U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

Case Report

Mestrado Integrado em Medicina

HEPATIC TRANSPLANT IN ACUTE ALCOHOLIC HEPATITIS: A CASE REPORT

Ana Raquel Génio Freire

Orientador:

Dr. Filipe Gaio Nery

Porto, 8 de Junho de 2012

CASE REPORT

Hepatic Transplant in Acute Alcoholic Hepatitis: A Case Report

Transplante Hepático na Hepatite Aguda Alcoólica: A propósito de um caso clínico

Ana Raquel Génio Freire – ICBAS-UP

freire_a@hotmail.com

Abstract

Alcoholic liver disease is a global health issue. This wide-ranging entity encompasses a distinct clinical syndrome induced by alcohol consumption known as acute alcoholic hepatitis. The clinical spectrum ranges from asymptomatic to symptomatic presentation with analytical changes, hepatic failure and death. With a 28-day mortality of up to 50%, treatment is essential. Within the various therapeutic agents proposed for treatment of acute alcoholic hepatitis, corticosteroids are still the first option in clinical practice. Nevertheless, it is not effective in all cases. In those patients defined as non-responders, corticotherapy does not improve long term survival, and thus a new approach to treatment is necessary. It is in these cases that we may look to hepatic transplant as a possible treatment route.

Hepatic transplant in patients with acute alcoholic hepatitis, however, has proven quite controversial. There is a reluctance to allot the scarce organs available to patients whom the public often views as responsible for their own disease. The concern that patients would relapse post-transplant has contributed to the implementation of a 6 month alcohol abstinence period still required for patients to be considered for transplant in some countries. Conversely, new studies point away from the use of this 6 month rule and instead enforce the implementation of selecting patients for transplant based on other criteria of greater importance to outcome.

We report the case of a 56 year old male presenting with acute alcoholic hepatitis, non-responder to therapy with corticosteroids, that was posteriorly proposed for hepatic transplant.

Key Words: acute alcoholic hepatitis, hepatic transplant, corticosteroids, non-responder, alcoholic abstinence.

Resumo

A doença hepática alcoólica é um problema de saúde global. A hepatite aguda alcoólica é caracterizada por ser uma síndrome clínica distinta induzida pelo consumo de álcool. O espectro clínico vai desde um estado assintomático até sintomas associados a alterações analíticas, insuficiência hepática e morte. Com uma mortalidade aos 28 dias de até 50%, um tratamento eficaz é essencial. Dentro dos vários agentes terapêuticos propostos para o tratamento, os corticosteróides constituem ainda a primeira opção na prática clínica. No entanto, a corticoterapia não é eficaz em todos os casos. Nos doentes definidos como não-respondedores, a corticoterapia não aumenta a sobrevida a longo prazo e, assim, uma nova abordagem terapêutica é necessária. Consequentemente, o transplante hepático torna-se nestes casos uma opção atraente.

O transplante hepático em doentes com hepatite aguda alcoólica, no entanto, permanece um assunto bastante controverso. Existe uma relutância em disponibilizar órgãos (que são escassos) para transplante a doentes que o público geralmente percepciona como tendo infligido em si a sua doença. A preocupação de que os doentes poderão vir a sofrer de uma recaída após o transplante, contribuiu para a implementação de um período obrigatório de 6 meses de abstinência alcoólica, ainda necessária para que tais doentes sejam considerados para transplante hepático em alguns países. Contudo, vários estudos recentes têm vindo a valorizar a criteriosa selecção de doentes candidatos a transplante hepático em detrimento da regra dos seis meses.

Reportamos o caso clínico de um doente de 56 anos de idade que se apresentou com hepatite aguda alcoólica, não-respondedor à corticoterapia, sendo posteriormente

submetido a transplante hepático. Um resumo mais detalhado pode ser consultado no Apêndice.

Palavras-chave: hepatite aguda alcoólica, transplante hepático, corticosteróides, não-respondedor, abstinência alcoólica.

Introduction

With increasing alcohol consumption worldwide, alcoholic liver disease (ALD) has become a significant global health concern.[1] According to the World Health Organization (WHO), alcohol consumption is the third leading cause of premature death and disability in the European Union and can be attributed to up to 9.2% of all disability adjusted life years.[2-4]

Acute alcoholic hepatitis (AAH) is a distinct clinical syndrome induced by alcohol consumption with a particularly poor prognosis with a 28-day mortality ranging from 30%-50%.[5] This syndrome encompasses a clinical spectrum ranging from asymptomatic to symptomatic forms with analytical changes, hepatic failure and death. The actual prevalence of AAH is difficult to gauge because it can be completely asymptomatic and many patients are underdiagnosed, though a prevalence of approximately 20% was observed in a cohort of 1604 patients with alcoholism who underwent a hepatic biopsy.[5] In addition, it is estimated that about 35% of alcoholics suffer from AAH, most cases occurring before the age of 60 years.[5-6]

In general, the risk of liver disease is associated with the pattern of drinking, the type of drink consumed and the amount of alcohol consumed.[2,5,7] A daily intake of alcohol for 10-12 years with doses in excess of 40-80 g/day for males and 20-40 g/day for females are generally needed to cause alcoholic liver disease.[8] However, current European guidelines refer that even the ingestion of small amounts of alcohol (< 25 g/day) may be enough to induce alcoholic liver disease.[9] Ethnicity,[2,5,10] as well as other risk factors including obesity[5], iron overload, concomitant infection with viral hepatitis and genetic factors are also implied.[2]

