A potential prognostic indicator of fulminant hepatic failure: A valuable adjunct in preliver transplant assessment?

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B YACYSHYN, CM CHEUNG, DG MALKIN, SC PAPPAS. A potential prognostic indicator of fulminant hepatic failure: A valuable adjunct in preliver transplant assessment? Can J Gastroenterol 1994;8(5):308-312. The use of thyroid function tests as a method of monitoring patients with fulminant hepatic failure has been previously proposed. The use of these indices in two cases with fulminant hepatic failure are described. Both patients had simultaneous ingestion of hepatotoxic mushroom (*amanita virosa*). Their parallel clinical courses and recovery without liver transplantation is described, outlining the potential long term cost-savings achievable by such tests in the selection of patients for liver transplantation and the need for further study of these indices for this application.

Key Words: Fulminant hepatic failure, Hepatotoxin ingestion, Thyroid indices

Indicateur potentiel du pronostic dans l'insuffisance hépatique fulminante: complément utile dans l'évaluation préparatoire à la transplantation hépatique

RÉSUMÉ : Le recours aux épreuves de fonction thyroïdienne comme méthode de surveillance des patients atteints d'insuffisance hépatique fulminante a déjà été proposé. L'utilisation de ces indices dans deux cas d'insuffisance hépatique fulminante est décrite ici. Les deux patients ont simultanément ingéré un champignon hépatotoxique (*amanite*). Leur évolution clinique parallèle et leur récupération sans transplantation hépatique sont décrites ici, soulignant les économies potentielles à long terme qu'il est possible de réaliser grâce à ces tests pour la sélection des patients en vue d'une transplantation hépatique et la nécessité de pousser la recherche sur ces indices dans des cas semblables.

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THE USE OF THYROID FUNCTION testing as a monitor of severe illness has been proposed in many diverse disease states (1). The measurement of the reverse triiodothyronine (rT₃) level has been shown to correlate with a poor prognosis (2). Although the measurement of thyroid function has been evaluated in cirrhosis and employed in the evaluation of liver transplantation candidates, the simultaneous evaluation of two patients (husband and wife) from the identical onset to the resolution of fulminant hepatic failure (FHF) using thyroid indices has not been reported (3). In these patients, the levels of rT₃ and triiodothyronine (T₃), and rT₃:T₃ ratios have been reported to parallel closely their clinical course (2). These indices may provide an adjunct to current methods of assessing patients before liver transplantation and should be considered.

CASE ONE

A 42-year-old Caucasian female was admitted to hospital with acute abdominal pain, diarrhea and encephalopathy. No pertinent previous medical history was obtained from relatives; however, the patient and her husband

TABLE 1
Liver and thyroid functions in fulminant hepatic failure for case 1

Day	Clinical status	AST (IU/L)	ALT (IU/L)	T ₃	rT ₃	rT ₃ T ₃	Prothrombin time (s)*	Total bilirubin	Creatinine
	Normal	10-55	5-40	1.2-3.4	0.15-0.75		—	—	—
1	Ingestion of amanita virosa								
5	Fulminant hepatic failure	2250	>1700	0.8	4.77	6	62	140	80
6	Fulminant hepatic failure	540	>1700	0.7	4.01	5.7	27.9	260	90
7	Fulminant hepatic failure	150	>1600	0.7	3.54	5.1	27.0	150	80
8	Fulminant hepatic failure	100	>1300	0.9	3.06	3.4	21.5	440	75
9	Fulminant hepatic failure	74	5000	0.7	2.67	3.8	24.2	480	95
10	Spontaneous bacterial peritonitis	42	625	0.5	2.28	4.6	23.7	460	90
11	Spontaneous bacterial peritonitis	35	450	0.7	1.48	2.1	24.1	350	90
12	Spontaneous bacterial peritonitis	40	350	0.7	1.47	2.1	23	300	90
13	Recovery	32	230	0.5	1.69	3.4	—	—	—
17	Recovery	32	20	0.7	1.07	1.5	18	350	105
18	Recovery	33	10	0.6	1.32	2.2	15	360	105
20	Recovery	42	5	0.8	1.50	1.9	14.3	310	130

*High International Standard Index reagent. ALT Alanine aminotransferase; AST Aspartate aminotransferase; rT₃ Reverse triiodothyronine (3,3',5'-triiodothyronine); T₃ Triiodothyronine

