13. Russell CD, Taylor A, Eshima D. Estimation of technetium-99m-MAG3 plasma clearance in adults from one of two blood samples. *J Nucl Med* 1989;30:1955–1959.
14. Moonen M, Granerus G. Subtraction of extra-renal background in ^{99m}Tc-DTPA renography: comparison of various regions of interest. *Clin Phys* 1992;12:453–461.
15. Neter J, Wasserman W, Kutner M. *Applied linear statistical models*, 3rd ed. Homewood, IL: Irwin Publishing Company; 1990.
16. Russell CD, Li L, Kahraman HN, Dubovsky EV. Renal clearances of technetium-99m-MAG3: normal values [Letter]. *J Nucl Med* 1995;36:706–708.
17. Tondeur M, Piepsz A, Dobbeleir A, Ham H. Technetium-99m-mercaptoacetyltriglycine gamma camera clearance calculations: methodological problems. *Eur J Nucl Med* 1991;18:83–86.
18. Granerus G, Moonen M. Effects of extra-renal background subtraction and kidney depth correction in the measurement of GFR by gamma camera renography. *Nucl Med Commun* 1991;12:519–527.
19. Shore RM, Koff SA, Mentser M, et al. Glomerular filtration rate in children: determination from the ^{99m}Tc-DTPA renogram. *Radiology* 1984;151:627–633.
20. Russell CD, Bischoff PG, Kontzen F, et al. Measurement of glomerular filtration rate using ^{99m}Tc-DTPA and the gamma camera: a comparison of methods. *Eur J Nucl Med* 1985;10:519–521.
21. Peters AM, George P, Ballardie F, Gordon I, Todd-Pokropek AT. Appropriate selection of background for ^{99m}Tc-DTPA renography. *Nucl Med Commun* 1988;9: 973–985.
22. Peters AM, Gordon I, Evans K, Todd-Pokropek A. Background in ^{99m}Tc-DTPA renography evaluated by the impact of its components on individual kidney glomerular filtration rate. *Nucl Med Commun* 1988;9:545–552.
23. Eshima D, Taylor A. Technetium-99m-mercaptoacetyltriglycine: update on the new ^{99m}Tc renal tubular function agent. *Semin Nucl Med* 1992;22:61–73.
24. Taylor, A, Nally J, Aurell M, et al. Consensus report on ACE inhibitor renography for the detection of renovascular hypertension. *J Nucl Med* 1996;37:1876–1882.
25. Blaufox MD, Dubovsky EV, Hilson AJW, Taylor A Jr, de Zeeuw R. Report of the working party group on determining the radionuclide of choice. *Am J Hypertens* 1991;4:747S–748S.

Evaluation of Fulminant Hepatic Failure by Scintigraphy with Technetium-99m-GSA

Susumu Shiomi, Tetsuo Kuroki, Maki Kuriyama, Tadashi Takeda, Shuhei Nishiguchi, Shinya Nakajima, Takashi Tanaka and Hironobu Ochi

Third Department of Internal Medicine Department of Public Health, and Division of Nuclear Medicine, Osaka City University Medical School, Osaka, Japan

We evaluated the usefulness of hepatic receptor imaging with ^{99m}Tc-diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) to establish the diagnosis and prognosis of fulminant hepatic failure (FHF). **Methods:** Of the 20 patients, 8 had acute hepatitis and 12 had FHF. Computer acquisition of gamma-camera data started just before the injection of 185 MBq ^{99m}Tc-GSA and stopped 20 min later. Time-activity curves for the heart and liver were generated from regions of interest (ROIs) for the whole liver and precordium. A receptor index was calculated by division of the radioactivity of the liver ROI by that of the liver plus heart ROIs 15 min after the injection. An index of blood clearance was calculated by division of the radioactivity of the heart ROI at 15 min by that of the heart ROI 5 min after the injection. **Results:** The receptor index was less than 0.83 in all patients with FHF, but it was more than 0.83 in all patients with acute hepatitis. The index of blood clearance was more than 0.72 in all patients with FHF but less than 0.72 in all patients with acute hepatitis. All six survivors of FHF had receptor indices of 0.58 or more, but in five of the six patients who later died, the receptor index was 0.58 or less. The index of blood clearance was 0.85 or less in all survivors but 0.85 or more in the same five patients who later died. **Conclusion:** Hepatic receptor imaging with ^{99m}Tc-GSA facilitated the evaluation of hepatic function reserve and was useful in establishing the diagnosis and prognosis of FHF.

