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Activity of urine arylsulfatase A in brain-dead graft donors is a predictor of early and late graft function

Aktywność arylosulfatazy A w moczu dawców narządów ze śmiercią mózgu jako czynnik prognostyczny wczesnej i późnej funkcji przeszczepu

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Objective: Human lysosomal arylsulfatase A (ASA) is a member of the sulfatase family. Arylsulfatase A is required to degrade sulfatides. Sulfatides occur in the myelin sheets of the central and peripheral nervous system. In this study we evaluated the urine activity of lysosomal enzyme arylsulfatase A in brain-dead donors as a marker and predictor of short – and long-term renal allograft function.

Patients/Methods: We analyzed data from kidney recipients who received organs from brain-dead donors. Data from 40 donors and 68 recipients were analyzed.

Results: Urine activity of arylsulfatase A in graft donors correlated positively with creatinine clearance in graft recipients after transplantation: : significantly after 30 days (Rs=0.38, p=0.004) and after 3 years (Rs=0.38, p=0.03), and with borderline significance after 14 days (Rs=0.25, p=0.08) and after one year (Rs=0.23, p=0.07).

Conclusions: The results of this study suggest that arylsulfatase A has a protective effect on kidney allograft, and the urine activity of this enzyme in kidney donors correlates positively with graft function.

Keywords: **arylsulfatase A • graft • kidney**

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Introduction

Donors with brain death (DBDs) are currently the main source of organs in transplantology. The short – and long-term outcomes of allografts obtained from these donors are inferior when compared to living donors [10]. In the case of organs obtained from DBDs delayed graft function more frequently was observed [12]. The explanation for this lies in the process of brain death (BD), itself resulting in a non-physiological environment culminating in significant organ injury prior to organ procurement. The procurement, preservation and reperfusion phases of transplantation result in significant additional injury to the allograft, rendering it susceptible to short – and long-term dysfunction [19]. BD causes complex disturbances of normal homeostatic systems resulting in hemodynamic instability, hormonal impairment, and inflammation [3,15]. BD results in significant cerebral ischemia and intracranial hypertension, resulting in parasympathetic activity followed by severe vasoconstriction [17]. BD is also associated with metabolic changes in cells and tissues.

Human lysosomal arylsulfatase A (ASA) is a member of the sulfatase family. It is synthesized as a 507 amino acid precursor and is processed in the endoplasmic reticulum to yield a 489 amino acid protein [18]. Each sulfatase is characterized by high substrate specificity. The human sulfatases located in the lysosomes are responsible for the degradation of glycosaminoglycans and sulfolipids [14]. Besides their physiological substrates, arylsulfatases also degrade synthetic chromogens and fluorogens [13]. ASA's major natural substrate is cerebroside 3-sulfate, which will accumulate if there is a deficiency in ASA, resulting in a lysosomal storage disorder known as metachromatic leukodystrophy [5].

In this study we evaluated the urine activity of lysosomal enzyme arylsulfatase A in DBDs as a marker and predictor of short – and long-term renal allograft function.

Material

We analyzed data from kidney recipients who received organs from brain-dead donors in the years 2009-2013. All patients were transplanted in the Department of Transplantology of Pomeranian Medical University and long-term outpatient care took place in the Department of Nephrology, Transplantology and Internal Medicine of Pomeranian Medical University. Data from 40 donors (16 females, 24 males) and 68 recipients (27 females, 41 males) were analyzed. All recipients received triple immunosuppressive therapy: tacrolimus, prednisone, mycophenolate mofetil.

We analyzed activity of tubular lysosomal enzyme ASA in urine of brain-dead donors before organ taking. In recipients we examined early and long-term kidney function. Early graft function was assessed as the necessity of hemodialysis treatment in the first week after kidney transplantation. Patients who required hemodialysis in this period were diagnosed with delayed graft function (DGF). Long-term kidney function was assessed as the level of serum creatinine at 1, 2, 3, 4 and 5 years after kidney transplantation. Estimated glomerular filtration rate (eGFR) was determined by the CKD-EPI formula using the calculator of the National Kidney Foundation.

