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BRIEF REPORT

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Multiorgan donation from a donor with unrecognized ornithine transcarbamylase deficiency

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Abstract Ornithine transcarbamylase (OTC) deficiency, the most common inherited urea cycle disorder, shows a spectrum of severity ranging from severe neonatal hyperammonemic coma to no symptoms among adults. We report on the multiorgan procurement from a donor who died of cerebral edema due to unrecognized late-onset OTC deficiency. The donor's OTC deficiency was diagnosed retrospectively since the liver graft recipient developed cerebral edema postoperatively due to hyperammonemia. Plasma ammonia was extremely elevated (3793 μmol/l), but was not accompanied by general liver dysfunction. Post mortem, the diagnosis of OTC deficiency was established by enzyme and molecular analysis in a biopsy of the transplanted liver. In contrast to the fatal course of the liver graft recipient, the kidney, lung, and heart transplantations were successful. Ten months after transplantation these recipients were alive and showed good graft function. This case demonstrates the importance of careful donor evaluation, particularly if the donor's cause of death is obscure.

Keywords Liver transplantation · Urea cycle disorders · Ornithine transcarbamylase deficiency · Cerebral edema · Hyperammonemia · Donor evaluation

Abbreviations *ALT* Alanine aminotransferase · *AST* Aspartate aminotransferase · *CT* Computed tomography · *OTC* Ornithine transcarbamylase · *PT* Prothrombin activity

Introduction

The urea cycle consists of five enzymes, carbamyl phosphate synthetase, ornithine transcarbamylase (OTC), argininosuccinic acid synthetase, argininosuccinase, and arginase, which are responsible for the detoxification of ammonia to urea [3]. OTC catalyzes the condensation of carbamyl phosphate and ornithine to citrulline in the second step of the urea cycle [3]. OTC deficiency is the most common inherited disorder of urea synthesis and is transmitted as an X-linked trait [3, 6, 18]. Symptoms are induced by the accumulation of precursors of urea, mainly ammonia and glutamine [3, 15, 18]. The clinical phenotype in affected patients shows a spectrum of severity ranging from neonatal hyperammonemic coma to no symptoms among adults [3, 6, 13, 15, 18]. The classic form with neonatal onset and hyperammonemic coma is generally well recognized, but the late-onset forms can be missed [5, 6]. In the present article, we report the first multiorgan donation from a patient who died of unrecognized late-onset OTC deficiency. We describe the clinical course of the donor and the liver graft recipient as well as the outcome of the patients after kidney, lung, and heart transplantation.

Case report

A 26-year-old man was admitted to a secondary care hospital because of nausea and vomiting. Upon clinical examination he was somnolent and subfebrile. Laboratory investigations showed abnormal liver-associated test results: alanine aminotransferase (ALT) was 288 U/l (normal: 1–23 U/l); aspartate aminotransferase (AST), 34 U/l (normal: 1–19 U/l); total bilirubin, 1.5 mg/dl (normal: 0.1–1.1 mg/dl); alkaline phosphatase, 76 U/l (normal: 60–200 U/l), γ-glutamyl transpeptidase, 19 U/l (normal: 6–28 U/l); and prothrombin activity (PT), 61% (normal: 70–130%). This was thought to be the result of his abuse of anabolic steroids. A computed tomography (CT) brain scan did not reveal any pathologic findings. During the next hours the patient showed atactic movements and abnormal extensions. Progression of neurologic symptoms resulted in coma, but a repeat CT scan of the brain was still normal. Generalized seizures occurred, and the patient became hypertensive (the systolic blood pressure was 230 mmHg). By the morning of the next day, the pupils were dilated and unreactive. Another CT revealed severe cerebral edema. On day 3, angiography showed loss of cerebral perfusion. Laboratory parameters at that time were as follows: ALT was 154 U/l; AST, 32 U/l; total bilirubin, 1.3 mg/dl; alkaline phosphatase, 65 U/l; γ-glutamyl transpeptidase, 15 U/l; and PT, 46%. After documentation of brain death, the organs were harvested for transplantation.