Key Words: technetium-99m-GSA; asialoglycoprotein receptor; fulminant hepatic failure

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Fulminant hepatic failure (FHF) is a syndrome in which jaundice and hepatic encephalopathy appear within 8 wk of the onset of symptoms in a patient without a history of liver disease (*1*). Survival rates in patients with FHF have improved in recent years, probably because of improvements in intensive care, but mortality remains high (*2*). Various blood biochemical tests have been used for evaluation of hepatic functional reserve (*3,4*), but their results are not always meaningful because patients with FHF may be treated by plasmapheresis and blood product supplementation. Imaging methods such as liver scintigraphy (*5–7*), abdominal CT scanning (*8*) and abdominal ultrasonography (*9*) are useful in the diagnosis of diffuse hepatic diseases such as FHF. Liver scintigraphy with a radiocolloid is the most useful of the three in establishing the diagnosis of FHF. Hepatic receptor imaging with ^{99m}Tc-diethylenetriaminepentaacetic acid galactosyl human serum albumin (GSA) is a new method for the diagnosis of hepatic disease on the basis of the specific binding of hepatocytes to asialoglycoprotein receptors (*10,11*). We evaluated the clinical usefulness of ^{99m}Tc-GSA scintigraphy in the diagnosis of FHF and in prediction of the outcome.

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For correspondence or reprints contact: Susumu Shiomi, MD, Third Department of Internal Medicine, Osaka City University Medical School, 1-5-7 Asahimachi, Abeno-ku, Osaka 545, Japan.

MATERIALS AND METHODS

Patients

We studied 12 patients with FHF, 8 with acute hepatitis (AH), 50 with chronic hepatitis and 120 with cirrhosis who were admitted to our hospital between April 1993 and October 1995. Patients with chronic hepatitis and cirrhosis were diagnosed by examination of specimens obtained by laparoscopy or needle biopsy done under ultrasonic guidance. The criteria for diagnosis of FHF was hepatic encephalopathy of grade 2 or more within 2 mo of the onset of signs and symptoms of hepatitis, with a plasma prothrombin level of less than 40% or massive or submassive necrosis of the liver found in biopsy or necropsy specimens (*12*). The clinical and laboratory findings of FHF and AH are summarized in Table 1.

The diagnosis was type A FHF if antibodies of the immunoglobulin M class to hepatitis A antigen were detected and type B FHF if both hepatitis B surface antigens and antibodies of the immunoglobulin M class to hepatitis B core antigen were detected. Type C FHF was diagnosed if hepatitis C virus (HCV) RNA was detected. The diagnosis was of FHF with non-A, non-B, non-C hepatitis if none of the following was detected: antibodies of the immunoglob-

TABLE 1
Clinical and Laboratory Findings of Patients with Fulminant Hepatic Failure or Acute Hepatitis

