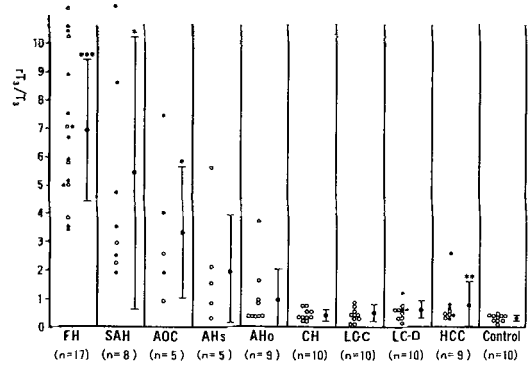

Fig. 3. The ratio of serum rT3 to T3 in patients with various hepatic diseases. Open and closed circles show surviving and fatal outcome cases, respectively. *P<0.05; **P<0.01; ***P<0.001, compared with healthy controls.

Table 2. Serum T4, TSH and TBG levels in patients with various hepatic diseases

Diseases	T_4 (μg/dl)	TSH (μU/ml)	TBG (μg/dl)
FH (n=19)	6.4±2.4	2.1±1.3	18.8± 8.4
SAH (n=13)	6.3±2.7	1.8±0.9	15.3±10.5
AOC (n= 5)	4.2±0.9***	2.8±1.5	15.3± 4.4
AHs (n= 5)	9.6±3.1	3.2±1.9	35.2± 7.7***
AHo (n=10)	9.2±1.5*	3.3±1.1	39.1± 5.3****
CH (n=14)	7.6±2.6*	3.8±1.3***	31.2± 7.4*
LC-C (n=12)	5.4±1.2*	4.1±2.1**	21.4± 4.8
LC-D (n=14)	4.7±1.5***	4.1±2.0***	17.4± 4.4
HCC (n=17)	7.6±4.1	3.9±1.8***	27.3± 8.9
Controls (n=10)	7.3±2.3	2.4±0.7	20.0± 8.5

*P<0.05; **P<0.02; ***P<0.01; ****P<0.001, compared with healthy controls.

patients with FH (6.9 ± 2.5, P<0.001), in SAH (5.4 ± 4.8, P<0.05), in AOC (3.3 ± 2.3, P<0.05)

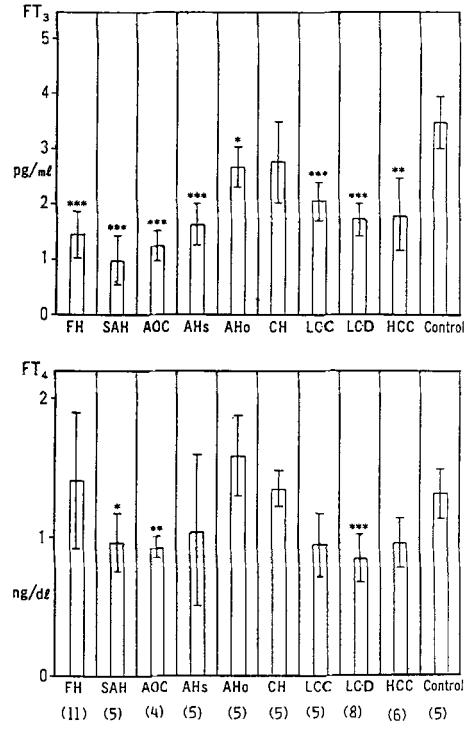

Fig. 4. Serum levels of free thyroid hormones (FT3 and FT4) in patients with various hepatic diseases. *P<0.05; **P<0.01; ***P<0.001, compared with healthy controls. Parentheses shows number of cases.

and HCC (0.8 ± 0.8, P<0.01) in comparison with controls (0.3 ± 0.1). Patients with FH showed a significant increase of the rT3/T3 ratio as compared with AOC (P<0.001), AHo (P< 0.001), AHs (P<0.001) and LC-D (P<0.001).