A short case report of the liver graft recipient has been published elsewhere [14]. The recipient was a 65-year-old woman with post-hepatitis-C liver cirrhosis and hepatocellular carcinoma. Orthotopic liver transplantation was unremarkable. Total allograft ischemia time was 6 h. Postoperatively, in the intensive care unit, the patient was hemodynamically stable and was intubated and mechanically ventilated. Serum levels of liver enzymes were extremely high, indicating severe ischemic damage. But no obvious cause was found for this marked hepatocellular injury. However, transaminases decreased over the following days (Fig. 1 a). The immunosuppressive regimen included tacrolimus and prednisolone. The patient was extubated on the first postoperative day and initially did well. Doppler ultrasound examination and indocyanine green clearance measurements [9, 10] confirmed normal hepatic perfusion and function. On day 3, the patient's condition deteriorated. She complained of nausea and became somnolent soon after. A CT scan of the brain did not show any abnormalities. Subsequently, the patient became comatose and developed status epilepticus. A repeat CT revealed severe brain edema. Plasma ammonia was markedly elevated (3793 µmol/l, normal: < 50 µmol/l), while transaminases and lactate dehydrogenase were still decreasing and prothrombin activity remained stable (Fig. 1 a,b). Doppler ultrasound examination revealed normal hepatic arterial and portal venous blood flow. The indocyanine green plasma disappearance rate was approximately 20% (normal range: 20–30%), suggesting adequate graft perfusion and function [9, 10]. The plasma level of ammonia was reduced by continuous hemofiltration (1513 µmol/l on day 5, 199 µmol/l on day 6), but the patient's condition deteriorated further. To support arterial blood pressure and cerebral perfusion, norepinephrine was infused at increasingly higher doses. Ventilatory support increased, and the patient was ventilated with 100% oxygen. Multiorgan failure developed, and on day 5 a severe acidosis was present (lactate = 18 mg/dl, pH = 6.99). The patient died on day 6 after transplantation.

The isolated finding of high plasma ammonia levels suggested a urea cycle defect, and we hypothesized that a genetically OTC-deficient liver had been transplanted. On day 6, urine and blood of the liver transplant recipient were analyzed for OTC deficiency. Urinary orotate excretion was 3500 mmol/mol creatinine (normal: < 10), whereas plasma citrulline was undetectable. This constellation is typical in OTC-deficient patients [3, 6, 15, 18]. Immediately after the recipient's death, a biopsy of the transplanted liver was performed to confirm the diagnosis. OTC activity was about 10% of the normal, whereas other enzymes of the urea cycle (carbamyl phosphate synthetase, argininosuccinate synthetase) showed normal activity. Molecular analysis of the liver specimen demonstrated a point mutation in exon 2 at codon 40 of the OTC gene (CGT to CAT, resulting in a change from arginine to histidine), which is a characteristic mutation in patients with late-onset OTC deficiency [18]. This finding proved that a genetically OTC-deficient liver had been transplanted. Subsequent investigation of the donor's family showed the same mutation of the OTC gene for the donor's mother. The family history demonstrated that a maternal uncle and another male relative had already died of cerebral edema of unknown origin.

In contrast to the unfavorable course of the liver graft recipient, OTC deficiency of the donor did not affect the outcome of patients that had received kidneys, lungs, and heart. These recipients all survived the early postoperative period and could be discharged from the hospital. Ten months after transplantation, the patients that had received kidneys, lungs, and heart were alive and showed good graft function (Table 1).

Discussion

The frequency of all urea cycle disorders is approximately 1 of 8000 newborns, and OTC deficiency is the most common [3, 15]. OTC deficiency is an X-chromosome-linked disorder, whereas the other four deficiences are inherited as autosomal recessive traits [3]. The clinical presentation of patients with urea cycle dis-