Patient no.	Age (yr)	Sex	Etiology	Disease	Days before onset of encephalopathy	PT (%)	Bilirubin (mg/dl)	Outcome	Receptor index	Index of blood clearance
1	51	M	HBV	FHF	7	12	17.3	Died	0.40	0.89
2	79	M	HBV	FHF	25	27	28.8	Died	0.45	0.93
3	62	F	non-ABC	FHF	26	16	34.7	Died	0.31	0.87
4	39	M	Drug	FHF	36	36	11.4	Died	0.49	0.87
5	67	M	Drug	FHF	24	27	28.1	Died	0.58	0.85
6	14	F	Drug	FHF	16	19	3.1	Died	0.66	0.81
7	30	F	HAV	FHF	8	35	8.2	Alive	0.82	0.75
8	43	F	HAV	FHF	20	33	17.9	Alive	0.77	0.79
9	68	F	HBV	FHF	21	23	12.5	Alive	0.60	0.83
10	33	M	non-ABC	FHF	16	38	21.4	Alive	0.80	0.73
11	47	M	non-ABC	FHF	15	38	15.2	Alive	0.73	0.73
12	42	F	Drug	FHF	38	21	8.5	Alive	0.58	0.85
13	31	M	HAV	AH	–	109	9.7	Alive	0.90	0.67
14	53	M	HAV	AH	–	94	7.2	Alive	0.94	0.57
15	49	F	HAV	AH	–	113	2.1	Alive	0.93	0.54
16	55	F	HAV	AH	–	104	8.4	Alive	0.88	0.60
17	44	F	HBV	AH	–	55	5.2	Alive	0.91	0.71
18	23	F	HCV	AH	–	93	8.6	Alive	0.87	0.65
19	45	F	Drug	AH	–	148	5.5	Alive	0.94	0.50
20	58	F	Drug	AH	–	83	8.6	Alive	0.84	0.68

PT = prothrombin time; HBV = hepatitis B virus; FHF = fulminant hepatic failure; non-ABC = non-A, non-B, non-C hepatitis; HAV = hepatitis A virus; AH = acute hepatitis; HCV = hepatitis C virus; – = encephalopathy did not appear.

ulin M class to hepatitis A, antibodies of the immunoglobulin M class to hepatitis B core antigen, antibodies to HCV and HCV RNA. Drug-induced hepatitis was diagnosed if the drug had been taken and if there was an overdose or if results of a lymphocyte stimulation test showed allergy to the drug.

Measurement of Receptor Index and Index of Blood Clearance

Technetium-99m-GSA (185 MBq) was injected intravenously, and dynamic images were recorded with the patient supine under a large field of view gamma camera with a low-energy, all-purpose, parallel-hole collimator. Computer acquisition of the gamma camera data was started just before injection of the ^{99m}Tc-GSA and stopped 20 min later. Digital images (128 × 128 pixels) were acquired in byte mode at the rate of 60 sec per frame. Accumulation images in an anterior abdominal view were obtained for the first 20 min after the injection. Time-activity curves for the heart and liver were generated from regions of interest (ROIs) for the whole liver and precordium. The receptor index was calculated by division of the radioactivity of the liver ROI by the radioactivity of the liver plus heart ROIs 15 min after the injection. The index of blood clearance was calculated by division of the radioactivity of the heart ROI at 15 min after the injection by the radioactivity of the heart ROI at 5 min.

Statistical Analysis

Results are expressed as medians with 25th and 75th percentiles. The significance of differences between medians was evaluated by the Mann-Whitney U test. Differences with probability values of less than 0.01 were considered to be significant.

RESULTS

The medians (25th and 75th percentiles) of the receptor index were 0.59 (0.47, 0.75) in patients with FHF, 0.91 (0.88, 0.94) in patients with AH, 0.94 (0.92, 0.96) in patients with chronic hepatitis and 0.85 (0.79, 0.90) in patients with cirrhosis (Fig. 1). The differences between the receptor index in patients with FHF and AH, chronic hepatitis or cirrhosis were significant (all $p < 0.01$). The receptor index was less than 0.83 in all patients with FHF but more than 0.83 in all patients with AH.

The medians (25th and 75th percentiles) of the index of blood clearance were 0.84 (0.77, 0.87) in patients with FHF, 0.63 (0.56, 0.68) in patients with AH, 0.52 (0.47, 0.60) in patients with chronic hepatitis and 0.71 (0.63, 0.77) in patients with cirrhosis (Fig. 2). The differences between the index of blood clearance in patients with FHF or with AH, chronic hepatitis or cirrhosis were significant (all $p < 0.01$). The index of blood clearance was more than 0.72 in all patients with FHF but less than 0.72 in all patients with AH.