Methods

Urine samples were collected from all donors for ASA and creatinine analysis before organ procurement. The collected samples were centrifuged at 4000 rpm for 10 min, and urine, without the sediment, was stored at –80ºC until the time of analysis. Urine ASA activity was determined using the method described previously by Werner et al. [20]. Urine creatinine concentrations were determined using picric acid as the regent. ASA activity was calculated in relation to creatinine concentration in urine (U/g creatinine).

Statistical analysis

We used Statistica 10 software (StatSoft, Poland) for statistical analysis. As the Shapiro-Wilk test showed that the distributions of most of the assessed quantitative variables were significantly different from normal ($p<0.05$), we used non-parametric Spearman's rank correlation coefficient (Rs) for the statistical analysis.

Results

Clinical characteristics of the renal donors are shown in Tables 1, 2.

Urine activity of arylsulfatase A in graft donors correlated positively with creatinine clearance in graft recipients after transplantation: statistically significant after 30 days (Rs=0.38, p=0.004) and after 3 years (Rs=0.38, p=0.03), and with borderline significance after 14 days (Rs=0.25, p=0.08) and after one year (Rs=0.23, p=0.07) (Fig. 1).

Discussion

Brain death triggers a complex cascade of molecular and cellular events including the release of various proinflammatory mediators, leading to a pronounced inflammatory state. The triggering stimulus of this phe-

Table 1. Clinical characteristics of the renal graft donors

Parameter	N	Median	Mean±SD	Range
Urine ASA activity [U/g creatinine]	40	2.76	3.45±2.68	0.13-12.86
Age [years]	40	48	46.2±11.7	22-75
Serum creatinine [mg/dL]	40	1.03	1.23±0.82	0.37-5.22
eGFR [mL/min/1.72 m^2]	40	69	80.3±43.6	12-209
Weight [kg]	31	70	73.7±13.9	52-120

N – number of subjects with data available, SD – standard deviation, eGFR – estimated glomerular filtration rate

Table 2. Clinical characteristics of the studied renal transplant recipients

Characteristic	N	Median	Mean±SD	Range
Age [years]	68	49	45.3±14.8	18-80
Dialysis before Tx [months]	47	24	27.1±18.2	0-84
Residual diuresis [mL/d]	44	350	611±1000	0-3000
Weight [kg]	46	70.5	69.9±12.9	47-98.5
CIT [hours]	50	21	21.4±9.3	6-42

N – number of subjects with data available, SD – standard deviation, Tx – transplantation, CIT – cold ischemia time

