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Association of pre- and early post-transplant serum amino acids and metabolites of amino acids and liver transplant outcome☆

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ABSTRACT

The aim of the present study was to investigate association of serum amino (AA) acids and metabolites of AAs with post-transplant outcome in liver transplant recipients.

Eighty-nine patients with end-stage liver diseases and available pre- and early post-transplant serum were characterised as patients with (GI) and without one-year mortality (GII) and patients with and without early graft dysfunction (EAD). A panel of pre- and early post-transplant serum levels of AAs and early and metabolites of tryptophan were measured using tandem mass spectrometry.

Patient groups had significantly higher pre-transplant serum levels of phenylalanine, tryptophan, and tryptophan metabolites than healthy controls (for all $p < 0.001$). Pre-transplant serum levels of all these parameters were significantly higher in GI than in GII (for all $p < 0.001$). GI had a higher MELD score and re-transplantation number than GII ($p \leq 0.005$ for both investigations). Serum bilirubin on day 5 and serum phenylalanine on day 10 post-transplant were associated parameters of mortality, whereas day 1post-transplant phenylalanine and kynurenine and female gender were associated parameters of EAD.

Our results indicate that pre- and early post-transplant levels of phenylalanine, tryptophan and metabolites of tryptophan are increased in patients and are associated with EAD and one-year mortality in liver transplant recipients.

1. Introduction

Post-transplant outcome in adult liver transplant recipients is associated with pre-, peri- and post-transplant risk factors including Model for End-Stage Liver Disease (MELD) score [1], pre-transplant nutritional status [2], pre- [3] and post-transplant kidney [4] and heart [4] disease, post-transplant infection [5], and venous thrombosis [6]. A multivariate analysis by McDiarmid et al. indicated that vascular thrombosis, bowel perforation, septicemia, and re-transplantation, each independently increased the risk of patient and graft loss by 3 to 4 fold during the first 6 post-transplant months [7]. Sun et al. identified MELD score > 30, Intensive Care Unit stay > 48 h prior to transplantation, intra-operative transfusion ≥ 15 units, re-transplantation, post-transplant dialysis, or reoperation as risk factors for infection during the first 3 post-transplant months [8].

AAs have direct or indirect inflammatory, anti-inflammatory and

Abbreviations: CMV, cytomegalovirus; CRP, C-reactive protein; EAD, early graft dysfunction; ESLD, end-stage liver diseases; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDO, indoleamine 2,3-dioxygenase; IFN, Interferon; MELD, Model for End-Stage Liver Disease; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic

☆ Authorship: Hani Oweira participated in the study design, operated the patients, gathered the samples and assisted in writing the manuscript. Imad Lahdou assisted in the design of the study and measured the parameters. Volker Daniel participated in writing the manuscript. Gerhard Opelz and Peter Terness assisted in writing the manuscript. Arianeb Mehrabi and Jan Schmidt operated the patients. Gerhard Fusch and Joerg Schefold measured tryptophan and tryptophan metabolites. Mahmoud Sadeghi assisted in developing the design of the study, analyzed the data, and wrote the manuscript.

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Table 1
Demographic and clinical characteristics of the study population.

Parameters	Non-survivor (n = 16)	Survivor (n = 73)	EAD + (n = 21)	EAD − (n = 68)
Age [mean ± SD years]	52 ± 10	52 ± 11	52 ± 12	53 ± 11
Female gender (n)	5	18	10**	13**
Child-pugh category A/BA/C (n)	6/4/6	28/21/24	4/7/10	27/19/22
Donor age [mean ± SD years]	59 ± 16	57 ± 18	56 ± 18	55 ± 19
Anti-viral IgG status				
HBV-Ab + (n)	1	9	1	9
HCV-Ab + (n)	6	16	7	15
CMV-Ab + (n)	10	44	18	36
Immunosuppressive drugs				
Cyclosporine A (n)	9	41	15	35
Tacrolimus (n)	5	31	9	27
Prednisolone (n)	15	72	24	62
MMF (n)	6	27	9	24
Original liver disease				
Congenital/autoimmune/toxic (n)	8	25	10	23
Alcoholic (n)	4	24	8	23
Viral hepatitis (n)	4	24	5	23
Risk factors for EAD and post-transplant mortality				
MELD score (mean ± SD)	24.3 ± 8.7**	17.3 ± 8.1**	22.0 ± 9.4*	17.0 ± 8.2*
Pre-Tx albumin (g/L)	27.0 ± 6.0**	32.0 ± 7.0**	31.0 ± 7.0	31.0 ± 7.0
1–10 days post-Tx SIRS (n)	7	17	9	15
Post-Tx bacterial infection (n)	13*	37*		
Re-transplant (n)	8***	10***	8*	10*
Pre-Tx bilirubin (mg/dL)	12.9 ± 8.8*	7.4 ± 8.6*	11.6 ± 10.8	6.9 ± 8.0
Pre-Tx neopterin (nmol/L)	43.0 ± 27.0* (Median = 34)	42.0 ± 67.0* (Median = 18)	38.0 ± 34.0 (Median = 33)	43.0 ± 66.0 (Median = 21)
Pre-Tx creatinine (mg/dL)	1.5 ± 1.0	1.3 ± 1.0	1.4 ± 0.9	1.3 ± 1.0
Pre-Tx CRP (mg/L)	32.0 ± 24.0*	21.0 ± 24.0*	19.0 ± 18.0	22.0 ± 25.0
Pre-Tx encephalopathy (n)	8	35	10	33
Intra-operative transfusion (n)	29.0 ± 25.0	27.0 ± 22.0	35.0 ± 28.0	24.0 ± 21.0
Rejection (n)	2	9	2	9