Of the 12 patients with FHF, six died; the median (25th and 75th percentiles) of the receptor index in this group was 0.47 (0.40, 0.58), but the median was 0.75 (0.60, 0.80) for the survivors ($p < 0.01$). The medians (25th and 75th

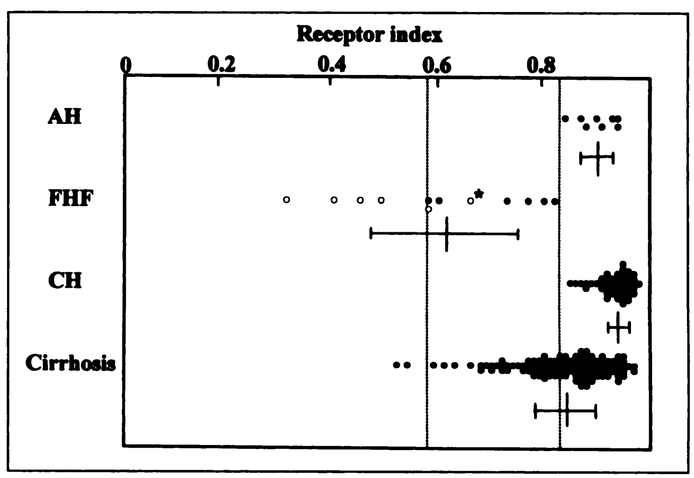

FIGURE 1. Receptor indices of fulminant hepatic failure, acute hepatitis, chronic hepatitis and cirrhosis of the liver. Vertical lines on the bars show the 25th percentile, median and 75th percentile, from left to right. Open circles, patients who died; closed circles, patients who survived. For data denoted by asterisk, see Results.

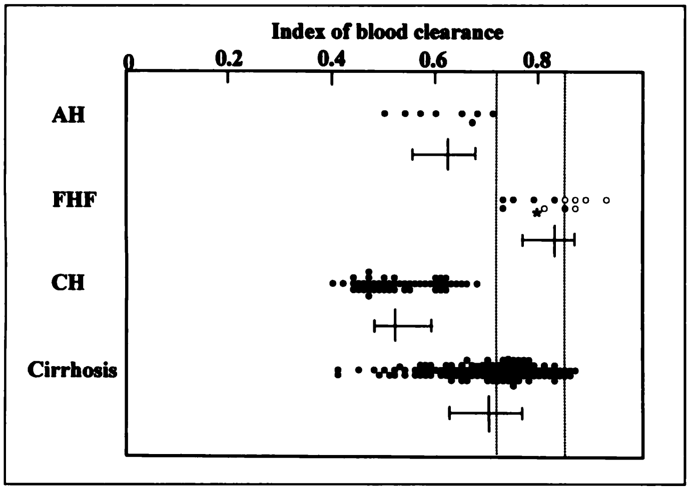

FIGURE 2. Indices of blood clearance of fulminant hepatic failure, acute hepatitis, chronic hepatitis and cirrhosis of the liver. Vertical lines on the bars show the 25th percentile median and 75th percentile, from left to right. Open circles, patients who died; closed circles, patients who survived. For data denoted by asterisk, see Results.

percentiles) of the index of blood clearance were 0.87 (0.85, 0.89) for the patients with FHF who died and 0.77 (0.73, 0.83) for the survivors ($p < 0.01$). One patient with FHF who died (marked with an asterisk in the figures) seemed to be recovering but died because of infection by methicillin-resistant *Staphylococcus aureus* complicated by disseminated intravascular coagulation. When that patient was excluded, the receptor index was 0.58 or more in all survivors but 0.58 or less in all who later died. The index of blood clearance was 0.85 or less in all survivors but 0.85 or more in all who died.

Case Reports

Patient 1. A 51-yr-old man with FHF. Both lobes of the liver were atrophic, and the heart was clearly delineated (Fig. 3). The receptor index and index of blood clearance were 0.40 and 0.89, respectively. The patient died 20 days after admission.