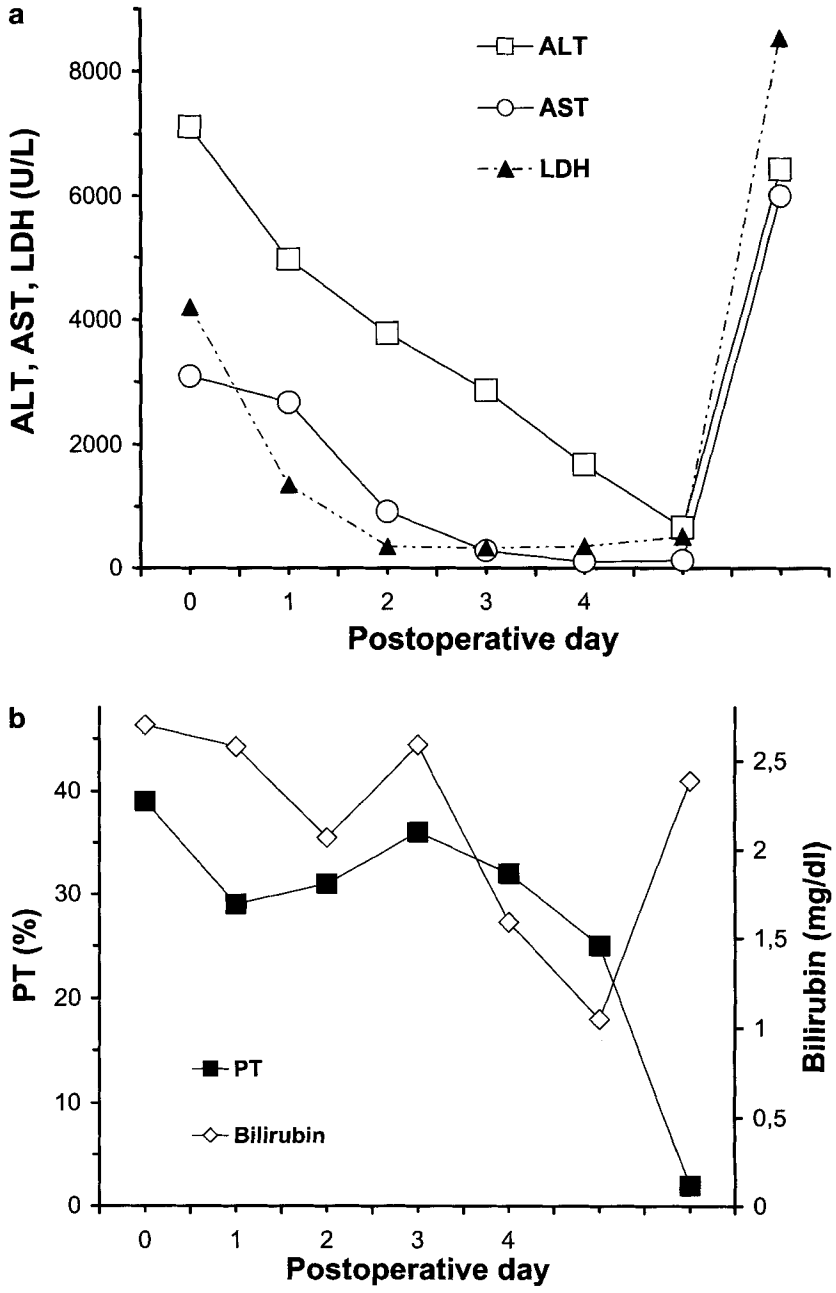

Fig. 1 **a** Serum levels of alanine aminotransferase (*ALT*), aspartate aminotransferase (*AST*), and lactate dehydrogenase (*LDH*) following liver transplantation. **b** Prothrombin activity (*PT*) (*left y-axis*) and total bilirubin levels (*right y-axis*) following liver transplantation

orders is very similar and is related to hyperammonemia, causing nausea, vomiting, lethargy, and coma [3]. The clinical manifestations may appear in the neonatal period (neonatal onset), or any time thereafter (late onset) with varying degrees of severity. Although OTC deficiency is an X-linked disorder, 15–20% of female carriers become symptomatic, depending on the proportion of the hepatocytes in which the normal or the mutant allele is on the activated X-chromosome [3, 13]. Symptomatic female carriers exhibit the same symptoms as affected male patients. In patients with urea cycle disorders of late onset, episodes of hyperammonemia may be triggered by infection, stress, protein overload, or drugs, although, not infrequently, they occur for no obvious reason [3, 15]. The major symptoms of these episodes include vomiting, an abnormal mental status as manifested by lethargy, somnolence often progressing to coma, irritability, agitation, disorientation, ataxia, and seizures [3, 15]. The milder episodes will often abate with cessation of protein intake, and many of these patients select a low-protein diet. Increased blood ammonia levels are diagnostic for this disorder. Impor-

Table 1 Outcome of kidney, lung, and heart recipients 10 months after transplantation (*TX* transplantation, *RTX* renal transplantation, *SLTX* single lung transplantation, *HTX* heart transplantation, *CREA* serum creatinine, *BUN* blood urea nitrogen, CL_{CREA} creatinine clearance, *VC* vital capacity [percentage of the predicted value], *FEV1* forced expiratory volume in 1 s [percentage of the predicted value], *EF* ejection fraction, *PFR* peak filling rate [end diastolic volume/s])

Recipient			TX	General condition	Parameters of graft function
Age (years)	Sex (male/female)	Indication for TX			
44	m	Renal insufficiency of unknown origin	RTX	Good	CREA = 1.4 mg/dl, BUN = 16 mg/dl, CL_{CREA} = 153 ml/min
34	m	Glomerulonephritis	RTX	Good	CREA = 1.5 mg/dl, BUN = 22 mg/dl, CL_{CREA} = 78 ml/min
45	m	Pulmonary fibrosis	SLTX	Good No dyspnea	VC = 3.56 l (71 %), FEV1 = 3.0 l (73 %)
54	m	Obstructive lung disease	SLTX	Good	VC = 3.23 l (83 %), FEV1 = 1.94 l (64 %)
48	m	Dilative cardiomyopathy	HTX	Good No dyspnea	Echocardiography: good global left and right ventricular function, EF > 50 %, PFR = 5.9 EDV/s

tantly, liver function, particularly synthetic function, is normal, although increased transaminase levels are not uncommon during episodes of hyperammonemia [3]. Characteristic patterns of plasma amino acids and the determination of orotic acid in the urine (extremely elevated in OTC deficiency) mostly discriminate the individual disorders of the urea cycle [3, 15]. Further diagnostic steps include liver or skin biopsy for measurement of enzyme activity and molecular genetic studies [3, 12].

