Outcome of Renal Transplantation in Patients with Non–Shiga Toxin–Associated Hemolytic Uremic Syndrome: Prognostic Significance of Genetic Background

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More than 50% of patients with non–Shiga toxin–associated hemolytic uremic syndrome (non–Stx-HUS) progress to ESRD. Kidney transplant failure for disease recurrence is common; hence, whether renal transplantation is appropriate in this clinical setting remains a debated issue. The aim of this study was to identify possible prognostic factors for renal transplant outcome by focusing on specific genetic abnormalities associated with the disease. All articles in literature that describe renal transplant outcome in patients with ESRD secondary to non–Stx-HUS, genotyped for *CFH*, *MCP*, and *IF* mutations, were reviewed, and data of patients who were referred to the International Registry of Recurrent and Familial HUS/TTP and data from the Newcastle cohort were examined. This study confirmed that the overall outcome of kidney transplantation in patients with non–Stx-HUS is poor, with disease recurring in 60% of patients, 91.6% of whom developed graft failure. No clinical prognostic factor that could identify patients who were at high risk for graft failure was found. The presence of a factor H (*CFH*) mutation was associated with a high incidence of graft failure (77.8 *versus* 54.9% in patients without *CFH* mutation). Similar results were seen in patients with a factor I (*IF*) mutation. In contrast, graft outcome was favorable in all patients who carried a membrane co-factor protein (*MCP*) mutation. Patients with non–Stx-HUS should undergo genotyping before renal transplantation to help predict the risk for graft failure. It is debatable whether a kidney transplant should be recommended for patients with *CFH* or *IF* mutation. Reasonably, patients with an *MCP* mutation can undergo a kidney transplant without risk for recurrence.

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Hemolytic uremic syndrome (HUS) is a rare disease with manifestations of microangiopathic hemolytic anemia, thrombocytopenia, and renal impairment. In most cases, HUS is triggered by Shiga-like toxin (Stx)-producing *Escherichia coli* (1) and manifests with watery or bloody diarrhea (D^+ HUS). Acute renal failure occurs in 55 to 70% of cases, but renal function recovers in up to 70% in various series (1,2).

Forms of HUS not caused by Stx-producing *E. coli* are more rare and may be familial (*i.e.*, more than one family member is affected by the disease, and exposure to Stx-*E. coli* is excluded) or may occur sporadically in a patient with no familial history. The latter may be associated with pregnancy, systemic diseases (*e.g.*, scleroderma, lupus, antiphospholipid syndrome), or HIV infection (3) or may be triggered by certain drugs (*e.g.*, antineoplastic, antiplatelet, immunosuppressive) (4). However, in approximately half of cases, no triggering condition is found (idiopathic forms) (5,6). The clinical outcome is unfavorable, with up to 50% of patients progressing to ESRD and 25% dying during the acute phase of the disease (7). Mutations in genes encoding complement regulatory proteins have been reported both in familial and in nonfamilial cases, mainly in idiopathic forms (5,6) but also in cases of pregnancy-associated (5) and postpartum HUS (8,9), ticlopidine-induced HUS (5), and postinfectious HUS (*Neisseria meningitidis*) (10). The first identified genetic cause was deficiency in complement factor H (CFH) (8,11–14), a plasma glycoprotein that plays an important role in the regulation of the alternative pathway of complement (15) by controlling both spontaneous fluid phase C3 activation and its deposition on host cells. To date, 54 different *CFH* mutations (Figure 1, top) have been identified in 80 patients (5,6,8,9,11,12,14,16–24). In nonfamilial cases, the mutation is either inherited from a healthy parent or, more rarely (only five cases reported), has ensued *de novo* in the proband (6,8). The majority of *CFH* mutations in patients with HUS are heterozy-

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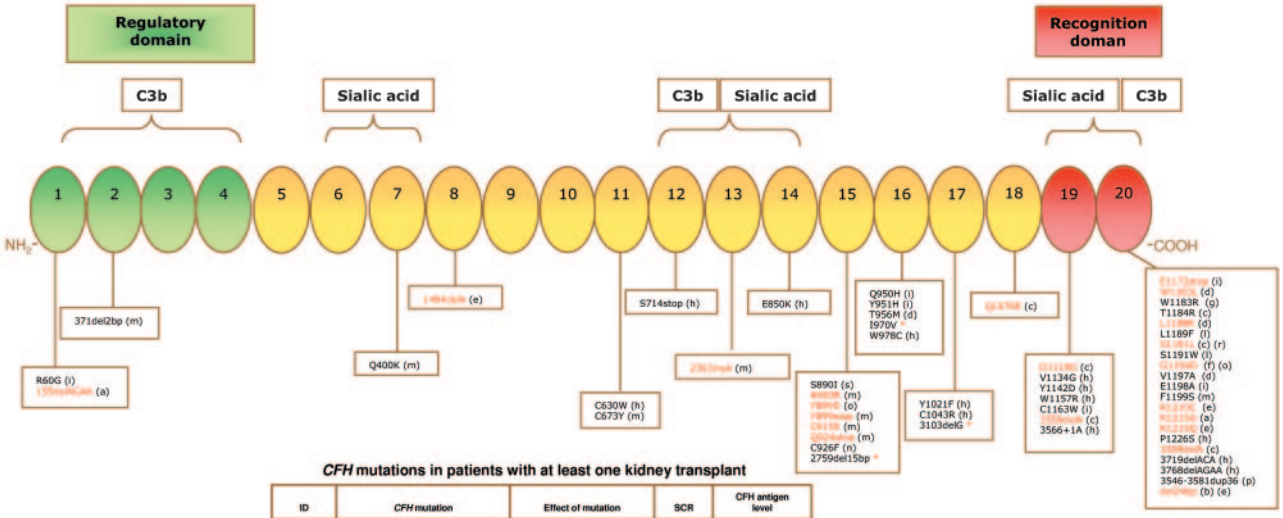

