TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Maturity onset diabetes of the young: clinical characteristics and outcome after kidney and pancreas transplantation in MODY3 and RCAD patients: a single center experience

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Keywords
maturity-onset diabetes of the young, renal cysts, terminal renal failure, transplantation.

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Conflicts of Interest
The authors have declared no conflicts of interest.

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Received: 15 May 2011
Revised requested: 9 July 2011
Accepted: 13 February 2012
Published online: 21 March 2012

doi:10.1111/j.1432-2277.2012.01458.x

Summary

The diabetes and renal phenotype of patients with maturity-onset diabetes of the young (MODY) on a transplantation waiting list is not known; neither is their outcome after pancreas (PT) and/or kidney transplantation (KT). Between 2002 and 2009, we screened 50 of 150 patients referred for kidney and pancreas transplantation to the Kremlin-Bicêtre center for *HNF1B* and *HNF1A* mutations if one or more of the following criteria was present (i) an atypical history of diabetes (ii) diabetes with at least one affected parent or two affected relatives, (iii) an absence of auto-antibodies at diagnosis (iv) a persistent secretion of fasting C peptide (v) a personal or a family history of renal cysts or dysplasia. Their phenotype and their outcome were analyzed. Four *HNF1A* (MODY3) and eight *HNF1B* mutations [renal cysts and diabetes (RCAD)] were identified. All MODY3 patients had diabetic nephropathy, but only 50% of RCAD patients. Four patients underwent a kidney and pancreas transplantation and two a kidney transplant alone. After 4.1 ± 1.1 years of follow-up, 83% of patients still have a functioning kidney and 75% a functioning pancreas. PT can be proposed with good results for MODY3 and RCAD patients.

Introduction

Maturity-onset diabetes of the young (MODY) belongs to the monogenic β-cell autosomal-dominant non-ketotic diabetes mellitus (DM) group. MODY usually occurs before the age of 25 in non-obese children or young adults, and accounts for 1 to 2% of all cases of diabetes in industrialized countries [1]. To date, six different genes responsible for MODY have been identified [2–7].

MODY 3 diabetes is associated with a progressive decrease in insulin secretion. Two-thirds of patients need treatment with oral hypoglycemic drugs (OHD) or insulin [8–10]. MODY5 related mutations (also called renal cysts and diabetes, RCAD) generate diabetes in only 50%

of patients;[11] with most of them necessitating insulin [12]. Although simultaneous pancreas and kidney transplantation (SPK) is classically performed during type-1 DM because of a benefit in survival especially in young patients [13], it could be an option for MODY patients with combined terminal renal failure and insulin-dependent diabetes. However, such transplantations have not yet been studied, except in one isolated case-report for a MODY3 patient [14].

Among the mutations responsible for MODY, only *HNF1A* (responsible for MODY3) and *HNF1B* (MODY5 or RCAD) molecular defects have been associated with a specific renal phenotype independently of diabetic nephropathy. HNF1A and HNF1B are both homeodomain transcription factors playing a role in liver, pancreas and kidney development [15] and are both expressed in the pancreas and kidneys in adults [16–18]. In *HNF1B* mutations, the renal phenotype typically precedes the development of DM [11]. The prominent feature of the renal phenotype in *HNF1B* mutations explains why this disease is now called RCAD instead of MODY5. Renal cysts [19], familial hypoplastic glomerulocystic kidney disease [20], renal malformations (for example, single and horseshoe kidney) [21], and atypical familial hyperuricemic nephropathy [22] are among the most frequent renal anomalies observed during *HNF1B* mutations. Renal malformations have also been described in MODY3 patients [23], although very infrequently. Terminal renal failure can occur in MODY3 and RCAD patients, but has been poorly documented so far. Whether terminal renal failure occurs more often as a consequence of a diabetic nephropathy, or of kidney malformations or cystic disease, still remains unknown, especially during RCAD.

Herein, we describe the clinical characteristics and renal phenotypes of the patients on our transplantation waiting list with MODY3 and RCAD. We also present the outcome of kidney transplantation (KT) and pancreas transplantation (PT) or simultaneous pancreas and kidney transplantation (SPK) in six adult patients with MODY3 or RCAD.

