ORIGINAL ARTICLE

AG-2017-113
dx.doi.org/10.1590/S0004-2803.201800000-06

Liver transplantation in hepatitis delta: South America experience

Daniel Souza **LIMA**[1,2], Abdon José **MURAD JÚNIOR**[1], Márcio Alencar **BARREIRA**[1], Guilherme Cardoso **FERNANDES**[3], Gustavo Rego **COELHO**[1,4] and José Huygens Parente **GARCIA**[1,4]

Received 22/8/2017
Accepted 16/11/2017

ABSTRACT – Background – The Amazon region is one of the main endemic areas of hepatitis delta in the world and the only one related to the presence of genotype 3 of the delta virus. **Objective** – To analyze the profile, mortality and survival of cirrhotic patients submitted to liver transplantation for chronic hepatitis delta virus and compare with those transplanted by hepatitis B virus monoinfection. **Methods** – Retrospective, observational and descriptive study. From May 2002 to December 2011, 629 liver transplants were performed at the *Walter Cantídio* University Hospital, of which 29 patients were transplanted due to cirrhosis caused by chronic delta virus infection and 40 by hepatitis B chronic monoinfection. The variables analyzed were: age, sex, MELD score, Child-Pugh score, upper gastrointestinal bleeding and hepatocellular carcinoma occurrence before the transplantation, perioperative platelet count, mortality and survival. **Results** – The Delta Group was younger and all came from the Brazilian Amazon Region. Group B presented a higher proportion of male patients (92.5%) compared to Group D (58.6%). The occurrence of upper gastrointestinal bleeding before transplantation, MELD score, and Child-Pugh score did not show statistical differences between groups. The occurrence of hepatocellular carcinoma and mortality were higher in the hepatitis B Group. The survival in 4 years was 95% in the Delta Group and 75% in the B Group, with a statistically significant difference (P=0.034). Patients with hepatitis delta presented more evident thrombocytopenia in the pre-transplantation and in the immediate postoperative period. **Conclusion** – The hepatitis by delta virus patients who underwent liver transplantation were predominantly male, coming from the Brazilian Amazon region and with similar liver function to the hepatitis B virus patients. They had a lower incidence of hepatocellular carcinoma, more marked perioperative thrombocytopenia levels and frequent episodes of upper gastrointestinal bleeding. Patients with hepatitis by delta virus had lower mortality and higher survival than patients with hepatitis B virus.

HEADINGS – Hepatitis delta virus. Chronic hepatitis B. Liver cirrhosis. Liver transplantation.

INTRODUCTION

In the world, there are eight virus genotypes in hepatitis delta[1,2]. Type 3 genotype is found in South America, more precisely in the Amazon Basin[1,2]. The Amazon region is one of the areas with the highest prevalence of hepatitis B virus (HBV) and has the highest incidence of hepatitis by delta virus (HDV) in the world[3]. Superinfection with HDV in an individual with chronic HBV may result, in most cases, in a chronic infection that may lead to the need for liver transplantation (LT)[2]. There is little information on the evolution of patients with HBV and HDV after liver transplantation[4]. The aim of this study was to analyze the profile, survival and mortality of cirrhotic patients submitted to LT by HDV and compare the results with those found in transplanted patients as a result of monoinfection by virus B.

METHODS

Study design

Retrospective, observational and descriptive study. The Center for Liver Transplantation at the *Walter Cantídio Hospital* (HUWC) performed 629 transplants between May 2002 and December 2011, of which 29 patients were submitted to LT due to HDV-related cirrhosis (Delta Group) and 40 patients due to chronic monoinfection by the virus of hepatitis B (Group B).

For diagnosis, the recommendations of the Brazilian Health Ministry were defined as the presence of HBsAg or anti-HBcIgM or HBeAg reagents associated with one or more of the following serological markers as a confirmed delta hepatitis case: Anti-HDV total reagent and/or Anti-HDVIgM reagent. Hepatitis B, in cases presenting one or more of the reactive serological markers or molecular biology examination for hepatitis B, such as HBsAg reagent, Anti-HBcIgM reagent, HBeAg reagent, detectable HBV DNA[5]. In our field, the HDV-RNA screening is not readily available.