TABLE 2
Liver and thyroid functions in fulminant hepatic failure for case 2

Day	Clinical status	AST (IU/L)	ALT (IU/L)	T ₃	rT ₃	rT ₃ T ₃	Prothrombin time (s)*	Total bilirubin	Creatinine
	Normal	10-55	5-40	1.2-3.4	0.15-0.75		—	—	—
1	Ingestion of amanita virosa						14.7	—	—
5		—	—	1.2	3.75	3.1	23.5	160	115
6	Fulminant hepatic failure	400	>1700	0.9	2.58	2.9	27.5	370	80
9	Fulminant hepatic failure	200	700	0.8	1.71	2.1	18	—	105
11	Fulminant hepatic failure	80	110	0.9	1.12	1.2	22.2	500	115
13	Fulminant hepatic failure	—	80	1	0.76	0.8	13.5	—	115
17	Recovery	70	50	1.2	0.52	0.4	12.8	240	85
18	Recovery	90	46	1.1	0.5	0.5	12.8	190	95
20	Recovery	80	48	1.5	0.43	0.3	12.8	150	80

*High International Standard Index reagent. ALT Alanine aminotransferase; AST Aspartate aminotransferase; rT₃ Reverse triiodothyronine (3,3',5'-triiodothyronine); T₃ Triiodothyronine

(case 2) had ingested wild mushrooms. The mushrooms had not been speciated, and were ingested because mushrooms picked from the same location had been eaten previously without undue effects. No other family member ingested the mushrooms. No medications had been taken by the patient. There was no history of illicit drug use, viral hepatitis, blood transfusions or recent travel. The patient was admitted to hospital with the diagnosis of FHF secondary to mushroom poisoning. In addition to standard supportive therapy, the patient was monitored with daily blood work including aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, gamma glutamyltranspeptidase, T₃ (Abbott T₃ RIA bead), T₄ (Abbott TDX fluores-

cence polarization assay), rT₃ (Serono RIA diagnostic kit ¹²⁵I Radio-assay), T₃ uptake (Abbott TDX fluorescence polarization assay), T₃ immunoassay, thyroid-stimulating hormone (TSH) (Hybritech enzyme assay) and thyroid binding globulin (Corning Immo phase TBG ¹²⁵I Radio-assay). Thyroid function on admission (day 1) were (normal range in brackets): T₄, 94 nmol/L (55 to 155); T₃U, 0.57 (0.75 to 1.55); T₃, 0.8 nmol/L (1.2 to 3.4); TSH, 1.2 mIU/L (0.5 to 6.0); and testosterone-binding globulin, 15.3 mg/L (15 to 30). Bilirubin and creatinine were obtained from the patient's common chemistry panel. Prothrombin time was measured in seconds with a standard laboratory assay (Organon-Teknika).

During slow recovery, a sudden fever

occurred, coincident with a small number of ascites, detected by shifting dullness and confirmed by ultrasound (Table 1). Diagnostic paracentesis revealed a leukocytosis of greater than 600 leukocytes/mL ascitic fluid. The patient was then started on intravenous antibiotics (ampicillin and gentamicin) and continued to recover. Identification of amanita virosa as the ingested mushroom was made by the patient after recovery, and confirmed by a mycologist after examining the area from which the mushrooms were picked.

CASE TWO

A 41-year-old Caucasian male was admitted to hospital after eating wild mushrooms five days previously. He developed FHF with hepatic encephalo-

Figure 1) A close relationship between reverse triiodothyronine and triiodothyronine (rT_3/T_3) and aspartate aminotransferase (AST) is shown for case 1

Figure 2) A close relationship between reverse triiodothyronine and triiodothyronine (rT_3/T_3) and aspartate aminotransferase (AST) is shown for case 2

Figure 3) A relationship between prothrombin time (PT) and reverse triiodothyronine and triiodothyronine (rT_3/T_3) was identified for case 1

Figure 4) A relationship between prothrombin time (PT) and reverse triiodothyronine and triiodothyronine (rT_3/T_3) was identified for case 2

pathy progressing to confusion and somnolence (stage II). With supportive therapy, profound hypoglycemia was controlled and gradual recovery of liver function occurred (Table 2). Thyroid function studies on admission were (normal range in brackets): T_4 , 116 nmol/L; thyroid uptake, 0.51; T_3 , 1.22

nmol/L (1.2 to 3.4); TSH, less than 0.3 mIU/L (0.5 to 6.0); and testosterone-binding globulin, 13.4 mg/L (15 to 30) (Table 2). Those values that were abnormal on admission normalized during hepatic recovery. As with case 1, the ingested mushrooms were confirmed to be *amanita virosa*.