Patients and methods

Between 2002 and 2009, out of 150 patients referred for kidney and pancreas transplantation in the Kremlin-Bicêtre hospital center, we identified 50 who had possible β-cell monogenic diabetes. They presented with at least one of the following criteria: (i) an atypical history of diabetes: i.e. beginning of noninsulin dependent diabetes before the age of 35 years, (ii) and/or diabetes with at least one affected parent or two affected relatives, (iii) and/or an absence of auto-antibodies at diagnosis when available and/or (iv) a persistent secretion of fasting C peptide (v) and/or a personal or a family history of kidney disease (i.e. renal cysts or renal agenesis or dysplasia). We also identified one non diabetic patient with familial nephropathy with cysts and a strong family history of diabetes resembling ß cell monogenic diabetes. Informed written consent was obtained from all patients and the study was conducted according the to the Declaration of Helsinky principles. A search for *HNF1A* and *HNF1B* mutations was carried out as these represent the most common mutations involved in monogenic diabetes associated with morphological and/or functional renal defects in adult patients [10]. We then carried out a retrospective single-center case-report study on the patients who were identified with either MODY3 or RCAD. We also describe the characteristics of the 39 patients screened for these mutations but who turned out to be negative as well as the 76 patients out of the 99 who were not screened for whom sufficient data and follow-up were available. However, the outcomes after KT, PT or SPK were assessed only in MODY3 and RCAD patients. Estimated GFR was performed using the simplified MDRD formula.

Molecular diagnosis

The search for molecular events was performed on genomic DNA extracted from peripheral lymphocytes. The 10 exons and flanking exon-intron junctions of *HNF1A* were screened by sequence analysis. A search for large rearrangements and mutations in *HNF1B* was then performed. Screening for large rearrangements was performed by a quantitative multiplex polymerase chain-reaction as previously described [24]. The nine exons of *HNF1B* were screened by sequence analysis [24].

The mutation nomenclature is based on the reference sequences NM_000545.5 for *HNF1A* and NM_000458.2 for *HNF1B*. Variant validation was based on bio-informational analysis using Alamut software v1.5 (Intercative Biosoftware, San Diego, CA, USA) and the exclusion of 320 geographically matched control chromosomes.

Statistical analyses

Results are expressed as mean ± SDs and frequencies (%). Frequencies were compared using the Yates corrected chi-square test or the Fischer chi-square test. Continuous variables were compared using the Mann–Whitney test. $P < 0.05$ was considered statistically significant.

Results

Mutation characteristics (Table 1)

Four patients had *HNF1A* mutations and eight had *HNF1B* defects; among these, two had recurrent whole-gene deletions [24]. The mutations identified are

Table 1. Origin and genotype of the patients.

Gene		Nucleotide change	Protein effect	Genetic Status	Reference
HNF1B	Exon 2	c.374T>C	p.Ile125Thr	de novo	This report
HNF1B	Exon 3	p.R235Q	c.704G>A; p.R235Q	autosomal dominant	Bellanne-Chantelot *et al.*, [24]
HNF1B	Intron 2	c.544 + 1_544 + 4del	unknown	autosomal dominant	This report
HNF1B	Exon 2	c.517G>A	p.Val173Ile	unknown	This report
HNF1B	Exon 5	c.1108G>A	p.Gly370Ser	autosomal dominant	Bellanne-Chantelot *et al.*, [24]
HNF1B	Exons 1-10	c.1-?_1671 + ?del	heterozygous whole gene deletion	unknown	Bellanne-Chantelot *et al.*, [24]
HNF1B	Exon 3	c.698G>A	p.Arg233His	unknown	This report
HNF1B	Exons 1-10	c.1-?_1671 + ?del	heterozygous whole gene deletion	unknown	Bellanne-Chantelot *et al.*, [24]
HNF1A	Exon 4	c.827C>G	p.Ala276Gly		Bellanne-Chantelot *et al.*, [40]
HNF1A	Exon 1	c.82C>T	p.Gln28X	autosomal dominant	Bellanne-Chantelot *et al.* [40]
HNF1A	Exon 4	c.872dupC	p.Gly292fs	unknown	Yamagata *et al.*, [3]
HNF1A	Exon 9	c.1637A>G	p.Asp546Gly	unknown	Bellanne-Chantelot *et al.*, [40]

described in Table 1. Amongst the mutations were four *HNF1B* mutations that have not been reported before. One was a 4-base-pair deletion that affects the donor splicing site of exon 2, which is a hot spot for mutations in *HNF1B*. Four other different mutations have already been reported at this splice site [25]. The other three mutations were nucleotide substitutions, leading to amino acid substitutions (p.Ile125Thr, p.Val173Ile and p.Arg233His) located in the DNA-binding domain. The affected residues are highly conserved between species and were absent from a geographically matched control population of 160 subjects.