Variables analyzed

The quantitative variables analyzed were: age, Model for End-Stage Liver Disease (MELD) score, and 5-year survival. The occurrence of thrombocytopenia (<150,000 μL) through platelet serum levels was also evaluated in five moments: pre-transplantation, 1st postoperative day (PO), 7th PO, 30th PO and 03 months.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Departamento de Cirurgia, Universidade Federal do Ceará, Fortaleza, CE, Brasil; [2] Faculdade de Medicina, Universidade de Fortaleza, Fortaleza, CE, Brasil; [3] Departamento de Cirurgia Geral, Hospital Universitário Walter Cantídio, Fortaleza, CE, Brasil; [4] Serviço de Transplante Hepático, Universidade Federal do Ceará, Fortaleza, CE, Brasil.
Research performed at: Departamento de Cirurgia e pós-graduação em cirurgia da Universidade Federal do Ceará.
Correspondence: Daniel Souza Lima. Rua Pedro Adriano, 550 / 400. Lagoa Redonda – CEP: 60832-380 – Fortaleza, CE, Brasil. E-mail: souzadl@hotmail.com

The qualitative variables of the study were: sex, origin, occurrence of upper gastrointestinal bleeding before transplantation, Child-Pugh classification, occurrence of hepatocellular carcinoma (HCC), and mortality.

Statistical analysis

The statistical significance level was considered for a $P \leq 0.05$. The *t*-Student test was used to evaluate differences between the groups in relation to age and platelet values in the pre-transplantation and 1st PO. To assess the incidence of HCC, Child's classification and the occurrence of upper gastrointestinal bleeding before transplantation, the chi-square test was used. The non-parametric Mann-Whitney test was used to analyze the MELD variables and platelets at the 7th PO, 30th PO and 90th PO. In order to evaluate mortality, the Fischer test was applied. The significance of the difference between patient survival times was assessed with the *logorank* test for two Kaplan-Meyer survival curves. The Statistical Package for the Social Sciences (SPSS), version 17.0 was used for statistical analysis.

Ethics approval

This study was performed according to the ethical standards of data collection and analysis of patients, which were analyzed retrospectively. All data were collected during patient care in the pre-transplant outpatient clinic, in the hospital for the surgical procedure and in the post-transplant outpatient follow-up. This study was approved by the Ethics and Research Committee of *Walter Cantídio* University Hospital and in accordance with the Declaration of Helsinki of 1975.

RESULTS

All patients with HDV are originated from the northern region of Brazil, especially in the state of Amazonas. Patients with hepatitis B were from several regions of Brazil. Men predominated in both groups, being younger in HDV. The evaluation of hepatic function and severity of liver disease were similar between groups. Child-Pugh score was not identified in one patient in the HDV group and six in the HBV group. In the group with HBV, 11 cases did not have MELD identified because they did not use this score to classify the priority for transplantation at the time. The occurrence of upper gastrointestinal bleeding before transplantation did not show statistical difference between groups. Regarding the association of viral infection and the presence of HCC, the HBV group had a higher number of patients with HCC (36.8% vs 17.2%). HBV monoinfected patients presented higher mortality (n=10) compared to the Delta Group (n=1). The inferential statistical analysis by the *Fischer* test allowed to state that the death incidence was group dependent (P=0.019) (TABLE 1).

In relation to the assessment of platelet levels between the groups, there was a statistical difference in the pre-transplantation (66,428.57 ± 34,126,27 vs 102,037,50 ± 96,823,33 µL, P=0.0295) and in POD 1 (mean 54,222, 86 ± 27,868.20 vs 94,063.89 ± 97,824.87 µL, P=0.041) in favor of a more significant thrombocytopenia in patients with HDV in relation to the HBV Group. After 7, 30 and 90 POD, platelet levels remained lower in the HDV Group, although without statistical significance (FIGURE 1).

In the analysis of survival between groups over a four-year period, patients in the Delta Group had 95% survival and 75% survival in Group B. According to the *logorank* test, using the Kaplan–Meier survival curves, the observed difference between groups was statistically significant (P=0.034). (FIGURE 2).

TABLE 1. Clinical and epidemiological characteristics among transplant patients with hepatitis Delta and hepatitis B

Variables	Hepatitis delta (n=29)	Hepatitis B (n=40)	*P*
Age	33.97 ± 8.68 (22.0-50.0)	52.93 ± 10.34 (27.0-73.0)	< 0.001
Sex	M = 17 (58.6%) F = 12 (41.4%)	M = 37 (92.5%) F = 03 (7.5%)	0.001
Child	A = 0 (0.0%) B = 15 (53.6%) C = 13 (46.4%) Missing = 1	A = 02 (0.0%) B = 17 (50.0%) C = 15 (44.1%) Missing = 6	ns
MELD	21.2 ± 5.9	20.5 ± 4.7	ns
UGB	12 (41.4%)	14 (36.8%)	ns
HCC	05 (17.2%)	14 (36.8%)	0.051
Mortality	01 (3.4%)	10 (25%)	0.019

M: male; F: female; ns: no significance; MELD: Model for End-Stage Liver Disease; UGB: upper gastrointestinal bleeding; HCC: hepatocellular carcinoma.