The diagnosis of ALD is based on a combination of features, including a history of significant alcohol intake, clinical evidence of liver disease, and supporting laboratory abnormalities.[2,8] AAH is associated with a broad clinical picture including asthenia, pain in the right hypochondrium, fever, tachycardia and frequently jaundice. Typically, the ratio of aspartate aminotransferase to alanine aminotransferase (ASAT/ALAT) is approximately 2:1.[2] Other common laboratory abnormalities include hyperbilirubinemia, leukocytosis and anemia.[2,8] In addition to the laboratory characteristics common to all forms of ALD, AAH is typically associated with elevated concentrations of gamma-glutamyl transpeptidase and of alkaline phosphatase.[11]

In addition to nutritional support and ensuring alcohol abstinence,[2,8,12-13] other therapeutic agents such as corticosteroids,[14-15] anti-oxidant therapy,[12,16-18] pentoxifylline,[19-20] TNF-α antibodies, propylthiouracil, colchicine, S-adenosyl-L-methionine,[8,21-23] and even molecular adsorbent recirculating system (MARS)[21-22,24-25] have been proposed. Of these therapies, only corticosteroids have found a place in regular practice, although even here, the data on their efficacy are controversial. Pentoxifylline and MARS do, however, show promise in specific cases. In addition, the association of N-acetylcysteine to corticosteroid treatment has recently been found to improve short term survival, and may be considered as an adjunct to standard treatment.[18]

As a result, standard medical treatment for patients with AAH may include the administration of corticosteroids to those who have a Maddrey discriminant function (DF) greater than or equal to 32, or more recently, a Glasgow Alcoholic Hepatitis Score (GAHS) greater than or equal to 9.[2,8,21,26] The Lille score will posteriorly evaluate the response to corticosteroids after 7 days, giving an indication of which patients will respond to and therefore benefit from maintenance of the corticoid therapy.[27-28] Patients

who do not respond to corticotherapy have a poor survival rate.[29] Consequently, new strategies are needed in order to address these cases.

Chronic liver disease with progression to cirrhosis and its inherent complications are the second most common reason for liver transplantation in the United States and Europe.[30-31] It is usual practice in most programs in North America and Europe to require patients with ALD to be abstinent for 6 months prior to transplantation.[22,32] However, the United Network for Organ Sharing (UNOS) and the French Consensus Conference do not consider it to be a rule since 2005.[29,33] For patients with severe alcoholic hepatitis who do not respond to corticosteroid treatment, deferring transplantation for six months may not be an option due to precocious mortality.[22]

In the following report the case of a male patient aged 56 years who presented with AAH, non-responder to corticotherapy, with progression to liver failure and posteriorly subjected to hepatic transplant, will be addressed. The role of hepatic transplant in context of alcohol intake will be discussed as well as the ethical implications inherent to the realization of this as of yet nonconsensual procedure.

Case Report

A 56-year-old autonomous male, married with a structured family life, with a history of alcohol ingestion greater than 100 g/day since the age of 30 in the context of social drinking and accompanying meals, presented with edema of the right foot one month prior to hospital admission. At this time the patient was observed by his family physician, and upon investigation, an altered hepatic profile was the only significant finding. The patient claimed to have ceased his alcohol consumption at this point in time. Previous analytical studies dating as far back as 2002, registered elevated liver enzymes, with a predominance of ALAT over ASAT, however, the patient was not alerted to this fact by his family practitioner.

Two weeks after the initial foot edema, the patient noted bilateral edema of the legs and a marked increase in abdominal perimeter, without the perception of jaundice by the patient himself or family members. The patient sought medical attention upon onset of these symptoms and was medicated with furosemide and spironolactone. After 4 days of treatment with diuretics with no medical improvement, the patient was admitted to the hospital for further investigation. Upon admission, laboratory findings exhibited a total bilirubin of 12.2 mg/dL (normal range, 0.2-1.2 mg/dL), ASAT of 351 U/L (normal range, 5.0-34.0 U/L), ALAT of 202 U/L (normal range, < 55.0 U/L), a hemoglobin value of 12.5 g/dL (normal range, 13.0-18.0 g/dL), a platelet count of 151000/μL (normal range, 150000-400000/μL), a leucocyte count of 7700/μL (normal range, 4000-11000/μL), a C-reactive protein of 4.12 mg/dL (normal range, < 0.50 mg/dL), and an INR of 3.4. Imaging tests also performed at this time depicted a pattern compatible with cirrhosis.

Having excluded a potential spontaneous bacterial peritonitis and pondering the possibility of being in the presence of an acute alcoholic hepatitis, with an elevated

Maddrey discriminant function score of 142, medical professionals initiated corticoid treatment with prednisolone (40 mg/day). The patient, however, was not responsive to corticosteroid treatment in accordance with the Lille criteria at the 7 day mark, having a documented score of 0.995. The deteriorating clinical picture with progressive increase of bilirubin levels, further worsening of the coagulation profile and the appearance of grade I encephalopathy, prompted the medical team to transfer the patient to a liver transplantation hospital of reference in Oporto (CHP-HSA) 12 days after initial hospital admission, under the diagnosis of acute alcoholic hepatitis.