The levels of serum T4, TSH and TBG are shown in **Table 2**. There was no significant difference in serum T4, TSH and TBG levels between FH and healthy controls. However, the serum T4 levels were significantly lower in patients with AOC (P<0.01) and LC-D (P< 0.01) and significantly higher in patients with AHo (P<0.05) and CH (P<0.05) as compared with healthy controls. Furthermore, patients with AHs and CH showed significantly increased levels of TBG in comparison with healthy controls (P<0.01 and P<0.05, respec-

tively).

FT3 and FT4 in the patients studied are shown in **Fig. 4**. The serum FT3 levels were significantly lower in the patients with FH (1.44 ± 0.45 pg/ml, P<0.001), in SAH (0.97 ± 0.44, P<0.001), in AOC (1.23 ± 0.27, P<0.001), in AHs (1.62 ± 0.38, P<0.001), in AHo (2.67 ± 0.37, P<0.05), in LC-C (2.04 ± 0.35, P<0.001), in LC-D (1.72 ± 0.31, P<0.001) and in HCC (1.79 ± 0.47, P<0.01) in comparison with healthy controls (3.47 ± 0.47). However, there was no significant difference in serum FT3 levels between FH and other liver diseases. On the other hand, the serum FT4 levels were significantly lower in patients with SAH (0.96 ± 0.21 ng/dl, P<0.05), in AOC (0.92 ± 0.07, P<0.01) and in LC-D (0.84 ± 0.17, P<0.001) in comparison with healthy controls (1.31 ± 0.18). No difference in serum FT4 levels was found between FH (1.41 ± 0.49) and healthy controls.

As shown in **Fig. 5**, serum T3 demonstrated a significant positive correlation with PT (%) (r=0.772, P<0.001), whereas a significant negative relationship was noted between serum rT3 and PT (r=−0.600, P<0.001). In addition, there was a significant positive correlation between the serum rT3/T3 ratio and plasma methionine level (r=0.711, P<0.001). **Figures 6** to **8** show the changes of serum T3 and rT3 levels and T3/T4 and rT3/T3 ratios in two patients with FH who survived and in one fatal case of FH. Repeated determinations of serum T3, rT3 and rT3/T3 ratio showed early and rapid normalization in two surviving cases with FH (**Fig. 6** and **Fig. 7**), but these indicators did not improve in a patient with fatal outcome (**Fig. 8**).

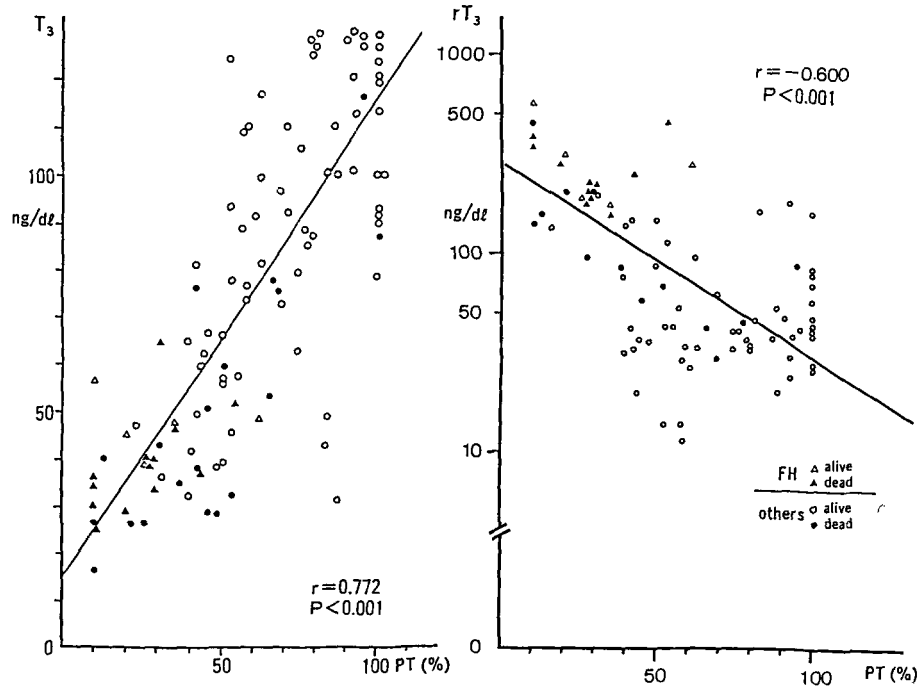

Fig. 5. Correlations between T3, rT3 and prothrombin time (%) in patients with various hepatic diseases.