Patients characteristics

Eight patients were diagnosed with RCAD and four with MODY3. A total of 39 screened patients were negative for both *HNF1A* and *HNF1B* mutations. A search for other MODY mutations was performed for four of them (MODY2 and MODY1) but was negative. A wider screening of these mutations is still underway for some of the patients.

Characteristics of the 39 patients negative for HNF1A and HNF1B mutations (Table 2a)

Among the 39 screened negative patients, 7 are deceased while on the waiting list, 12 received a kidney transplant and all of them still have a functioning graft at the last follow-up. The other 20 patients are still on our kidney waiting list but not on our pancreas waiting list as they were considered to have type 2 diabetes. Compared with the 76 nonscreened patients on our kidney and pancreas waiting list (i.e. with typical type 1 diabetes), they have a significantly higher number of proband with diabetes ($P < 0.001$), they were older when diabetes occurred ($P < 0.001$) and they have an elevated level of C-peptide (5.6 ± 3.8 ng/ml vs. 0.47 ± 0.43 ng/ml, $P < 0.0001$)

Characteristics of RCAD patients (Table 2a and b)

RCAD patients were aged 48 ± 14 years, with a female to male ratio of 6:2.

Diabetes history

Among the eight patients with *HNF1B* mutations, all but two had a family history of diabetes. All patients but one developed DM at a mean age of 30 ± 14 years. Their mean body-mass index (BMI) at the time of the diabetes discovery was 21 ± 3 (kg/m^2), which was significantly lower than MODY3 and the screened negative patients ($P < 0.05$). Antidiabetic treatment was OHD for two patients, OHD then insulin for four patients, and insulin straight away for one patient. One patient had no DM, and presented with end-stage renal disease (ESRD) and a family history of cystic kidney disease and diabetes. Among the seven diabetic patients, six had microangiopathy and one had macroangiopathy. Their mean fasting C peptide level was 2.7 ± 1.5 ng/ml (normal level between 1.1 and 3.5 ng/ml) before PT which are values incompatible with type 1 DM and significantly lower then the 39 screened negative patients and MODY3 patients. All RCAD patients with insulin dependent DM are on our kidney and pancreas waiting list ($n = 3$) or have been transplanted ($n = 2$). The remaining patients (diabetes treated with OHD alone or not diabetic) are on our kidney transplantation waiting list ($n = 1$) or received a K transplant ($n = 2$).

Renal phenotype (Table 2b)

Three of the eight patients had a family history of renal failure. Only three patients had renal cysts, and three patients had renal dysplasia. Cysts were found in the

Table 2. (a) Diabetes characteristics and renal phenotype. (b) Renal phenotypes.

(a)

	MODY 3	RCAD	Screened (negative)	Not screened
Number of patients	**4**	**8**	**39**	**76**
Current age (years) ±SD	50 ± 7	48 ± 14	51 ± 9	46 ± 10
Number of probands with diabetes	3.2 ± 0.5	1.8 ± 1.3	2.0 ± 1.4	0.6 ± 1.0*
Sex ratio (female/male)	1/2	6/2	17/22	27/49
Age at diagnosis of diabetes	23 ± 6	30 ± 14	30 ± 11	15 ± 7*
BMI at diagnosis (kg/m2)	27 ± 7	21 ± 3***	26 ± 6	23 ± 4
Peptide C (ng/ml)	7.0 ± 7.5	3.3 ± 1.6***	5.6 ± 3.8	0.29 ± 0.41
HbA1c (%)	6.5 ± 0.9	7.8 ± 1.2	7.2 ± 1.2	8.2 ± 1.4
Diabetes treatment :				
Initial insulin therapy	1/4 (25%)	1/8 (12.5%)	10/31 (32%)	63/65 (97%)*
OHD before insulin therapy	3/4 (75%)	4/8 (50%)	17/31 (54%)	2/65 (3%)*
OHD alone	0	2/8 (25%)	3/31 (9%)	0/65
Nondiabetic	0	1/8 (12.5%)	1/31 (3%)	0/65
Microangiopathy	4/4 (100%)	6/8 (75%)	31/32 (97%)	69/71 (97%)
Macroangiopathy	0/4**	1/8 (25%)	16/33 (48%)	18/71 (25%)
Elevated liver enzymes	0/4	5/8 (62%)***	4/33 (12%)	0
Delay between diabetes and ESRD (years ± SD)	27 ± 3	16 ± 10	16 ± 7	24 ± 8
Cause of terminal renal failure :				
Diabetic nephropathy	4/4 (100%)	4/8 (50%)	27/39 (69%)	43/76 (56%)
Nephroangiosclerosis	0	0	2/39 (5%)	1/76 (1.3%)
Renal Dysplasia	0	3/8 (37%)	2/39 (5%)	2/76 (2.6%)
Chronic or acute interstitial nephropathy	0	1/8 (12.5%)	1/39 (2.5%)	1/76 (1.3%)
IgA nephropathy	0	0	1/39 (2.5%)	1/76 (1.3%)
Unknown	0	0	6/39 (15%)	28/76 (37%)
Renal cysts	0/4	3/8 (37%)	4/39 (10%)	4/41 (9%)