On arrival at that institution, the patient was vigil and oriented, however, slightly sluggish. There was no evidence of flapping. On physical examination, the patient presented with jaundice, hydrated mucosa, spider veins on torso and atrophy of temporal muscles. His blood pressure was documented at 151/72 mmHg with a pulse of 102 beats per minute, and he was afebrile. Upon pulmonary auscultation, vesicular murmur was diminished at pulmonary bases and no audible heart murmurs were found on cardiac exam. On inspection of the abdomen, large volume ascites was present without tension or pain. Discrete edema of pretibial and malleolar regions was also noted. One day following admission, the patient was admitted into the intermediate care unit and also underwent a transjugular biopsy which confirmed the diagnosis of acute alcoholic hepatitis in context of preexisting cirrhosis. There was no evidence of sepsis and portal thrombosis was also excluded. Within 3 days, there was frank deterioration of the patient's clinical picture, rapidly progressing from grade II encephalopathy to grade III encephalopathy, with further worsening of the coagulation disorder and renal function. At this point in time the patients MELD score was calculated to be 39.

The patient was consequently transferred to the intensive care unit this same day and a hepatic transplant was proposed, with indication for molecular adsorbents

recirculation system as a means of bridging the gap until actual transplant. Subsequently, the patient received a hepatic transplant 2 days later.

On the days following the procedure, the patient began to present with hepatic ischemia with poor prognosis as documented on surgical transcripts, consequently being subjected to 2 further surgical interventions. Four days following the transplant, however, the patient succumbed to the post-operative complications and died due to multi-organ failure.

Discussion

The severity of AAH is best assessed using the Maddrey DF (or more recently with the GAHS), which is reproducible and an unbiased criterion to predict the risk of early death in these patients.[26,31] A DF $\geq$ 32 indicates high risk of early mortality in the absence of treatment.[31] AAH is considered severe if the Maddrey DF is greater than or equal to 32, threshold for which initiating glucocorticoid treatment is also recommended.[2,13,28,34] Thus, to reduce the probability of early death, patients with a DF $\geq$ 32 need to be offered treatment.[31] Upon consulting patient information we know that the patient in question had a presenting Maddrey DF of 142, having begun corticotherapy at this time. The standard medical care for severe hepatic insufficiency continues to be the administration of glucocorticoids (40 mg per day of prednisolone for at least 7 days),[14,35] which also corresponds to what our patient was offered. In absence of treatment, spontaneous survival of patients with a DF $\geq$ 32 at 2 months is 50%, in comparison to a spontaneous survival at 28-days in patients with a DF < 32 close to 90%.[33]

When assessing the effect of the aforementioned corticotherapy, nonresponse to treatment is defined according to the Lille model as a score of 0.45 or greater after 7 days of medical therapy, or a continuous increase in the Model for End-Stage Liver Disease (MELD) score, reflecting an early worsening of liver function.[14, 28-29] Medical reports confirm that the patient was a non-responder in accordance with the Lille model and eventually progressed to a MELD score of 39. In responders, the beneficial effect of corticosteroids renders other treatment options unnecessary.[33] Conversely, non-responders to corticosteroids have a poor survival rate and require new strategies. Recently, it was observed that non-responders show a strong resistance profile to various medications, including pentoxifylline.[33] Even though corticosteroids are

efficient in severe AAH to improve short-term survival, new treatment options are indeed required to improve the probability of being alive within the year following the onset of disease.[15]

The study conducted by Yu et al. (2010) demonstrated that the mortality rate of alcoholic hepatitis patients is positively correlated with the severity of the disease. The pooled analysis also showed that hepatic failure, gastrointestinal bleeding and infection were the 3 main causes of early death of alcoholic hepatitis patients.[1,15] The high risk of early death in patients with severe AAH not responding to medical therapy makes it necessary to consider all available treatment options, including transplantation, in targeted patients.[29] According to Mathurin et al. (2011) patients whose alcoholic hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%.[29] Being that most alcoholic hepatitis deaths occur within 2 months, early liver transplantation is an appealing option, although still fairly controversial.[29]

In regards to transplantation in ALD patients, approximately 85% of the transplant programs in the United States require 6 months of abstinence prior to the procedure,[29,31] with about 75% of centers expecting patients to sign a formal contract to that effect.[33] However, despite the frequent use of the 6 month rule, in 2005 the UNOS and the French Consensus Conference on liver transplant in view of absence of enough evidence to support the 6 month sobriety rule no longer consider it to be a formal guideline.[29,33]

In the study conducted by Mathurin and colleagues, patients with severe AAH, without meeting the 6 month abstinence period, were selected from 7 centers for early liver transplantation.[29] Those selected for hepatic transplant had to meet various prerequisites. In addition to being non-responders, the following criteria also had to be

met: no prior episodes of AAH and no severe coexisting conditions, well integrated individual with an active role in the community, excellent support group with supportive family members, as well as a commitment to alcohol abstinence.[29] These same patients also needed to earn the consensus of the multidisciplinary group assessing their case. Upon applying such criteria, fewer than 2% of patients defined as non-responders to corticotherapy were recruited at the various centers, elucidating the stringency of such selection criteria.[29] The patient presented in our case report fulfilled all the criteria set by Mathurin et al. (2011) in regards to the eligibility for hepatic transplant in individuals with AAH. We can conclude that in relation to prerequisites the patient was correctly selected for the procedure.

