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LETTER TO THE EDITORS

Outcome of kidney transplantation in type I oral-facial-digital syndrome

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Type I oral-facial-digital syndrome (OFDI) is characterized by malformations of the face, the oral cavity and the fingers. The inheritance pattern is X-linked dominant, with male lethality [1–3]. In addition to typical malformations, OFDI is associated in 48% of cases with cerebral abnormalities, sometimes responsible for mental retardation, usually mild, and seizures [4,5]. Polycystic kidney disease (PKD) is present in 40–69% of OFDI patients after the age of 18 [6–8]. PKD leads to end-stage renal disease (ESRD) in 82% of cases, with a median age of 36 years (range 11–70 years) [6–9]. The outcome of OFDI patients after renal transplantation (RT) has never been specifically examined.

We report on our experience with five OFDI women who received a kidney transplant at the age of 22–53 years. They had reached ESRD at an age ranging from 22 to 51 years. Four of them were treated with an erythropoietin-stimulating agent before RT. This cohort represents a cumulative post-transplant follow-up of 34 years. The disease-causing mutation in *OFD1* gene was identified in four out of five patients, which is in line with the 67% detection level recently reported in a French-Belgian cohort of 25 patients with OFDI [2].

Table 1 summarizes pertinent clinical features. Mild mental retardation was present in two patients. *Patient 1* was living in an institution for disabled persons; she had a history of seizures with *corpus callosum* and cerebellar vermian agenesis. *Patient 2* had suffered seizures and psychiatric disorders in childhood with *corpus callosum* agenesis.

Donor type and immunosuppressive regimen are described in Table 1. All patients still had at least one native polycystic kidney at the time of RT.

One patient died from colon adenocarcinoma 8 years after RT, at the age of 59, with a well-functioning kidney graft, while the four other patients are currently alive 11–177 months after RT.

Three patients are currently rejection-free, whereas the two others experienced an acute cellular rejection episode. This occurred 10 days after RT in *Patient 2* and was successfully treated with anti-CD2 monoclonal antibody. Serum creatinine levels (SCr) at discharge was 1.3 mg/dl (115 μmol/l). An acute cellular rejection episode also occurred 3 years after RT in *Patient 3*, soon after the introduction of primidone treatment and was probably triggered by a lower tacrolimus level induced by an interaction between the two drugs. This highlights the importance of close drug-level monitoring whenever antiepileptic agents are introduced or withdrawn in RT recipients.

Regarding the potential complications related to polycystic kidneys, only a single episode of probable intracystic hemorrhage or infection in the native kidney occurred in *Patient 3* early after RT. She presented with fever and right loin pain 2 months after RT. Although magnetic resonance imaging (MRI) did not reveal any sign of infection, levofloxacin treatment was initiated, with prompt resolution of fever. Remarkably, no mention of complications related to kidney cysts in OFDI patients can be found in the literature. The generally smaller size of cysts as compared with autosomal dominant PKD (ADPKD) might explain this apparently lower propensity to complications [10].

The mild mental retardation present in two of our patients did not impair post-RT outcome. Both of them had sufficient cognitive ability to comply with the need for life-long immunosuppression and medical follow-up [11,12]. As recently reported, even with a more severe intellectual disability, RT offers significant advantages when compared with the need of regular dialysis [13].

A serious post-RT complication occurred in *Patient 4*. One year after RT, Caroli's disease was suspected on the basis of an increase in gamma-glutamyl transferase levels associated with a saccular dilation of intrahepatic bile ducts on MRI. Five years after RT, the patient presented with a severe sepsis caused by a cholangitis secondary to choledochal obstruction in the context of Caroli's disease. Though Caroli's disease is not listed in the manifestations of OFDI, there are strong arguments to consider this association as not fortuitous. First, the OFD1 protein is a ciliary protein that is also present on the surface of the cholangiocytes [14]. Second, a previous case of Caroli's disease in a 20-year-old girl with the OFDI syndrome has been reported [15]. Third, Caroli's disease is a very rare

Table 1. Clinical characteristics and post-RT course in five OFDI patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Head					
Facial dysmorphism	+	–	–	–	+
Hypertelorism	+	–	+	–	+
Tooth abnormalities	+	–	–	+	–
Oral cavity					
Cleft palate	–	+	–	+	+
Pseudocleft of the upper lip	–	–	+	–	+
Bifid tongue	+	–	+	–	–
Lingual hamartoma	–	+	–	+	–
Extremities					
Syndactyly	–	–	+	–	–
Brachydactyly	+	+	–	+	+
Clinodactyly	–	+	–	–	+
Polydactyly	+	–	–	–	–
CNS					
Corpus callosum agenesis	+	+	ND	–	–
Cerebellar vermian agenesis	+	–	ND	–	–
Mental retardation	+	+	–	–	–
Epilepsy	+	+	–	–	–
Polycystic kidney disease (echography)	+	+	+	+	+
OFD1 testing					
DNA level	c.895_896insGA	c.1655-?_(*3292-?)del	No change detected	c.1099C>T	c.1103_1106delTGAT
Protein level	p.Arg899fsX4	RNA processing defect		p.R367X	p.L368fsX18
Kidney donor (L,D)	D	D	L	D	L
Immunosuppressive regimen	T,M,P	C,A,P	T,M,P	T,M,P	C,A,P → T,M
Acute rejection	None	1	1	None	None
Last follow-up (months since RT)	Alive, 67 months	Deceased, 96 months	Alive, 56 months	Alive, 11 months	Alive, 177 months
Scr (mg/dl–μmol/l)	0.7–62	1.6–141	3.1–274	1.5–133	1.14–101

CNS (central nervous system) defects evaluated by either CT (computed tomography) or MRI (magnetic resonance imaging); ND, not done; L, living; D, deceased; T, tacrolimus; M, mycophenolate mofetil; P, prednisolone; C, cyclosporine; A, azathioprine; → , followed by.

disorder and a still more rarely isolated entity, making a fortuitous association very unlikely. Taken together, these findings support the existence of a true association between Caroli's disease and OFDI, the prevalence of which is unknown. We therefore recommend screening patients with OFDI who are candidates for RT for associated biliary dysgenesis.

In conclusion, RT is an excellent therapeutic option for OFDI patients with ESRD. Cystic kidneys usually remain asymptomatic. Mental retardation does not preclude RT in our experience. Attention should be paid to the potential interaction of antiepileptic drugs with calcineurin inhibitors. Pretransplant work-up should include screening for an associated biliary dysgenesis.

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Delphine Halleux,[1] Karin Dahan,[2]
Christel Thauvin-Robinet,[3] Bernard Aral,[4]
Claire Pouteil-Noble,[5] Olivier Devuyst[1]
and Yves Pirson[1]
1 Division of Nephrology,
Cliniques Universitaires St-Luc,
Université Catholique de Louvain, Brussels, Belgium
2 Division of Genetics,
Cliniques Universitaires St-Luc,
Université Catholique de Louvain,
Brussels, Belgium

3 Centre de Référence Maladies Rares, Anomalies du Développement et Syndromes Malformatifs, de la Région Grand-Est, Centre de Génétique, Hôpital d'Enfants, Centre Hospitalier Universitaire, Dijon, France
4 Laboratoire de Génétique Moléculaire, Plateau Technique de Biologie, Centre Hospitalier Universitaire, Dijon, France
5 Division of Nephrology, Dialysis, and Transplantation, Centre Hospitalier Lyon Sud, Pierre Bénite, France

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