(b)

	Sex	Age		Cysts	Diabetic nephropathy	Renal dysplasia	Interstitial nephropathy
Patient 1	M	54	MODY 3	0	+	0	0
Patient 2	F	39	MODY 3	0	+	0	0
Patient 3	M	53	MODY 3	0	+	0	0
Patient 4	F	56	MODY 3	0	+	0	0
Patient 5	F	33	RCAD	0	0	+	0
Patient 6	F	57	RCAD	0	+	0	0
Patient 7	M	34	RCAD	+	0 (nondiabetic)	+	0
Patient 8	F	51	RCAD	+	+	0	0
Patient 9	F	67	RCAD	0	0	0	+
Patient 10	F	56	RCAD	+	0	+	0
Patient 11	M	64	RCAD	0	+	0	0
Patient 12	F	31	RCAD	0	+	0	0

*P < 0,001 vs. MODY 3, RCAD, Screened negative.

**P < 0,01 vs. RCAD, Screened negative and Not screened.

***P < 0,05 vs. MODY 3, Scrrened negative.

ESRD, end-stage renal disease; MODY, maturity-onset diabetes of the young; OHD, oral hypoglycemic drugs; RCAD, renal cysts and diabetes.

cortex of hypoplastic kidneys in two patients, and less than three cortical cysts were found in each normal-sized kidney of the third one.

Thus, three of the eight patients developed ESRD as a consequence of renal hypoplasia at a mean age of 34 ± 16 years and relatively few cysts were found at the time of terminal renal failure. Four out of 8 patients did not have cysts or dysplasia: among these patients, one of them had biopsy proven chronic tubulo-interstitial nephritis (without any tubular dilatation), and 3 had

diabetic nephropathy, biopsy proven in one of them. A total of four out of 8 patients had a renal phenotype that evoked diabetic nephropathy (i.e. massive proteinuria without haematuria, with enlarged kidneys as determined by ultrasonography and was associated with diabetic retinopathy after a long history of diabetes) biopsy proven in one case. One patient with diabetic nephropathy had cysts in both of his normal-sized kidneys despite terminal renal failure. ESRD secondary to diabetic nephropathy occurred at a mean age of 46 ± 12 years. The delay between the discovery of diabetes and terminal renal failure was 20 ± 11 years.

In addition, one patient developed urolithiasis without overt renal malformations.

Extra-renal anomalies

Among patients with *HNF1B* mutations, four patients had elevated liver-enzyme levels. There were also incidences of unexplained pancreatitis ($n = 2$). None of our patients had a history of gout. No patient presented with genital malformations.

Relationship between genotype and phenotype

Both patients who had a complete *HNF1B* deletion did not have an early onset of DM (49 and 20 years old) and their DM was well controlled with OHD at first. One patient had terminal diabetic nephropathy and the other terminal renal failure as a consequence of renal dysplasia. Both patients presented with elevated liver-enzyme levels.

Characteristics of MODY 3 patients (Table 2a)

These patients were aged 49 ± 7 years (median 52), with a female to male ratio of 2:2.