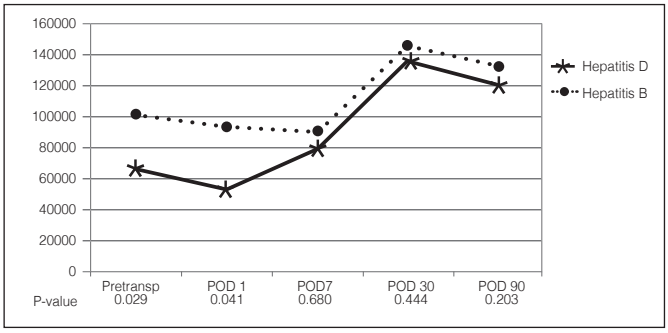

FIGURE 1. Monitoring of platelet levels among transplant patients with hepatitis B and hepatitis delta. Pretransp: pretransplant; POD: postoperative day.

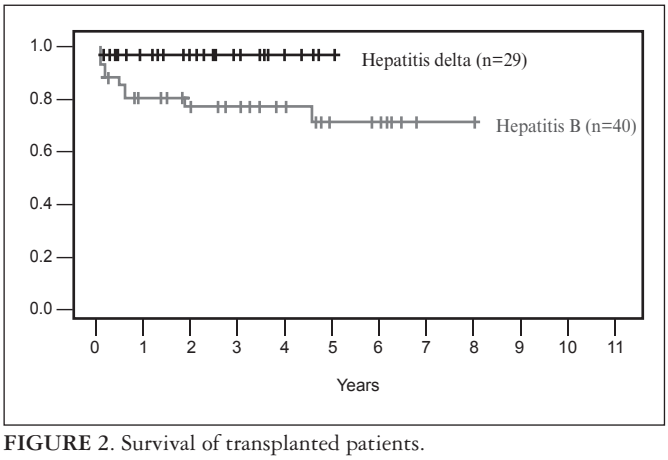

FIGURE 2. Survival of transplanted patients.

DISCUSSION

A study carried out between 1972 and 1997 evaluated 23 patients transplanted due to viral infection by delta hepatitis and showed a long survival[6]. Most studies are conducted in Europe, where there is a predominance of delta virus 1[1] genotype. In this

study, all transplanted patients with chronic hepatitis delta came from northern Amazonas where the predominant genotype is type 3 and mortality was lower than that of patients with HBV.

HDV reaches a higher prevalence between the third and fourth decades of life[7]. The average age of individuals diagnosed with hepatitis D varies between 30 and 44 years old[8,9]. Because hepatitis B is endemic in the Amazon region and often affects individuals in childhood, the disastrous consequences of association with delta virus can be noted in the second decade of life[10]. In Brazil, 67.6% of the clinical forms of hepatitis D are chronic[5].

In 2006, the Brazilian government adopted the MELD score to determine the priority for performing liver transplantation[11]. The severity scores of MELD and Child did not differ between transplanted patients with HBV and HDV demonstrating that the groups had similar levels of impaired liver function. Among the complications of hepatic cirrhosis, varicose hemorrhage is an important cause of morbidity and mortality among patients. It occurs in 50% to 90% of them being a direct consequence of portal hypertension[12]. It was observed that the two groups had similar levels of upper digestive hemorrhage, with no statistical difference. However, there was a significant occurrence of this complication in each group which shows the risk that these patients have while waiting for a new organ.

A common clinical situation following liver transplantation is the reduction of platelet levels that tend to recover with liver function restoration. A possible cause of thrombocytopenia soon after surgery may be related to platelet consumption due to loss of graft and even sepsis. However, the causes or factors that contribute to persistent thrombocytopenia need better clarification[13]. Severe thrombocytopenia may lead to increased morbidity and mortality related to postoperative hemorrhage[14].

The hepatitis B virus is an established risk factor for the development of HCC[15] and HDV has been associated with high rates of hepatocyte proliferation and oncogenic potential[16,17]. A study with 186 patients with HDV, most with type 1 genotype, showed that 46 patients developed HCC after 83 months of follow-up[18]. A British study showed similar prevalence of HCC between groups with HDV and HBV[19]. In the present study, the incidence of HCC in the transplanted patients was higher in those who belonged to the HBV Group in relation to HDV, with results showing borderline or marginal statistical significance (P=0.0515). In Brazil, the predominant genotype type 3 seems to be related to the lower number of cases of liver cancer associated with HDV. However, more studies need to be developed to verify the possible difference between genotypes.