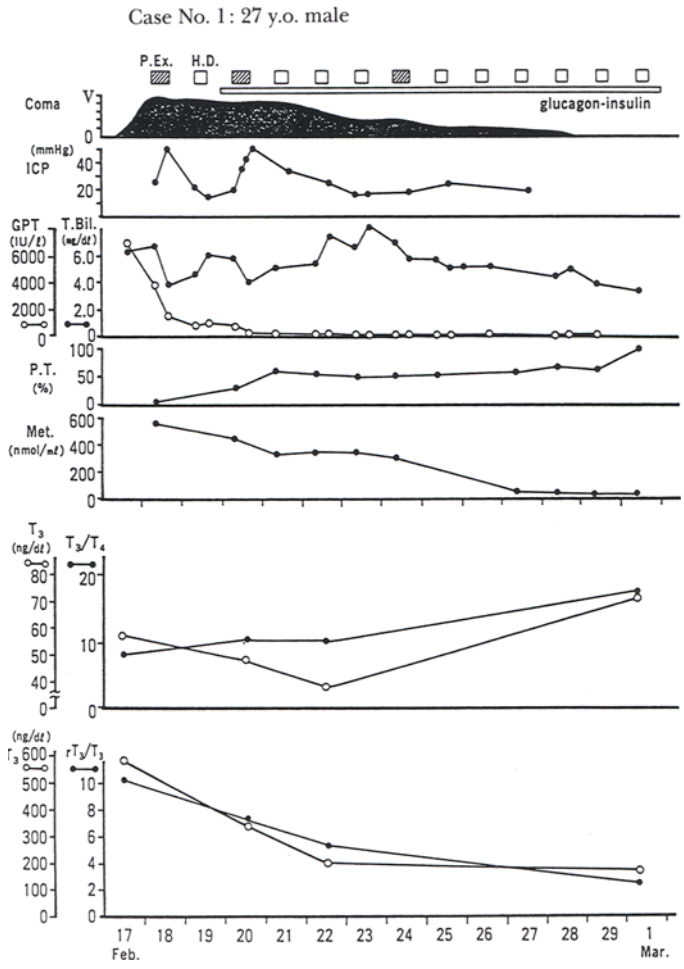

Fig. 6. Changes in values of serum T3, rT3, rT3/T3 and liver function tests in a surviving case with FH. P.Ex., plasma exchange; H.D., hemodialysis; ICP, intracranial pressure.

Discussion

It is well known that the liver plays an important role in thyroid hormone metabolism, being involved in their conjugation, excretion, monodeiodination and in synthesis of TBG[4,9–11]. Some previous studies have reported low serum T3 concentrations and elevated rT3 levels in patients with liver diseases[1–6]. Furthermore, T3 and rT3 levels have been used to follow the clinical response to medical therapy of alcoholic liver disease and to predict the short-term survival of patients with advanced chronic diseases[3,12]. Recently, Itoh et al.[13] have reported that the T3/T4 ratio in patients with FH was significantly less than those in the controls and patients with other liver diseases. However, changes of serum thyroid hormone levels after admission and differences between cases of FH and SAH, AOC and AHs have not been examined. No report regarding serum rT3 levels in cases of FH has yet been made.