Although patients meet a strict number of criteria and are put through a rigorous selection process, there is still some reluctance in listing these patients for hepatic transplant. The perception that patients with ALD have played a significant role in their illness seems to be a contributing factor to the negative view of such patients.[21] Much of the hesitancy to list patients for orthotopic liver transplantation (OLT) in the setting of acute alcoholic hepatitis arises from concern that patients will return to drinking and concern about inappropriately transplanting a patient who may recover with medical therapy.[8] The reluctance to perform transplantation in patients with alcoholism can therefore often be summed up by two general ideas: that these patients are responsible for their illness and that they are likely to resume alcohol use after transplantation.[31]

Although numerous studies have lent support to the validity of the sobriety period, they have also observed that the enforcement of this period alone delays listing for transplantation in a considerable number of candidates with a low probability of relapse.[21,29] Indeed, the duration of abstinence before transplantation is a poor indicator of the likelihood of remaining abstinent after transplant,[8,22,29] and the price of insisting

on a fixed abstinence period may be equivalent to death in some patients.[8,21-22,30,36] Therefore, in facing such a dismal outcome, hepatic transplant might be considered appropriate in null responders selected using criteria such as absence of other comorbidities, social integration and the existence of family members able to support the patient through liver transplantation programme,[27] even without meeting the 6 month abstinence mark, as confirmed by the study conducted by Mathurin et al. (2011).

While isolated cases of relapse with consequent damage to the graft have been recorded, most studies have found that alcoholism relapse leading to allograft injury is a relatively unusual complication among those patients with alcoholism who are selected for hepatic transplantation.[32] Even in cases of relapse, studies have reported similar 1 and 5 year survival rates for patients undergoing OLT for ALD in comparison with other indications, and in most studies alcohol relapse also did not influence 1 and 5 year rates after OLT for ALD alone.[13,31]

Even though there is strong evidence to support OLT in AAH, medical and ethical concerns about the appropriate use of scarce resources and the degree of priority given to patients with ALD continues to be a controversial issue.[31] The ever increasing demand for donor organs and the inadequate rate of organ donation, combined with the concern that alcoholic patients might relapse to drinking, thereby damaging the transplanted liver, has been a large deterrent.[31] The limited supply of donor organs frequently biases what should be equal access to potential medical benefits for all patients.[29]

Modifications in guidelines for hepatic transplantation in patients with alcoholism may conflict with public preferences for liver-transplant allotment and may decrease public willingness to donate.[29] Interestingly, this has not occurred in response to transplantation being offered to patients with fulminant hepatic failure due to

voluntary acetaminophen poisoning, nor to intravenous-drug users with acute hepatitis B virus infection.[28,36] In fact, the European Association for the Study of the Liver (EASL) already consider OLT as a treatment option in highly selected patients in their recent clinical practical guidelines on the management of alcoholic liver disease.[9] It is thus vital that the public are made aware that patients are only offered transplantation if they fail to recover after a period of abstinence and medical treatment and that the incidence of significant post-transplant recidivism is low.[21]

The continuing imbalance between the few available livers and the increasing numbers of patients on waiting lists has led physicians to develop prognostic factors to determine disease severity in order to list and allocate donor organs to the sickest patients.[37] Among available scores, the MELD is now considered the gold standard when selecting candidates for liver transplantation.[38-39] Optimal timing for liver transplantation in alcoholic patients varies drastically between transplant programs, and decisions on transplant eligibility should be made on an individual basis, with careful prediction of short-term survival.[33] An American conference held in 2003 stated that the Model for End-Stage Liver Disease meets the goal of providing a system that emphasizes the urgency of the candidate.[33] Candidates with a MELD score < 15 had a lower mortality risk than transplanted patients with a similar MELD score.[33] With scores of 18-20, studies show the mortality risk was lower among transplant recipients when compared with candidates.[39] Survival benefit increased with increasing MELD score with recommendations stating that the best option is to list patients with a MELD score ≥ 15.[37] Some investigators, however, have suggested that a cutoff point at 40 may be used to define a patient as too ill for liver transplantation.[33] Nonetheless, although recipients with a MELD score ≥ 40 had greater post-transplant mortality, their survival rate was still greater than that for candidates who were not transplanted.[39] According to

the study conducted by Mathurin et al. (2011), the cumulative 6-month survival rate (±SE) was higher among patients who received early transplantation than among those who did not (77±8% vs. 23±8%).[29] Our patient at time of transplant proposal had a MELD score of 39. Even though we have ascertained that regardless of the high MELD score, transplanted patients in those cases continue to have a higher survival rate in comparison to those not transplanted, we can speculate that the negative outcome and consequent death in our patient could have been predicted based on the severity pre-transplant as denoted by the MELD score.