Diabetes history

All four MODY3 patients developed DM at a mean age of 23 ± 7 years. They all had a family history of DM, with a mean of three affected relatives. Their mean BMI at the time of diabetes diagnosis was 27 ± 7 (kg/m^2), which is significantly higher then RCAD patients and typical type 1 patients. C peptide levels revealed values incompatible with type-1 diabetes, i.e. 7.0 ± 5.3 ng/ml. The antidiabetic treatment was OHD, then insulin for three patients, and insulin straight away for one patient. All patients had microangiopathy and none had macroangiopathy.

Renal phenotype

All patients had suspected diabetic nephropathy (heavy proteinuria without hematuria and enlarged kidneys), which was biopsy-proven in one case. Terminal renal failure occurred 27 ± 3 years after the diagnosis of diabetes at a mean age of 48 ± 3 years. None of these patients had renal cysts. One MODY3 patient had urolithiasis without any obvious renal malformations.

Transplantation procedures (Table 3)

Six of our twelve patients were transplanted, two died while waiting for transplantation from a sudden cardiac arrest of unknown cause, and four patients are still on a waiting-list for transplantation. Amongst the six transplant patients, three had a SPK, one had sequential KT then a PT 4 months later, and two patients had a KT only from deceased donors.

Outcome of transplantations (Table 4)

Patient- and graft-survival rates

The mean follow-up time for these patients was 4.1 ± 1 years (Table 4). All patients survived. The number of kidney and pancreas graft survivals at 4 years was, respectively, five out of six and three out of four. One patient lost both kidney and pancreas grafts as a consequence of acute rejection.

Table 3. Transplantation conditions.

	MODY 3	RCAD	Total
Number of transplant patients	2 (SPK)	4(1 SPK, 1 KT → P, 2KT)	6
Number of HLA mismatches	4 ± 0	3.2 ± 1.7	3.5 ± 1.3
Donor age (years ± SD)	28 ± 9	40 ± 15	36 ± 13
Cold ischemia time of kidney (h ± SD)	12 ± 1	17 ± 7	15 ± 6
Induction therapy	Thymoglobulin (2/2)	Thymoglobulin (3/4). Basiliximab (K 1/4)	
Presence of delayed graft function	0/2	1/4	1/6
Initial immunosuppressive treatment	FK, MMF, Cs (1 early steroid withdrawal)	FK, MMF, Cs (2 early steroid withdrawal)	

Cs, corticosteroids; FK, tacrolimus; KT, kidney transplantation; MMF, mycophenolate mofetil; MODY, maturity-onset diabetes of the young; PT, pancreas transplantation; RCAD, renal cysts and diabetes; SPK, simultaneous pancreas and kidney transplantation.

Table 4. Transplantation outcome.

Number of pancreas transplantations	MODY 3 2	RCAD 2	Total 4
Length of follow-up (years)	5.1 ± 1.6	4.4 ± 1.2	4.3 ± 1.1
Pretransplant treatment	Insulin (2/2)	Insulin(2/2)	
HbA1c pre-transplant	6.5 ± 0.9	8.3 ± 1.6	7.4 ± 1.5
HbA1c 6 months	5.3 ± 0.3	5.5 ± 0.5	5.4 ± 0.3
HbA1c 1 year	5.6 ± 1	6.5 ± 1.4	6.1 ± 1.1
HbA1c 2 years	5.4 ± 0.6	5.9	5.6 ± 0.5
Antidiabetic treatment	No treatment (2/2)	No treatment (1/2) No treatment then Insulin since graft loss (1/2)	
Number of K transplantations	2	4	6
Length of follow-up (years)	4.1 ± 1.0	4.4 ± 1.2	4.3 ± 1.1
Best serum creatinine value eGFR	76 ± 38/101 ± 44	107 ± 69/71 ± 40	97 ± 58/81 ± 40
Creatinine Month 3/eGFR	109 ± 50/65 ± 24	119 ± 80/69 ± 45	115 ± 62/68 ± 33
Creatinine 1 year/eGFR	100 ± 5/65 ± 7	151 ± 73/42 ± 18	134 ± 62/50 ± 18
Creatinine 2 years/eGFR	103 ± 9/62 ± 3	158 ± 113/44 ± 23	136 ± 86/51 ± 19

Serum creatinine (μmol/l).
eGFR (MDRD formula: ml/min/1.73m^2).
MODY, maturity-onset diabetes of the young; RCAD, renal cysts and diabetes.