In this study, it was disclosed that patients

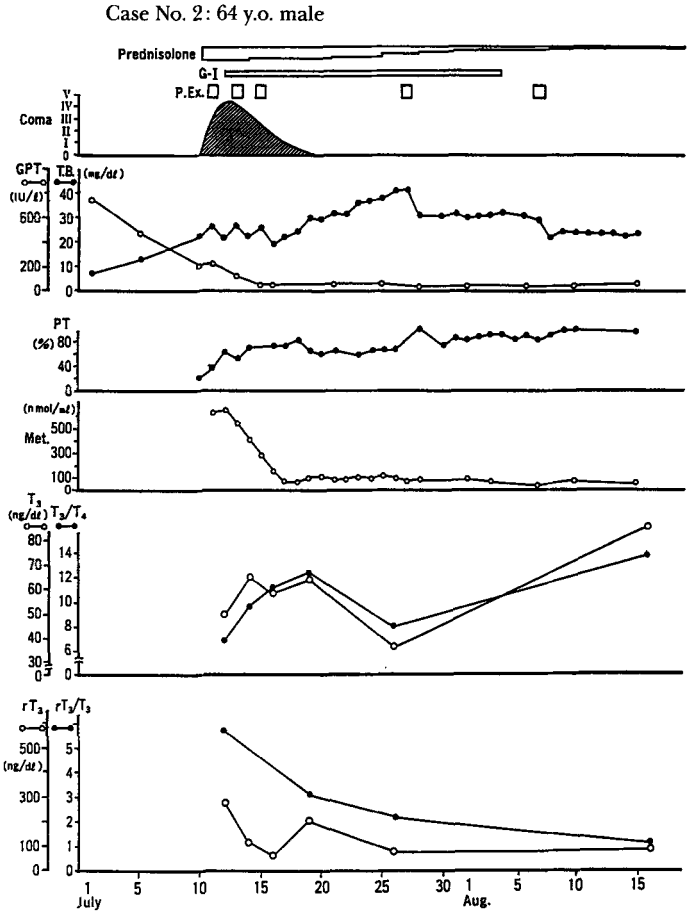

Fig. 7. Changes in values of serum T3, rT3, rT3/T3 and liver functions tests in a surviving case with FH. G-I, glucagon-insulin therapy.

with FH showed the lowest values of serum T3 and the highest levels of rT3 among all liver diseases studied. Serum rT3 concentrations increased in the following order, healthy controls, AHo, AHs, AOC, SAH and FH, suggesting that rT3 is a sensitive indicator to estimate differences in the amount of functioning liver in acute liver diseases.

It was also found that serum T3 and rT3 and rT3/T3 ratio correlated significantly with PT and plasma methionine levels, which were considered to be useful indicators for estimating the severity of liver dysfunction[16]. More importantly, serum rT3 levels elevated further even in patients with FH, showing a PT of less than 10% (**Fig. 5**). This result shows that rT3 can be regarded as a more sensitive index than PT for estimating extremely impaired liver dysfunction. In addition, it was revealed that serum T3 and rT3 concentrations and the rT3/T3 ratio returned towards normal in the early phase in FH cases that survived, but they did not improve in a case with fatal outcome, indicating that serum T3, particularly rT3 levels and rT3/T3 ratio may be useful indicators for assessing the prognosis of patients with FH. Several studies have shown that serum T3 and rT3 concentrations