One of the largest series involving hepatic transplantation in patients with HDV (n=76), identified 88% of survival after 5 years. These results could be related to patients being relatively young and presenting low HBV recurrence rate[20]. This study showed that patients with HDV had lower mortality and, also, were younger. Some studies suggest that double infection may lead to a better course[21].

CONCLUSION

Patients with delta hepatitis who were submitted to liver transplantation were predominantly male, coming from the Brazilian Amazon region and with liver function similar to the patients with HBV. They had a lower incidence of HCC, more marked perioperative thrombocytopenia levels and frequent episodes of upper gastrointestinal bleeding. Patients with HDV had lower mortality and higher survival than patients with HBV.

ACKNOWLEDGEMENTS

Thanks to the Surgery Department and post-graduation in surgery of the Federal University of Ceará.

Authors' contributions

Lima DS: conception and design of the study, technical procedures, acquisition, interpretation and analysis of data, manuscript preparation and writing. Murad Júnior AJ: acquisition, interpretation and analysis of data, critical revision. Fernandes GC: acquisition, interpretation and analysis of data, technical procedures. Lima PG: manuscript writing/editing, technical procedures. Coelho GR: conception and design of the study, critical revision, final approval. Barreira MA: technical procedures, manuscript preparation and critical revision. Garcia JHP: conception and design of the study, interpretation and analysis of data, critical revision, final approval.

Lima DS, Murad Júnior AJ, Barreira MA, Fernandes GC, Coelho GR, Garcia JHP. Transplante hepático na hepatite delta: experiência da América do Sul. Arq Gastroenterol. 2018;55(1):14-7.

RESUMO – Contexto – A região Amazônica é uma das principais áreas endêmicas da hepatite delta no mundo e a única relacionada com a presença do genótipo 3 do vírus delta. **Objetivo** – Analisar o perfil, mortalidade e sobrevida dos pacientes cirróticos submetidos a transplante hepático por hepatite crônica pelo vírus delta e comparar com os transplantados pela monoinfecção do vírus da hepatite B. **Métodos** – Estudo retrospectivo, observacional e descritivo. Entre maio de 2002 a dezembro de 2011, foram realizados 629 transplantes de fígado no Hospital Universitário Walter Cantídio, dos quais 29 pacientes foram transplantados por cirrose causada pela infecção crônica do vírus delta e 40 pela monoinfecção crônica da hepatite B. As variáveis analisadas foram: origem, idade, sexo, escore de MELD, classificação de *Child-Pugh,* ocorrência de hemorragia digestiva alta e carcinoma hepatocelular antes do transplante, número de plaquetas perioperatória, mortalidade e sobrevida. **Resultados** – O Grupo Delta foi mais jovem e todos oriundos da região Amazônica Brasileira. O Grupo B apresentou maior proporção de pacientes do sexo masculino (92,5%) em relação ao Grupo D (58,6%). A ocorrência de hemorragia digestiva alta antes do transplante, escore de MELD e classificação de *Child-Pugh* não obtiveram diferenças estatísticas entre os grupos. A ocorrência de carcinoma hepatocelular e a mortalidade foram maiores no grupo com hepatite B. A sobrevida em 4 anos foi de 95% no Grupo delta e 75% no Grupo B com diferença estatisticamente significante (P=0,034). Pacientes com hepatite delta, apresentaram mais acentuada plaquetopenia no pré-transplante e no pós-operatório imediato. **Conclusão** – Os pacientes com hepatite por vírus delta submetidos ao transplante hepático eram predominantemente homens, vindos da região da Amazônia brasileira e com função hepática semelhante a dos pacientes com vírus da hepatite B. Apresentavam menor incidência de carcinoma hepatocelular, níveis de trombocitopenia perioperatória mais acentuados e episódios frequentes de hemorragia digestiva alta. Os pacientes com hepatite por vírus delta apresentaram menor mortalidade e maior sobrevida que os pacientes com vírus da hepatite B.

DESCRITORES – Vírus delta da hepatite. Hepatite B crônica. Cirrose hepática. Transplante de fígado.