With exception of those patients considered to be too ill, the outcome for patients who undergo transplantation for ALD is similar to that seen in patients transplanted for other forms of end-stage chronic liver disease.[22,30] The study conducted by Tome et al. (2002) clearly demonstrated that survival after liver transplantation in patients with alcoholic cirrhosis plus alcoholic hepatitis detected in explanted liver was similar to that of patients transplanted for non-alcoholic disease.[40] In addition, it is known that ALD patients post OLT have reduced incidence of acute cellular rejection.[31] Chronic ductopenic rejection is also reportedly less common or the same in the patients receiving OLT for ALD from those for other indications.[31]

Infections, on the other hand, are reportedly more common following OLT in patients with ALD. The incidence of bacterial infections is greater in these patients while the incidence of cytomegalovirus infection is comparable to those patients transplanted for non-alcoholic liver disease.[31] Mathurin et al. (2011) reported that 5 of the 6 deaths post-transplant of a total of 26 case patients, were premature and a consequence of infection, 4 deaths of which were attributed to invasive aspergillosis.[29] Even before transplantation, infection appears to be a consequence of absence of improvement in liver function, as assessed by response to therapy.[41] In addition, we can

not rule out the brief course of corticotherapy in non-responders as a contributing factor, at least in part, to susceptibility to infection.[41] Studies evaluating the usefulness of fungal prophylaxis as well as prophylactic antibiotics before transplantation, duration of glucocorticoid use before and after transplantation, and the tailoring of immunosuppressive regimens[29,41] are needed in order to develop possible strategies for improving outcome in face of infection. Sequential screening for possible infections may also have some value in these patients.

Choosing the appropriate moment for transplantation is in fact crucial. Optimal timing in regards to transplantation will be imperative in avoiding the adverse effects of intervening too early or too late. We can speculate that the patient presented in this case report, although considered to be the "perfect candidate", was not transplanted within the ideal window of time, leading to additional complications post-transplant and consequently death.

Conclusion

The management of patients with alcoholic liver disease is a challenge. The high rate of mortality associated with severe AAH urges the need for more effective treatment options. Whereas corticotherapy may be of worth in those patients defined as responders, it is a different question when we discuss those that are defined as non-responders. In this group of patients new therapeutic options are necessary. Hepatic transplant can be one of those options in selected patients that fulfill various criteria including the absence of other comorbidities, social integration and the existence of a strong support group. The recent EASL clinical practical guidelines on the management of alcoholic liver disease already consider OLT in highly selected patients, altering the paradigm regarding the conduct and treatment of AAH.

Alcoholic hepatitis is indeed an acceptable indication for liver transplant, as survival in well selected patients after transplantation is similar to those seen in patients who receive grafts for other causes. Relapse to heavy drinking is uncommon and as yet, has not shown to adversely affect outcome. At present, there is no evidence to deny liver transplantation to patients with shorter periods of abstinence based on either poorer survival or higher relapse rate. Decisions on transplant eligibility, however, should be made on an individual basis, as patient selection is important for rationing scarce organs.

Although more data are required, the benefit of OLT in patients with severe AAH who fail to respond to corticotherapy is a promising area of research. While this is true, early liver transplantation is relevant only for a minority of patients whereas new therapeutic strategies are urgently needed for the majority of non-responders. As well, we need to better define the optimal timing to transplant eligible patients. In addition to

timing, new measures must also be considered in order to circumvent possible infections post-transplant in these patients.

References

1. Yu C, Xu C, Ye H, et al (2010) Early mortality of alcoholic hepatitis: A review of data from placebo-controlled clinical trials. World J Gastroenterol 16(19):2435-2439.

2. O'Shea R, Dasarthy S, McCullough AJ (2010) Alcoholic Liver Disease. Hepatology 51(1):307-328.

3. Thomson SJ, Westlake S, Rahman TM, et al (2008) Chronic Liver Disease- An Increasing Problem: A Study of Hospital Admission and Mortality Rates in England, 1979-2005, with Particular Reference to Alcoholic Liver Disease. Alcohol & Alcoholism 43(4):416-422.

4. Cortez-Pinto H, Gouveia M, Pinheiro L, et al (2010) The Burden of Disease and the Cost of Illness Attributable to Alcohol Drinking- Results of a National Study. Alcohol Clin Exp Res 34(8):1442-1449.

5. Basra S, Anand BS (2011) Definition, epidemiology and magnitude of alcoholic hepatitis. World J Hepatol 3(5):108-113.

6. Adachi M, Brenner DA (2005) Clinical syndromes of alcoholic liver disease. Dig Dis 23:255-263.

7. Mailliard ME, Sorrell MF (2012) Alcoholic Liver Disease. In: Harrison´s Principles of Internal Medicine 18th Ed. (Fauci AS et al, ed), pp2589-2591. New York: McGraw-Hill Companies, Inc.

8. Frazier TH, Stocker AM, Kershner LS, et al (2011) Treatment of alcoholic liver disease. Ther Adv Gastroenterol 4:63-81.

9. European Association for the Study of the Liver (2012) EASL Clinical Practical Guidelines: Management of Alcoholic Liver Disease. J Hepatol (in press).

10. Basra G, Basra S, Parupudi S (2011) Symptoms and signs of acute alcoholic hepatitis. World J Hepatol 3(5):118-120.

11. Cohen SM, Ahn J (2009) Review article: the diagnosis and management of alcoholic hepatitis. Aliment Pharmacol Ther 30:3-13.