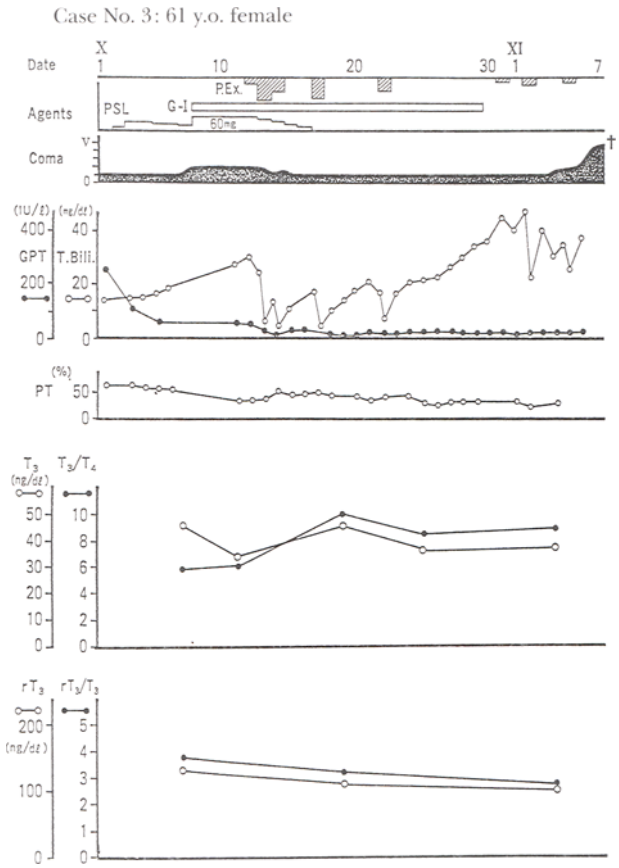

Fig. 8. Changes in values of serum T3, rT3, rT3/T3 and liver function tests in a fatal outcome case of FH. PSL, prednisolone.

may be useful prognostic indices in euthyroid sick syndrome, including liver cirrhosis[1–3,6,12].

The liver is the principal site of T3 production and rT3 degradation and accounts for greater than 80% of the daily production of T3 from T4[7]. It has been recognized that both formation of T3 and degradation of rT3 are catalyzed by a similar and possibly identical enzyme-iodothyronine 5′-deiodinase[9–11]. This enzyme is located predominantly in the microsomes and plasma membranes of the liver. Gershon et al.[2] reported that the aminopyrine breath test (ABT), which was a semiquantitative method for assessing hepatic microsomal drug metabolizing capacity, correlated significantly with serum T3 and rT3 values and the rT3/T3 ratio. Itoh et al.[13] also showed that there was a significant positive relationship between the serum T3/T4 ratio and microsomal arylamidase activity in the liver. On the other hand, Ramsoe et al.[17] have reported that the plasma clearance of phenazone, which is metabolized in hepatic microsomes, was significantly low in patients with FH. Therefore, alterations in serum T3 and rT3 in patients with FH may be attributable to a severe disturbance of hepatic iodothyronine 5′-deiodenase activity. Furthermore, Chopra[18] recently demonstrated the existence of a potent inhibitor of extrathyroid conversion of T4 to

T3 in sera of patients with nonthyroidal illness. It is also known that rT3 inhibits hepatic conversion of T4 to T3[10,19].

Serum FT3 was also significantly reduced in parallel to serum total T3, while total and free T4 levels were within normal limits in patients with FH. The reduction of serum FT3 levels obtained in this study is in agreement with that observed in chronic liver diseases by Borzio et al.[5]. On the other hand, serum concentrations of TSH and TBG were normal in patients with FH, indicating that the reduction in serum T3 is possibly mediated by a reduction of T3 production in liver rather than by a decrease of plasma thyroid hormone-binding proteins.

In the present study, serum total T4 levels were found to be significantly lower in patients with AOC, LC-C and LC-D and significantly higher in patients with AHo and CH. However, there was no significant difference in serum T4 between FH and healthy controls. High levels of serum total T4 in patients with AHo and CH were related to the increases in the serum concentrations of TBG. On the other hand, serum free T4 levels were significantly lower in patients with SAH, AOC and LC-D without any significant changes in serum TBG concentrations. Conflicting results concerning total and free T4 in serum have been reported in various liver diseases[2,4–7,9]. The precise mechanism of the lowering of total and free T4 levels in extremely ill patients with SAH, AOC and LC-D remains unclear. However, several factors may be involved, such as a decrease in the serum concentration of T4 binding proteins (mainly TBG, and, to a lesser extent, T4-binding prealbumin and albumin), a reduced thyroid hormone-binding capacity, because of a circulating inhibitor, enhanced metabolic clearance rate of T4 and dampening of hypothalamo-hypophyseal-thyroid axis function[20,21].

In all event, these results strongly suggest that serum T3 and rT3 concentrations are useful indicators for assessing the severity and prognosis of patients with FH and considered to be a sensitive index for functioning hepatic microsomal reserve. In addition, the rT3/T3 ratio was regarded as a more sensitive marker than T3/T4 for differentiating FH from other liver diseases. The most important factor underlying this phenomenon may be a reduction in conversion of T4 to T3 and degradation of rT3 to 3,3′-diiodothyronine (3,3′-T2), presumably due to reduced activity of iodothyronine 5′-deiodinase in the liver.

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