Kidney function
The mean glomerular filtration rate (MDRD) was 50 ± 18 ml/min/1.73m^2 at 1 year. Overall, three patients presented with acute graft rejection (grade Ia = 2; grade Ib = 1).

Pancreas function
All of the patients who received a PT were insulin-free immediately after transplantation. HbA1c was 6.1 ± 1.1% at 1 year and 5.6 ± 0.5 at 2 years. Of the four pancreas transplant patients, three don't need any treatment at last follow-up. The patient who lost both his grafts almost 3 years after transplantation (as a consequence of obstructive nephropathy and grade Ib rejection) is now being treated with insulin (and hemodialysis).

Infectious complications
We documented at least one episode of severe infection in three of the six patients. These infectious complications were pneumocystosis ($n = 1$), BK virus nephropathy ($n = 1$), and cholecystitis ($n = 1$).

Discussion

We present here for the first time the phenotype of a cohort of MODY3 and RCAD patients on a pancreas and or kidney transplantation waiting list and their outcome after transplantation.

Diabetes phenotype of our cohort

When at least one of the following criteria was present : i.e. (i) An atypical history of type 1 diabetes: i.e. beginning of non insulin dependent diabetes before the age of 35, (ii) and/or diabetes with at least one affected parent or two affected relatives, (iii) and/or an absence of autoantibodies at diagnosis when available and/or (iv) a persistent secretion of fasting C peptide (v) and/or a personal or a family history of kidney disease (i.e. renal cysts or renal agenesis or dysplasia), patients were screened for *HNF1A/1B* mutations. We found that ∼ 20% of our patients with atypical type-1 diabetes and/or renal anomalies had either *HNF1A* or *HNF1B* mutations. These findings are in accordance with those of Raile *et al.* and Shields *et al.* [26,27], who found 5–10% of *HNF1B* mutations in children and young adults with autoantibody-negative diabetes.

The diabetes characteristics of our patients are similar to those described in the literature: approximately 2.4 family members also affected by diabetes, diabetes occurring at a young age, and, rarely, immediate insulin-dependence. However, we found differences between MODY3 and RCAD patients. Diabetes was discovered at a younger age for MODY3 patients (∼10 years earlier) and patients had a higher BMI and higher levels of C-peptide. Three out of four MODY3 patients needed insulin after a period of OHD alone which is classically

not what is described (i.e. usually a good response to sulfonylureas) [28]; however, the use of sulfonylureas was not possible because of severe renal failure in our cohort. In contrast, and in accordance with the literature [12,24], ß-cell dysfunction was a less prominent feature in our RCAD patients (only 70% rate treated with insulin). As expected by the precocity and severity of their diabetes, MODY3 patients developed microangiopathy more frequently than RCAD patients, as described in the literature [29].

In the 3 years of follow-up, we observed two sudden deaths: one MODY3 and one RCAD patient waiting for transplantation. This represents a ~7% death rate per year, which is what is observed for the French diabetic population on a transplantation waiting list [30].

Pancreas transplantation in our cohort

Pancreas transplantation remains an excellent option to treat type 1 DM, especially for young patients. Indeed, Ojo *et al.* reported that SPK increases survival of patients before the age of 50 because it halts the progression of micro and macrovascular complications [13]. The exact pathophysiology for ß-cells dysfunction is not totally understood for MODY3 and RCAD as most patients end up with insulin need although they display detectable levels of insulin and C-peptide, contrary to type 1 DM. During MODY3 diabetes there is a progressive ß-cells dysfunction [10] but the defect mainly results in impairment of glucose-stimulated insulin secretion [14]. In RCAD, insulin-resistance has been described in a cohort of eight patients, but the insulin requirement tends to be low [12]. The main mechanism for ß-cells dysfunction in RCAD may also be related to pancreas atrophy [11] which is why PT could also be a good option in RCAD. There are no reports of such transplantations during insulin-dependent MODY diabetes, except the case report by Saudek *et al.* describing the outcome of a SPK in one MODY3 patient [14]. To date, no PT for RCAD has been reported except in our study. Our results suggest that PT allows good glycemic control in MODY3 and RCAD patients: all of whom were insulin-free immediately after transplantation with also good long term results. This also suggests that our patients present few or no insulin resistance but mainly an inappropriate glucose dependent insulin secretion.