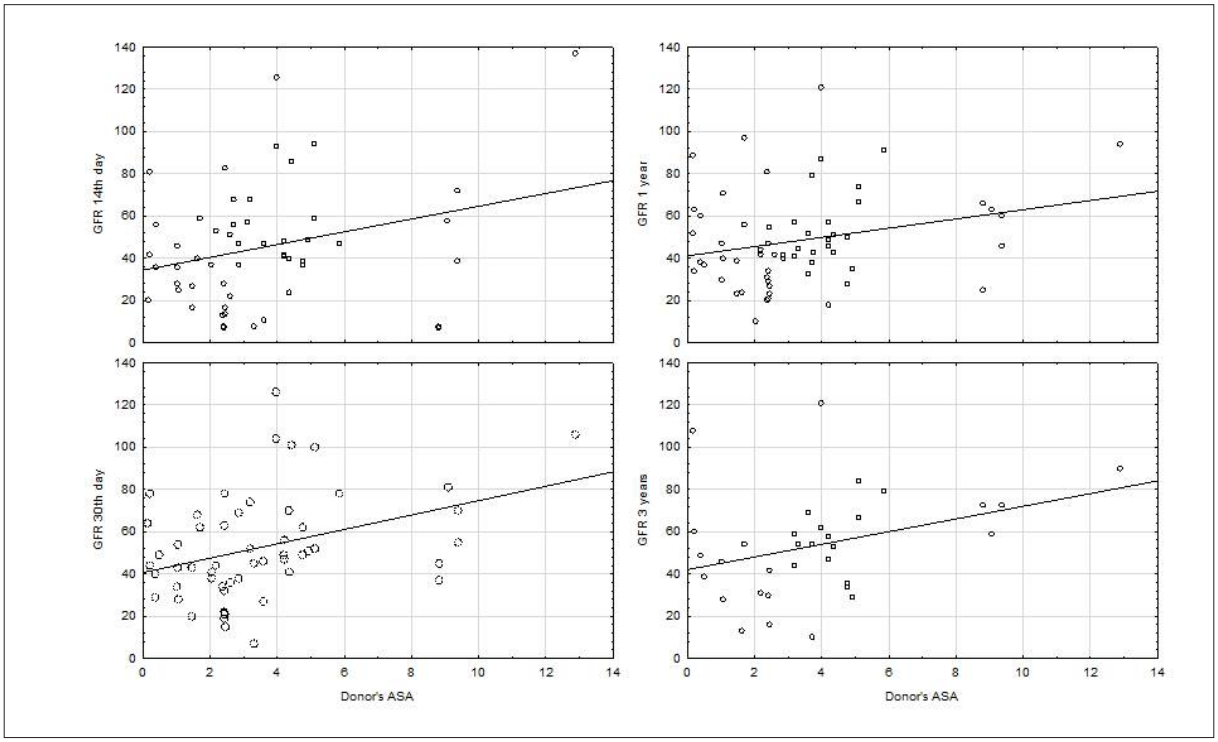

Fig. 1. Correlations between kidney graft donor's urine ASA activity and recipient's eGFR measured 14 days, 30 days, 1 year and 3 years after transplantation

nomenon remains unknown, but it eventually results in endothelial and complement activation, massive cytokine release, hemodynamic impairment and ultimately an immunologically activated organ before transplantation [4]. These changes increase the susceptibility for both ischemia-reperfusion injury and rejection, and may provide an explanation for the inferior results following transplantation of organs from deceased donors as compared with living donors [19].

In our study we analyzed the activity of urine arylsulfatase A in brain-dead graft donors as a predictor of early and late graft function. This activity correlated positively with creatinine clearance after transplantation. These results suggest protective activity of arylsulfatase A in kidney allografts.

Arylsulfatase A is required to degrade sulfatides. Sulfatides, such as galactosylceramide I^3-sulfate, occur abun-

dantly in the myelin sheets of the central and peripheral nervous system and in glandular epithelial tissues of mammals. Sulfatides of more complex structure have been found in the kidney [6]. In the human renal cell carcinoma line SMKT-R3, high levels of sulfatides including gangliotriaosylceramide-II^3 sulfate were observed [8,9]. In addition, complex sulfatides have been recognized to rank among the strongest ligands for natural killer receptor-p1. This membrane protein, with an extracellular Ca^{2+}-dependent lectin domain, is expressed on natural killer cells that display innate immunity [1]. More recently it has been shown that intracellular sulfation of lactosylceramide suppresses the expression of integrins [7] Sulfatides show structural, and possibly physiological similarities to gangliosides. Kidney dysfunction might be correlated with changes in sulfatides, the major acidic glycosphingolipids in this organ. In protein-overload nephropathy mice, the level of sulfatide in serum decreases as the disease progresses. Acute kidney dysfunction lowers the level of sulfatide in serum through downregulation of CST gene expression in lipoprotein-producing organs such as the liver [16]. Reduction of serum sulfatide level in patients with end-stage renal disease was detected prior to induction of hemodialysis therapy [11]. Kidney function itself also seems to be associated with regulation of sulfatide level in serum and lipoprotein-producing organs. Hypoxia in brain death donors may reduce activity of arylsulfatase. Bhattaryya et al. analyzed the effect of hypoxia on arylsulfatase B activity [2]. Hypoxia, like N-acetylgalactosamine-4-sulfatase (arylsulfatase B) silencing, significantly increased the total cellular sulfated glycosaminoglycans and chondroitin-4-sulfate content.

The results of this study suggest that arylsulfatase A has a protective effect on kidney allograft and the urine activity of this enzyme in kidney donors correlates positively with graft function.

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