12. Moreno C, Langlet P, Hittelet A, Lasser L, Degré D, Evrard S, et al (2010) Enteral nutrition with or without N-acetylcysteine in the treatment of severe acute alcoholic hepatitis: A randomized multicenter controlled trial. J Hepatol 53:1117-1122.

13. Day CP (2007) Treatment of Alcoholic Liver Disease. Liver Transplantation 13:S69-S75.

14. Mathurin P, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, et al (2011) Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. Gut 60:255-260.

15. Mathurin P (2005) Corticosteroids for alcoholic hepatitis – what´s next? J Hepatol 43:526-533.

16. Mezy E, Potter JJ, Rennie-Tankersley L, Caballeria J, Pares A (2004) A randomized placebo controlled trial of vitamin E for alcoholic hepatitis. J Hepatol 40:40-46.

17. Stewart S, Prince M, Bassendine M, Hudson M, James O, Jones D, et al (2007) A randomized trial of antioxidant therapy alone or with corticosteroids in acute alcoholic hepatitis. J Hepatol 47:277-283.

18. Nguyen-Khac E, Thevenot T, Piquet MA, Benferhat S, Goria O, Chatelain D, et al (2011) Glucocorticoids plus N-Acetylcysteine in Severe Alcoholic Hepatitis. N Engl J Med 365(19):1781-1789.

19. De BK, Gangopadhyay S, Dutta D, Baksi SD, Pani A, Ghosh P (2009) Pentoxifylline versus prednisolone for severe alcoholic hepatitis: A randomized controlled trial. World J Gastroenterol 15(13):1613-1619.

20. Assimakopoulos SF, Thomopoulos KC, Labropoulou-Karatza C (2009) Pentoxifylline: A first line treatment option for severe alcoholic hepatitis and hepatorenal syndrome? World J Gastroenterol 15(25):3194-3195.

21. Stewart SF, Day CP (2003) The management of alcoholic liver disease. J Hepatol 38:S2-S13.

22. Madhotra R, Gilmore IT (2003) Recent developments in the treatment of alcoholic hepatitis. Q J Med 96:391-400.

23. Rongey C, Kaplowitz N (2006) Current concepts and controversies in the treatment of alcoholic hepatitis. World J Gastroenterol 12(43): 6909-6921.

24. Sougioultziz S, Dalakas E, Hayes C, Plevris JN (2005) Alcoholic hepatitis: from pathogenesis to treatment. Curr Med Res Opin 21(9):1337-1346.

25. McCullough AJ, O'SHEA RS, Dasarathy S (2011) Diagnosis and management of alcoholic liver disease. Journal of Digestive Disease 12:257-262.

26. Forrest EH, Morris AJ, Stewart S, Phillips M, Oo YH, Fisher NC (2007) The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. Gut 56:1743-1746.

27. Dureja P, Lucey MR (2010) The place of liver transplantation in the treatment of severe alcoholic hepatitis. J Hepatol 52:759-64.

28. Mathurin P, Lucey M (2012) Management of alcoholic hepatitis. J Hepatol S39-S45.

29. Mathurin P, Moreno C, Samuel D, et al (2011) Early Liver Transplantation for Severe Alcoholic Hepatitis. N Engl J Med 365:1790-1800.

30. Lucey MR (2011) Liver Transplantation in Patients With Alcoholic Liver Disease. Liver Transpl 17:751-759.

31. Varma V, Webb K, Mirza DF (2010) Liver transplantation for alcoholic liver disease. World J Gastroenterol 16:4377-4393.

32. Lucey MR (2002) Is liver transplantation an appropriate treatment for acute alcoholic hepatitis? J Hepatol 36:829-831.

33. Mathurin P (2005) Is Alcoholic Hepatitis an Indication for Transplantation? Current Management and Outcomes. Liver Transpl 11:S21-S24.

34. Tan HH, Virmani S, Martin P (2009) Special Feature – Controversies in the Management of Alcoholic Liver Disease. Mt Sinai J Med 76:484-498.

35. Mathurin P (2010) The use of corticosteroids in severe alcohol hepatitis: We need to look beyond this controversy. J Hepatol 53:392-393.

36. Burroughs AK (2012) Liver transplantation for severe alcoholic hepatitis saves lives. J Hepatol (in press).

37. Mathurin P, Lucey MR (2007) A Patient With Alcoholic Liver Failure Referred for Liver Transplantation. Liver Transplantation 13:S83-S86.

38. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al (2001) A model to predict survival in patients with end-stage liver disease. Hepatology 33:464-470.

39. Merion RM, Schaubel DE, Dykstra DL, Freeman RB, Port FK, Wolfe RA (2005) The survival benefit of liver transplantation. Am J Transplant 5:307-313.

40. Tome S, Martinez-Rey C, Gonzalez-Quintela A, Gude F, Brage A, Otero E, et al (2002) Influence of superimposed alcoholic hepatitis on the outcome of liver transplantation for end-stage alcoholic liver disease. J Hepatol 36:793-798.

41. Louvet A, Wartel F, Castel H, Dharancy S, Hollebecque A, Canva-Delcambre V, et al (2009) Infections in Patients With Severe Alcoholic Hepatitis Treated With Steroids: Early Response to Therapy Is the Key Factor. Gastroenterology 137:541-548.