Patient 10. A 33-yr-old man with FHF. Both lobes of the liver were atrophic, and the distribution of radioactivity was not uniform, with the heart being clearly delineated (Fig. 4). The receptor index and index of blood clearance were 0.80 and 0.73, respectively. The patient underwent intensive therapy including plasmapheresis and recovered. While the patient's condition was improving, both lobes of the liver enlarged, and the distribution of radioactivity became uniform at 2 mo. Delineation of the heart had gradually become less distinct. The receptor index slowly rose to reach 0.86 at 2 mo, and the index of blood clearance slowly declined, reaching 0.64.

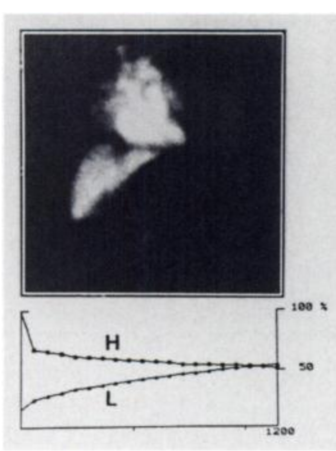

FIGURE 3. Patient 1. Image summed over 20 min and TACs for the liver and heart after injection of ^{99m}Tc-GSA. L = liver; H = heart.

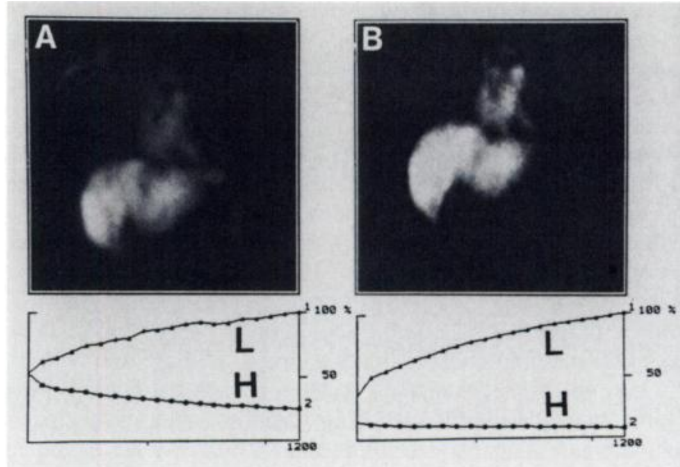

FIGURE 4. Patient 10. Image summed over 20 min and TACs for the liver and heart after injection of ^{99m}Tc-GSA. L = liver; H = heart; A = on admission; B = after 2 mo.

DISCUSSION

Technetium-99m-phytate and sulfur colloid, both of which have been used as liver imaging agents, are transported to the liver when injected intravenously and taken up by Kupffer cells (*13*). Waxman (*5*) found hepatomegaly in 6 (46%) of 13 survivors of FHF and no hepatomegaly among the nine patients who died. Uptake was not seen in any of the survivors. On the other hand, it was seen in three (33%) of the nine nonsurvivors. When we performed liver scintigraphy with ^{99m}Tc-phytate in 44 cases of AH and 12 cases of FHF (*6*), we found that evidence of liver atrophy and delineation of bone marrow seen by scintigraphy are useful in establishing the diagnosis of FHF. In that study, the lungs were not delineated by scintigraphy in any of the seven survivors among the 12 patients with FHF, but the lungs were delineated in three of the five patients who later died.

Technetium-99m-GSA, which is used for the noninvasive assessment of liver function, is a synthetic radioligand that binds to the asialoglycoprotein receptor on the plasma membrane of liver cells. After binding, it is transferred to hepatic lysosomes by receptor-mediated endocytosis (*9,10*). Results of liver scintigraphy with a radiocolloid are affected by the functioning of Kupffer cells. Therefore, hepatic reticuloendothelial failure may be identified by poor uptake of the radiocolloid into the liver among abusers of alcohol (*14,15*). However, hepatic receptor imaging with ^{99m}Tc-GSA is affected by hepatocyte function only, not by Kupffer cell function. Furthermore, hepatic receptor imaging with ^{99m}Tc-GSA permits numerical evaluation of the hepatic functional reserve by the receptor index and index of blood clearance, providing a more objective diagnosis than before.