The classic form of OTC deficiency with neonatal onset is generally well recognized, but diagnostic delay and error are common with late-onset forms [3, 5, 6]. Although typical symptoms of OTC deficiency were present in the donor, an acute metabolic disease was not suspected and blood ammonia was not measured. His neurologic symptoms and the slightly elevated transaminases were thought to be the result of his abuse of anabolic steroids. There are some rare reports in the literature in which cerebrovascular accidents were associated with anabolic steroid use [1]. However, the family history with two male relatives who had died of coma of unknown origin would have given an important indication of a hereditary metabolic disease. Although the donor's cause of death remained obscure, the organs were harvested for transplantation.

In contrast to the donor, in the case of the recipient the clinical presentation of OTC deficiency was confounded by the specific situation after liver transplantation. The acute onset of neurologic symptoms and the rapid development of coma in the recipient were initially thought by the consulted neurologist to be of cerebrovascular origin. It was also speculated whether tacrolimus, which was used for immunosuppression, might be the cause [11]. Primarily, hepatic coma was not considered because laboratory values and diagnostic tests indicated adequate postoperative liver function. Therefore, the high ammonia levels seemed to be inexplicable since, after liver transplantation, significant rises in ammonia levels are usually accompanied by poor liver function and dysfunction of other organ systems: elevated transaminases, coagulopathy, increased glucose requirements, metabolic acidosis, renal failure, and hemodynamic instability [4, 7, 9]. But in this case, transaminases were decreasing, no clotting factor support was necessary, and tests for hepatic perfusion and function were normal. The high ammonia levels could therefore not be related to general graft dysfunction. Re-evaluation of the donor's medical history and the fact that two male relatives had died of coma of unknown origin made us suspect late-onset OTC deficiency. This was supported by the high values for urinary orotate excretion measured on day 6 [3, 6, 18]. Hyperammonemic coma as a rare complication in the early postoperative period has been reported in two patients after lung transplantation [17] and one patient after heart-lung transplantation [2]. But in these three patients, orotic acid in the urine was normal and hyperammonemia was not related to an inherited disease [2, 17]. In the present case, further enzymatic and molecular tests established the diagnosis of OTC deficiency and proved that an OTC-deficient liver had been transplanted.

Successful transplantation requires a selection of healthy organs. One major implication of this case is the importance of careful donor evaluation, which should include the donor's family history to avoid the transmission of hereditary diseases [8]. In the case of potential donors with brain death of unclear origin, maximum efforts are required to establish the diagnosis, for which blood ammonia determinations should be per-

formed. Whether the cause of brain death must be fully established in the context of scarcity of transplantable organs remains a point of discussion. However, as late-onset forms of urea cycle disorders are not necessarily manifest at the time of death, and as brain death might be due to other causes, e.g., head injury, these diseases remain a potential hazard for liver transplantation.

Although OTC principally plays its most important role in the mitochondria of the hepatocytes, it is also expressed in other organs as well. OTC activity in the gut epithelium is approximately 20% of that in the normal liver, but in other tissues (e.g., kidneys) activity is only at trace levels [3, 16]. Liver transplantation is known to be an effective treatment for patients with OTC deficiency and other urea cycle disorders [19]. Although these patients have an abnormal metabolism after liver replacement, most importantly in the intestinal mucosa and the kidney, this seems to have little clinical importance [19]. This explains why the transplantation of kidneys, lungs, and heart from a donor with OTC deficiency was successful. Ten months after transplantation, these recipients were still alive and in good general condition. OTC deficiency of their grafts did not result in impaired graft function. This is the first report documenting that kidney, lung, and heart transplantation from a donor with OTC deficiency can be successful. Whether the long-term outcome might be adversely affected by transmitted enzyme deficiency remains to be evaluated.

Summary

In patients with urea cycle disorders and later symptom onset, diagnostic error is not uncommon. They can die of hyperammonemic coma already during the initial presentation of the illness. Therefore, in all patients with coma of unknown origin, an acute metabolic disease has to be considered and plasma ammonia must be determined. If the underlying disease remains unrecognized, it can become even more dramatic if such patients are considered as potential liver transplant donors. In order to prevent the inadvertent transplantation of organs with genetic defects, it is essential to obtain a careful donor history. OTC deficiency of the donor is a clear contraindication for liver transplantation. In contrast, kidney, lung, and heart transplantation can be safely performed as these organs are not affected by the disease.

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