Appendix

Transplante Hepático na Hepatite Aguda Alcoólica: Resumo

A doença hepática alcoólica é um problema de saúde global. A doença hepática crónica com progressão para a cirrose e suas complicações inerentes são o segundo motivo mais frequente de transplante hepático na Europa e nos Estados Unidos. Em geral, o risco de desenvolver doença hepática está associado ao padrão de ingestão, tipo de bebida ingerida, e a quantidade de álcool consumido. A ingestão de álcool durante 10 ou mais anos com doses em excesso de 40-80 g/dia no sexo masculino e 20-40 g/dia no sexo feminino, são geralmente necessárias para provocar doença hepática alcoólica. No entanto, as actuais directrizes europeias referem que mesmo pequenas quantidades de álcool ingerido (inferior a 25 g/dia) pode ser suficiente para induzir a doença hepática alcoólica. A raça, bem como a obesidade, sobrecarga de ferro, infecção concomitante com hepatite viral e factores genéticos, entre outros, também podem estar implícitos. A doença hepática alcoólica engloba uma síndrome clínica distinta induzida pelo consumo de álcool. Esta síndrome é conhecida por hepatite aguda alcoólica e tem um espectro clínico amplo que vai desde assintomático até às alterações analíticas, insuficiência hepática e morte. Estima-se que aproximadamente 35% dos alcoólicos sofrem de hepatite aguda alcoólica, sendo que a maioria dos casos ocorrem antes dos 60 anos de idade.

O diagnóstico de doença hepática alcoólica baseia-se numa combinação de características, incluindo uma história de consumo de álcool significativa, evidência clínica de doença hepática e alterações laboratoriais típicas. A hepatite aguda alcoólica está associada a um quadro clínico vasto, com astenia, dor no hipocôndrio direito, febre e taquicardia, e normalmente com icterícia. Caracteristicamente, a proporção de

aspartato aminotransferase para alanina aminotransferase é de aproximadamente 2:1 e, habitualmente encontram-se em níveis não muito elevados. Outras alterações laboratoriais comuns na hepatite aguda alcoólica incluem a hiperbilirrubinemia, leucocitose e anemia.

Com uma mortalidade aos 28 dias de até 50%, terapêutica eficaz nestes casos é essencial. Para além do suporte nutricional e garantir a abstinência destes doentes, os corticosteróides permanecem como terapêutica de primeira linha na prática clínica. A administração de corticóides é preconizada em doentes que tenham um factor discriminador de Maddrey superior ou igual a 32. Recentemente, o score de Glasgow para a hepatite alcoólica revelou-se como sendo preditivo da gravidade da doença e de indicação para iniciar corticoterapia para valores superiores ou iguais a 9. A administração de 40 mg por dia de prednisolona durante pelo menos 7 dias constitui o padrão terapêutico. O score de Lille irá posteriormente avaliar a resposta à corticoterapia após 7 dias, dando indicação de quais os doentes que respondem e, portanto, beneficiam da manutenção do corticóide em comparação com aqueles que não obtiveram resposta. Ao avaliar o efeito da referida corticoterapia, não-respondedores são definidos com uma pontuação de 0,45 ou superior após 7 dias de terapêutica médica, de acordo com o modelo de Lille. Nos doentes que não respondem, esta terapêutica não aumentará a sobrevida a longo prazo, e assim, novas estratégias terapêuticas são necessárias. Será nestes casos que podemos olhar para o transplante hepático como uma opção possível de tratamento para melhorar a sobrevida neste grupo de doentes.

O transplante hepático em doentes com hepatite aguda alcoólica, no entanto, permanece um assunto bastante controverso entre a comunidade de profissionais de saúde e do público. Existe uma relutância em disponibilizar os órgãos escassos para

transplante a doentes que o público habitualmente percepciona como tendo infligido em si a sua doença decorrendo de um comportamento voluntário e nocivo. Inclusive, a preocupação de que os doentes poderão vir a sofrer de uma recaída após o transplante, contribuiu para a implementação de um período obrigatório de 6 meses de abstinência alcoólica, necessária para que tais doentes viessem a ser considerados para transplante hepático em alguns países. Contudo, vários estudos indicam que a duração da abstinência prévia ao transplante é um indicador pobre do risco de recaída após o transplante. Para além disso, sabemos que estamos perante doentes cuja regra dos 6 meses de abstinência não deverá ser aplicável, dado que, a maioria dos doentes graves abstinentes morrem antes desse período devido à gravidade da situação clínica.

Recentemente existem vários estudos que apontam para a necessidade de definir novos critérios de inclusão destes doentes, não necessitando de cumprir o período de 6 meses de abstinência. Os critérios de selecção para transplantação de doentes com hepatite aguda alcoólica, de acordo com o estudo de Mathurin et al. (2011), incluem a hepatite aguda alcoólica como o primeiro episódio de descompensação da doença hepática, ausência de outras co-morbilidades, integração social e a existência de um grupo de apoio, para além do candidato reunir o consenso dos profissionais envolvidos no processo da decisão clínica. De facto, as recentes orientações clínicas da Associação Europeia para o Estudo do Fígado já consideram o transplante hepático como possível terapêutica em doentes altamente seleccionados.