In our 12 patients with FHF, the index of blood clearance was significantly higher and the receptor index was significantly lower than those indices in patients with AH. A receptor index of 0.83 and an index of blood clearance of 0.72 were cutoff points between FHF and AH. Patients with FHF could be divided into survivors and nonsurvivors at the receptor index of 0.58 and the index of blood clearance of 0.85. These findings suggest that hepatic functional reserve can no longer be restored once it decreases past a certain point, even though the liver has strong powers of regeneration. Liver scintigraphy with ^{99m}Tc-

GSA may enable us to evaluate hepatic functional reserve accurately and to predict whether liver function will improve or not. That there is almost complete overlap between acute and chronic hepatitis in the receptor index and index of blood clearance shows that hepatic functional reserve is similar in the two conditions. The smaller overlap between cirrhosis and FHF shows that some patients with cirrhosis have the same hepatic functional reserve as some patients with FHF.

In decision making about the indications for liver transplantation in FHF, early prediction of the outcome is important. Bernuau et al. (*16*) found the patient's age, serum factor V concentration and serum alpha-fetoprotein concentration to be useful in the prediction of the outcome of FHF. O'Grady et al. (*17*) found that the prognosis was poor when the etiology was non-A, non-B hepatitis or a drug reaction, when the patient's age was less than 11 yr or more than 40 yr, or when jaundice had been present for more than seven days before the onset of encephalopathy. These various factors are not direct indicators of functional reserve. In a study by Donaldson et al. (*18*), patients with FHF underwent transjugular liver biopsy. Necrosis of 70% or more of the area of a section prepared from the specimen was found in 2 of the 19 patients who survived but in 20 of the 35 patients who later died, so the results of histological examination were useful in the prediction of survival. However, this method is invasive and hemorrhage may result. Our method is noninvasive.

CONCLUSION

Hepatic receptor imaging with ^{99m}Tc-GSA could be used to evaluate the hepatic function reserve of various liver diseases noninvasively. This method should be useful clinically in the establishment of the diagnosis and prognosis for patients with FHF.

REFERENCES

1. Trey C, Davidson C. The management of fulminant hepatic failure. In: Popper H, Schaffner F, eds. *Progress in liver disease.* Philadelphia: Grune and Stratton; 1970:282–298.
2. O'Grady JG, Gimson AES, O'Brien CJ, Pucknell A, Hughes RD, Williams R. Controlled trials of charcoal hemoperfusion and prognostic factors in fulminant hepatic failure. *Gastroenterology* 1988;94:1186–1192.
3. Christensen E, Bremmelgaard A, Bahnsen M, Andreasen PB, Tygstrup N. Prediction of fatality in fulminant hepatic failure. *Scand J Gastroenterol* 1984;19:90–96.
4. Harrison PM, O'Grady JG, Keays RT, Alexander GJM, Williams R. Serial prothrombin time as prognostic indicator in paracetamol induced fulminant hepatic failure. *Br Med J* 1990;301:964–966.
5. Waxman AD. Scintigraphic evaluation of diffuse hepatic disease. *Semin Nucl Med* 1982;12:75–88.
6. Shiomi S, Ikeoka N, Minowa T, et al. Diagnostic value of liver scintigraphy in fulminant hepatitis and severe acute hepatitis. *Acta Hepatol Jpn* 1985;26:592–597.
7. Fleischer MR, Sharpstone P, Osborn SB, Williams R. Liver scintiscanning in acute hepatic necrosis. *Br J Radiol* 1971;44:401–402.
8. Kumahara T, Muto Y, Moriwaki H, Yoshida T, Tomita E. Determination of the integrated CT number of the whole liver in patients with severe hepatitis as an indicator of the functional reserve of the liver. *Gastroenterol Jpn* 1989;24:290–297.
9. Kurtz AB, Rubin CS, Cooper HS, et al. Ultrasound findings in hepatitis. *Radiology* 1980;136:717–723.
10. Stadalnik RC, Vera DR, Woodle ES, et al. Technetium-99m-NGA functional hepatic imaging: preliminary clinical experience. *J Nucl Med* 1985;26:1233–1242.
11. Kudo M, Todo A, Ikekubo K, Hino M. Receptor index via hepatic asialoglycoprotein receptor imaging: correlation with chronic hepatocellular damage. *Am J Gastroenterol* 1992;87:865–870.
12. Takahashi Y, Shimizu M, Study Group of Fulminant Hepatitis. Aetiology and prognosis of fulminant viral hepatitis in Japan: a multicenter study. *J Gastroenterol Hepatol* 1991;6:159–164.
13. Stern HS, McAfee JG, Subramanian G. Preparation, distribution and utilization of technetium-99m-sulfur colloid. *J Nucl Med* 1966;7:665–675.
14. Antar MA, Sziklas JJ, Spencer RP. Liver imaging during reticuloendothelial failure. *Clin Nucl Med* 1977;2:293–295.
15. Rao BK, Weir GJ Jr, Lieberman LM. Dissociation of reticuloendothelial cell and hepatocyte functions in alcoholic liver disease: a clinical study with a new ^{99m}Tc-labeled hepatobiliary agent. *Clin Nucl Med* 1981;6:289–294.
16. Bernuau J, Goudeau A, Poynard T, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986;6:648–651.
17. O'Grady JG, Alexander GJM, Hayllar KM, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439–445.
18. Donaldson BW, Gopinath R, Wanless IR, et al. The role of transjugular liver biopsy in fulminant liver failure: relation to other prognostic indicators. *Hepatology* 1993;18:1370–1374.