DISCUSSION

The need for objective biochemical indices to monitor patients with FHF before liver transplantation has been more pressing due to health care budgetary pressures (4). The long term expense in the care of liver transplant patients is not trivial, and the decision

to perform a transplant therefore has long term considerations and should be buttressed by laboratory and clinical data best able to identify those patients in whom transplantation is necessary, although supportive care to allow native liver regeneration is the preferable management when possible.

O'Grady et al (5) reviewed 588 patients with acute hepatic failure using unvaried and multivariate analysis. They identified several criteria to determine prognosis of FHF to assist in determining when liver transplantation is indicated (5). These parameters include blood pH, serum bilirubin, prothrombin time, serum creatinine, age and degree of encephalopathy among others.

Hepatotoxin ingestion resulting in FHF is frequently managed by liver transplantation. Of these, certain poisonous mushrooms have long been known to contain hepatotoxins, and identification of their specific toxins have provided models of hepatotoxicity (6,7). The ingestion of *amanita virosa* by these patients inadvertently provided an opportunity to evaluate serial thyroid function testing in two patients with acute FHF.

A direct primary action of toxic mushroom ingestion on the thyroid gland is not described. The liver has been identified as an important regulator of thyroid hormone homeostasis (8-12). Identification of specific patterns of thyroid hormone abnormalities has been described for different hepatic diseases. For instance, serum T₃ has been proposed as an index of the severity of alcoholic liver disease (13). Several tissues convert T₄ to T₃ (the active hor-

mon) and the biologically inert rT₃ (3,3',5'-triiodothyronine). However, degradation of rT₃ and T₃ is catalyzed by the enzyme iodothyronine 5'-deiodinase located primarily in liver and kidney (14). Severe forms of hepatic disease with a deficiency of this enzyme result in a reduction in plasma T₃ levels and an increase in rT₃ levels in association with a normal TSH level. This pattern of thyroid indices is known as the 'low T₃ syndrome' and is prognostically useful in alcoholic liver disease and in assessing potential liver transplant recipients (3,13-15). Furthermore, replacement thyroid hormone therapy has not been shown to benefit euthyroid-sick patients (16).

The prognostic use of rT₃ in patients with hepatocellular disease has been described with one study attributing an 11-fold increased risk of death to an rT₃ value greater than 0.590 ng/mL which is equal to 0.761 nmol/L (3). As shown in case 1, the elevation of rT₃ corresponded to clinical deterioration with development of spontaneous bacterial peritonitis on day 10 with this measurement decreasing progressively with clinical improvement (Table 1). This correlation of rT₃:T₃ to hepatocellular damage corresponds with the aspartate aminotransferase levels of each patient (Figures 1,2). Similarly, the more serious clinical course was experienced by case 1 who consistently had a higher rT₃:T₃ ratio than case 2 (Table 1).

The depressed thyroid hormone level associated with poor prognosis in severe liver disease was at first shown in our patients, but returned to normal as both patients returned to euthyroid

status (Tables 1,2) (13). Furthermore, a good relationship was shown between rT₃:T₃ and prothrombin time (Figures 3,4). This finding is consistent with that from a group at Oxford – identification of prothrombin time as a prognostic factor in FHF (5).

With acute forms of hepatitis, an increase in serum thyroxine and thyroxine-binding globulin has been shown. These increases have been postulated to be secondary to increased thyroxine-binding globulin in regenerating hepatocytes, the release of thyroxine-binding globulin by damaged hepatocytes or decreased thyroxine-binding globulin clearance (17-19).

As these two patients illustrate, the level of rT₃ and T₃, and the rT₃:T₃ ratio correlate well with the clinical status of FHF due to hepatotoxic mushroom ingestion. These patients exhibit a high rT₃:T₃ ratio, reflecting the clinical course of FHF. Overall, this pattern is consistent with the low T₃ syndrome; however, the low TSH found in case 2 is likely due to the severe physiological stress of FHF. The use of thyroid indices as adjunctive indicators of hepatic function in FHF allowed for prediction of clinical deterioration before the development of spontaneous bacterial peritonitis in one patient, and subsequently paralleled their eventual complete recovery. Such measurements are useful in the assessment of hepatic disease in view of the liver's key role in thyroid hormone metabolism and homeostasis. Such information should be studied in other etiologies of FHF and may be of valuable assistance in treating a patient in whom the need for liver transplantation is borderline.

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