O modelo para a doença hepática terminal conhecido por MELD, cumpre o objectivo de fornecer um sistema que enfatiza a urgência dos candidatos em termos de necessidade de terapêutica. Um doente com uma pontuação de MELD inferior a 15 tem um risco menor de mortalidade em comparação com doentes transplantados com a mesma pontuação. Os estudos demonstram que pontuações de MELD ente os 18-20

valores estão associados a menor risco de mortalidade nos doentes que forem submetidos a transplantação em comparação com candidatos que não forem transplantados. A sobrevida aumenta com o aumento da pontuação de MELD e recomenda-se a listagem de doentes para transplante com uma pontuação de MELD superior ou igual a 15.

Alguns investigadores, no entanto, sugerem que deverá existir um ponto de limite para definir um doente que estará demasiado doente para ser submetido a um transplante. Contudo, apesar de recipientes com uma pontuação de MELD superior ou igual a 40 terem uma maior taxa de mortalidade pós-transplante, a sua taxa de sobrevida continua maior pós-transplante em comparação com os candidatos que não foram submetidos à transplantação. Escolher o momento adequado para o transplante é de facto crucial. O momento ideal em relação ao transplante é imperativo para evitar os efeitos adversos de intervir demasiado cedo ou demasiado tarde.

De acordo com vários estudos, podemos concluir que a hepatite aguda alcoólica pode ser uma indicação aceitável para transplante hepático, com taxas de sobrevivência pós-transplante, em doentes bem seleccionados, semelhantes às observadas em doentes transplantados por outras etiologias. A recaída pós transplante é incomum e quando ocorre não demonstrou afectar adversamente os resultados a prazo de um e cinco anos pós transplantação. Actualmente, portanto, não há nenhuma evidência para negar o transplante hepático a doentes com base em períodos mais curtos de abstinência ou por maior taxa de recaídas e consequente lesão do fígado transplantado.

A incidência de infecções bacterianas, contudo, é maior em doentes transplantados por doença hepática alcoólica, enquanto a incidência de infecção por citomegalovírus é comparável com as taxas observadas em doentes transplantados por

doença hepática não alcoólica. Deveremos, portanto, estar atentos a esta ocorrência em doentes após a transplantação.

Apesar de serem necessários mais estudos, o benefício de transplantação em doentes com hepatite aguda alcoólica grave que não respondem a corticoterapia é uma área de estudo promissora. Apesar de se evidenciar este benefício, o transplante hepático precoce é relevante em apenas uma minoria de doentes, e portanto, novas estratégias terapêuticas são urgentemente necessárias para a maioria de doentes não-respondedores à corticoterapia.

Necessitamos, ainda, de melhor definir o momento ideal para a transplantação em doentes elegíveis. O reconhecimento da janela de oportunidade óptima é essencial para podermos intervir da forma a obter os melhores resultados possíveis. Novas medidas devem, também, ser consideradas a fim de contornar possíveis infecções pós-transplante nestes doentes. Estudos avaliando a utilidade da profilaxia fúngica, bem como antibióticos profilácticos prévios ao transplante, a duração da utilização de corticosteróides, antes e após o transplante, e o acerto de regimes de imunossupressão, irão ser necessários a fim de desenvolver estratégias possíveis para melhorar os resultados em face da infecção nestes doentes.

No caso clínico apresentado foi proposto abordar o caso de um doente de 56 anos de idade com hepatite aguda alcoólica, não respondedor à terapêutica com corticóides, com uma história pregressa de alcoolismo em contexto social desde os 30 anos de idade. O papel da transplantação hepática em contexto de ingestão de álcool e as implicações éticas inerentes que advêm da realização deste procedimento ainda não consensual são discutidos em redor deste doente.

Um mês anterior ao internamento, o doente apresentou com edema do pé direito, evoluindo para edema bilateral dos membros inferiores em associação com um aumento

do perímetro abdominal correspondente a ascite duas semanas após o início do quadro clínico.

Na admissão ao hospital foram evidenciadas alterações analíticas marcadas, incluindo um aumento das transaminases hepáticas, hiperbilirrubinemia, anemia e alterações do perfil da coagulação, para além de um factor discriminador de Maddrey elevado. O doente foi nesta altura medicado com prednisolona, mas posteriormente rotulado como não-respondedor de acordo com o score de Lille. Com a continuada degradação do estado clínico do doente, este foi transferido para um hospital de referência na transplantação hepática. Aqui, já apresentava com ligeiras alterações da consciência, icterícia, ascite de grande volume, e ainda, ligeiro edema pré-tibial e maleolar. A biópsia transjugular efectuada nesta altura confirmou o diagnóstico de hepatite aguda alcoólica em contexto de uma cirrose preexistente.

Ao nível que o estado clínico do doente veio a piorar, com encefalopatia de grau II rapidamente progredindo para encefalopatia de grau III, com uma pontuação de MELD elevada, o doente foi proposto para a transplantação hepática. O doente satisfez os critérios enumerados pelo estudo de Mathurin et al. (2011). Contudo, após a transplantação, o doente eventualmente cedeu a um número de complicações e morreu por falência multiorgânica.

Palavras-chave: hepatite aguda alcoólica, transplante hepático, corticosteróides, abstinência alcoólica.