REFERENCES

1. Pascarella S, Negro F. Hepatitis D virus: an update. Liver Int. 2011;31:7-21.
2. Hughes SA, Wedemeyer H, Harrison PM. Hepatitis delta virus. Lancet. 2011;378:73-85.
3. Parana R, Kay A**,** Molinet F, Viana S, Silva LK, Salcedo JM, Tavares-Neto J, et al. HDV genotypes in the Western Brazilian Amazon region: a preliminary report. Am J Trop Med Hyg. 2006;75:475-9.
4. Rifai K, Wedemeyer H, Rosenau J, Klempnauer J, Strassburg CP, Manns MP, Tillmann HL. Longer survival of liver transplant recipients with hepatitis virus coinfections. Clin. Transplant. 2007;21:258-64.
5. Cunha ARC, Pereira GFM, Givisiez JM, Coelho RA, Pereira SMC, Oliveira SB, Amorim TR. Boletim Epidemiologico – Hepatitis Virais. Ministerio da Saude do Brasil. 2010;1:15-51.
6. Rifai K, Wedemeyer H, Rosenau J, Klempnauer J, Strassburg CP, Manns MP, Tillmann HL. Longer survival of liver transplant recipients with hepatitis virus coinfections. Clin. Transplant. 2007;21:258-64.
7. Fonseca JCF. Hepatite D. Rev Soc Bras Med Trop. 2002;35:181-90.
8. Gulsun S, Tekin R, Bozurt F. Treatment of chronic delta hepatitis: a nine-year retrospective analysis. Hepat Mon. 2011;11:731-5.
9. Genne D, Rossi I. Hepatitis delta in Switzerland: a silent epidemic. Swiss Med Wkly. 2011;141:w13176.
10. Ribeiro LC, Souto FJD. Hepatite Delta no Estado de Mato Grosso: apresentacao de cinco casos. Rev Soc Bras Med Trop. 2000;33:599-602.
11. Coelho GR, Vasconcelos KF, Vasconcelos JBM, Barros MAP, Costa PEG, Borges GCO, Junior JTV, et al. Orthotopic liver transplantation for hepatocellular carcinoma: one center's experience in the Northeast of Brazil. Transplant Proc. 2009;41:1740-2.
12. Odelowo OO, Smoot DT, Kim K. Upper gastrointestinal bleeding in patients with liver cirrhosis. J Natl Med Assoc. 2002;94:712-5.
13. Chang JH, Choi JY, Woo HY, Kwon JH, You CR, Bae SH, Yoon SK, et al. Severe thrombocytopenia before liver transplantation is associated with delayed recovery of thrombocytopenia regardless of donor type. World J Gastroenterol. 2008;14:5723-9.
14. Chatzipetrou MA, Tsaroucha AK, Weppler D, Pappas PA, Kenyon NS, Nery JR, Khan MF, et al. Thrombocytopenia after liver transplantation. Transplantation. 1999;67:702-6.
15. Huo TI, Wu JC, Lai CR, Lu CL, Sheng WY, Lee SD. Comparison of clinico-pathological features in hepatitis B virus-associated hepatocellular carcinoma with or without hepatitis D virus superinfection. J Hepatol. 1996;25:439-44.
16. Verme G, Brunetto MR, Oliveri F, Baldi M, Forzani B, Piantino P, Ponzetto A, et al. Role of hepatitis delta virus infection in hepatocellular carcinoma. Dig Dis Sci. 1991;36:1134-6.
17. Oliveri F, Colombatto P, Derenzini M, Trere D, Papotti M, David E, Negro F, et al. Hepatocellular carcinoma: pathogenetic implications of the hepatitis delta virus. Prog Clin Biol Res. 1993;382:165-70.
18. Romeo R, Del Ninno E, Rumi M, Russo A, Sangiovanni A, de Franchis R, Ronchi G, et al. A 28-year study of the course of hepatitis Delta infection: a risk factor for cirrhosis and hepatocellular carcinoma. Gastroenterology. 2009;136:1629-38.
19. Cross TJ, Rizzi P, Horner M, Jolly A, Hussain MJ, Smith HM, Vergani D, et al. The increasing prevalence of hepatitis delta virus (HDV) infection in South London. J Med Virol. 2008;80:277-82.
20. Samuel D, Zignego AL, Reynes M, Feray C, Arulnaden JL, David MF, Gigou M, et al. Longterm clinical and virological outcome after liver transplantation for cirrhosis caused by chronic delta hepatitis. Hepatology. 1995;21:333-9.
21. Steinmuller T, Seehofer D, Rayes N, Muller AR, Settmacher U, Jonas S, Neuhaus R, et al. Increasing applicability of liver transplantation for patients with hepatitis B-related liver disease. Hepatology. 2002;35:1528-35.