Renal phenotype in our cohort

All of our MODY3 patients presented with terminal renal failure because of diabetic nephropathy without any other renal anomalies. Conversely, the renal phenotype in RCAD patients was more heterogeneous, as reported previously [31–34]. Only four of the eight patients had a clinical history of diabetic nephropathy (biopsy-proven in one case) and microangiopathy although RCAD patients were typically reported to have a milder course of diabetes. The most typical renal phenotype associated with *HNF1B* mutations were cysts and dysplasia (two patients), cysts alone (one patient), dysplasia with no cysts (one patient). Cysts and dysplasia were only present in half of our patients which are a lot less frequent then in children where cysts and dysplasia is the most prominent feature [35]. In addition, we found biopsy-proven tubulo-interstitial nephritis with chronic renal failure in one patient who had no cysts or renal dysplasia.

Terminal renal failure has already been described in RCAD patients, but seems an infrequent feature as reported by Heidet *et al.* in a recent cohort [34]. However, in this study, patients were mainly children and half of the adult population (i.e. four adults) had reduced GFR (<65 ml/min/1.73m^2) and this corresponded to ESRD in only one case. Genetic screening for *HNF1B* mutations was performed in a cohort consisting of patients with renal anomalies detected by ultrasound (cysts and dysplasia mainly). Ultrasound was done before birth for more then two-thirds of their patients, and renal morphological anomalies were detected in all of them. In contrast to the study by Heidet *et al.* [34], half of our adult patients with ESRD have a normal renal ultrasound. Persistent renal morphological anomalies in adulthood could be of a good prognosis factor in RCAD patients [11,34] RCAD nephropathy might be under-diagnosed, as some patients, as reported in our study (three out of eight patients) and that of Edghill *et al.* [36], may not develop diabetes or renal cysts. Although HNF1B is involved in the development of cysts, it appears that when *HNF1B* inactivation occurs at a later stage in kidney development, cysts do not develop [37]. This phenomenon could account for the absence of cysts in almost half of our RCAD adult patients, in contrast to their occurrence in children. Moreover, in mice, repression of HNF1B-expression induced by Snail over-expression leads to renal fibrosis [38]. This suggests a potential anti-fibrotic role for HNF1β and could, therefore, account for the chronic renal failure with few or no cysts in almost half of our adult RCAD patients. However, a higher number of patients will be needed to analyze the correlation between different *HNF1B* mutations and the occurrence of cysts and/or the progression to ESRD. It should be noted that renal ultrasound anomalies are not associated with a poor renal prognosis [34]. These findings are in accordance with a recent study by Faguer *et al.* who describe four adult patients with RCAD and terminal renal failure [39].

Conclusion

Our results demonstrate for the first time that terminal renal failure has very different causes in MODY3 and RCAD adult patients: diabetic nephropathy for all MODY3 patients and only for half of RCAD adult patients. Also, our study describes for the first time the largest series of terminal renal failure in RCAD adult patients. Contrary to children, half of our patients do not have cysts or dysplasia. For those with no diabetic nephropathy, renal phenotype during terminal renal failure in RCAD was renal dysplasia and chronic tubulointerstitial nephritis. However, terminal renal failure seems a very infrequent phenotype in children with RCAD. As a result of this discrepancy, already reported [39], the term RCAD may not be suitable for adult patients…

> The other conclusion that can be drawn from our study is that PT can be proposed with good results for MODY3 and RCAD patients, although they do not have type 1 DM, especially in MODY3 patients because diabetes is the most prominent feature contrary to RCAD patients. Therefore, a careful clinical screening of insulin dependent type 2 diabetic patients should be done if they are referred for KT not to misdiagnose HNF1A and B mutations as these patients could benefit from PT as well.

Moreover, if detectable levels of insulin and/or C peptide are found in insulin dependent DM, screening for MODY3 and RCAD should be performed. Our results suggest the absence of insulin resistance in MODY3 and RCAD patients, and the importance of a defect in glucose-dependent insulin secretion.

Authorship

CP and HF: wrote the paper and performed the study, collected and analysed data. CB-C and SC: performed the genetic study. CN, AJ, SB, HD, HH and YH: collected data. GB and BC: designed the study. AD: performed the study, analysed data and also designed the study.

Funding

The authors have declared no funding.

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