Brain Perfusion after Treatment of Childhood Acute Lymphoblastic Leukemia

Arja H. Harila-Saari, Aapo K.A. Ahonen, Leena K. Vainionpää, Eija L. Pääkkö, Juhani Pyhtinen, A. Sinikka Himanen, Pentti J.Torniainen and B. Marjatta Lanning

Departments of Pediatrics and Diagnostic Radiology, and Division of Nuclear Medicine, Department of Clinical Chemistry, Oulu University Central Hospital, Oulu, Finland

Children with acute lymphoblastic leukemia (ALL) have impairment in their neuropsychological functioning and morphological changes in their brain after cranial irradiation and chemotherapy. The aim of this study was to identify possible brain perfusion defects caused by different types of treatment and their association with abnormalities in cerebral MRI and neuropsychological and clinical neurological findings. **Methods:** Twenty-five consecutive children with ALL at the cessation of chemotherapy or after 1 yr were included. All of the children were given intravenous and intrathecal methotrexate for central nervous system therapy, 13 of them received cranial radiation therapy. Brain SPECT, cerebral MRI, clinical neurological and neuropsychological evaluations were performed. **Results:** Eleven of the 25 patients (44%) had brain perfusion defects in SPECT, eight of whom were treated with chemotherapy alone, and three received cranial irradiation. Two patients had small bilateral white matter changes on MRI; their brain SPECT scans were abnormal, although the findings were not related. Impairment of neuropsychological functioning was found in 86% of the patients tested. No significant difference between the patients with abnormal and normal SPECT were found. Those patients with abnormal SPECT were younger than those with normal SPECT and had received more frequent intravenous methotrexate infusions. **Conclusion:** Brain SPECT detected perfusion defects that had occurred after treatment for childhood ALL. These defects may be related to frequent administration of a combination of intravenous and intrathecal methotrexate and/or young age.

Key Words: SPECT; brain perfusion; acute lymphoblastic leukemia; methotrexate neurotoxicity

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Along with the improved prognosis for childhood acute lymphoblastic leukemia (ALL), the importance of the late treatment-related sequelae has increased. Central nervous system treatment, typically consisting of intrathecal and intravenous methotrexate with or without cranial irradiation, is an

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For correspondence or reprints contact: Arja Harila-Saari, MD, Department of Pediatrics, University of Oulu, Oulu, 90220, Finland.