Mann-Whitney U test, χ^2 or Fisher exact test were used.

* $p \leq 0.05$.

** $p \leq 0.01$.

*** $p \leq 0.001$.

immunomodulatory effects. Recently, we reported on an association of phenylalanine and tryptophan metabolites with activated cytomegalovirus (CMV) infection in kidney transplant recipients [9] and pre-transplant plasma kynurenine as a predictor of acute rejection in kidney transplant recipients [10]. Almost all published research on the kynurenine pathway is restricted to inflammatory responses to nervous system [11] diseases. Indoleamine 2,3-dioxygenase (IDO) degrades the essential AA tryptophan into kynurenine and other downstream metabolites that suppress effector T-cell function [12] and favor the differentiation of regulatory T cells [13]. IDO is widely distributed in mammals and is inducible preferentially by interferon (IFN)-γ [14]. IDO is traditionally regarded as a general suppressor of T-cell activation and mediator of immune escape in cancer [13]. Recently, evidence has emerged to support a greater functional complexity of IDO1 as modifier of pathogenic inflammation [13]. For instance, IDO1 activity may sustain autoantibody production by B cells, and elicit the development of cancer in the context of chronic inflammation [13]. Studying an old population, Capuron et al. showed that increased inflammation was related to reduced tryptophan concentrations and increased kynurenine levels. In the study by Capuron, inflammation was associated with increases in phenylalanine concentrations [15]. In a recent study we reported on association of plasma quinolinic acid and severity of hepatic dysfunction in patients with liver cirrhosis [16]. The results showed that quinolinic acid and neopterin are more sensitive markers for severity of liver disease than established markers of inflammation such as C-reactive protein (CRP), and IL-6 and that quinolinic acid provided the most sensitive index with regard to the identification of patients with hepatic encephalopathy [16]. We also reported on an association of early post-transplant neopterin (IFN-γ-dependent response) and one-year patient survival and bacteremia in liver transplant recipients [17]. Associations of pre- and early post-transplant serum AAs and their metabolites with recipient outcome in liver transplantation have not been studied. In the present study, we investigated whether pre-transplant serum AA and AA metabolites -especially the IFN-γ-dependent kynurenine pathway, among other risk factors, are associated with recipient survival in liver transplant recipients.

2. Material and methods

2.1. Characteristics of the study population

The retrospective study was conducted in accordance with local ethical guidelines and all individuals gave informed consent for the analysis of their plasma samples. Between January 2008 and April 2010, 178 patients underwent liver transplantation at the university hospital Heidelberg, Germany. Pre- and early post-transplant concentrations of all essential amino acids including tryptophan and phenylalanine and metabolites of tryptophan such as kynurenine, kynurenic acid and quinolinic acid were measured in available serum samples of 89 adult (age 52.2 ± 10.6 years; 23 female) patients. Patients showed different disease severity based on MELD staging. Fifty patients experienced first bacterial infections including urinary tract infection, blood stream infection, pneumonia, wound infection and cholangitis during 29 ± 31 days post-transplant. Sixteen patients (8.9% of all patients and 18% of the study group, GI) died during one-year post-transplant due to graft failure and sepsis, whereas 73 patients