***CFH* mutations in patients with at least one kidney transplant**

ID	*CFH* mutation	Effect of mutation	SCR	CFH antigen level
1	G3717A heterozygous	Arg1215Gln	20	Normal (1)
2	C3701T heterozygous	Arg1210Cys	20	Normal (1)
3	1494delA heterozygous	Premature Stop	8	Normal (1)
4	del24bp homozygous	Premature Stop	20	Low (1)
5	G3587T heterozygous	Glu1172Stop	20	High (1)
17	A3429G heterozygous	Asp1119Gly	19	Normal (1)
18/19	C3299G/3559delA heterozygous	Gln1076Glu/Premature Stop	18/19	? / Low (1)
20/21/22	C3716G heterozygous	Arg1215Gly	20	Normal (1)
23	155delAGAA heterozygous	Premature Stop	1	Low (1)
27	G3621T heterozygous	Trp1183Leu	20	High (2)
28	T3639G heterozygous	Leu1189Arg	20	High (2)
34	T2770A homozygous	Tyr899Stop	15	Undetectable (2)
35	C2852T heterozygous	Gln924Stop	15	Low (2)
36	2303insA heterozygous	774Stop	13	Low (2)
37	T2816A heterozygous	Cys915Ser	15	Low (2)
38	A2751G heterozygous	His893Arg	15	Low (2)
39	C3572T heterozygous	Ser1191Leu	20	Normal (1)
41	T2768G/G3654A heterozygous	Tyr899Asp/Gly1194Asp	15/20	Low (1)

Figure 1. (Top) Factor H (*CFH*) mutations associated with non–Shiga toxin–associated hemolytic uremic syndrome (non–Stx-HUS). The figure shows the structure of human CFH with the 20 short consensus repeats (SCR). The locations of the (N-terminal) regulatory domain responsible for co-factor activity and the binding sites for C3b and polyanions (sialic acid) are indicated. The majority of the mutations found in patients with non–Stx-HUS cluster in the C-terminus of CFH (SCR 19 to 20), which is important for binding to polyanions and surface-bound C3b and for the control of C3b deposition on cell membranes and extracellular matrix. *CFH* mutations in patients with at least one kidney transplant are in red. References: *This paper; a, 12; b, 18; c, 14; d, 8; e, 11; f, 22; g, 20; h, 6; i, 5; l, 17; m, 9; n, 23; o, 21; p, 19; r, 16; s, 24. (Bottom) Detailed information on type and effect of *CFH* mutations and CFH levels in patients with kidney transplantation are reported. For the six patients of Neumann et al. (6), the data of *CFH* mutations were cumulative, so the type of mutation for each patient could not be deduced. Plasma factor H measurement: 1, radial immunodiffusion assay; 2, ELISA assay.

gous and cause either single amino acid changes or premature translation interruption, mainly clustering in the C-terminal short consensus repeats (SCR 19 to 20). More recently, an acquired deficiency of CFH as a result of the presence of anti-CFH autoantibodies in the blood was reported in three children with nonfamilial HUS (25). Two reports from independent groups have described mutations in the gene encoding membrane co-factor protein (MCP), a transmembrane complement regulator, in affected individuals of four families (26,27). Finally, five mutations in the gene encoding factor I (IF), a serine proteinase that inhibits the formation of the alternative pathway C3 convertase (C3bBb) by inactivating cell-bound C3b through proteolytic cleavage to iC3b, have been reported in patients with non–Stx-HUS (28,29). Such defects result in impaired protection of endothelial surface against complement activation (30,31), and it is likely that they predispose to rather than directly cause the thrombotic microangiopathy. Upon exposure to an agent that activates complement, C3b is formed in higher-than-normal amounts, and its deposition on vascular endothelial cells cannot be prevented adequately because of impaired function of complement regulatory proteins (3). This results in the formation of the membrane attack complex and recruitment of inflammatory cells, all events that cause damage and retraction of endothelial cells and adhesion and aggregation of platelets (3).

In this review, we use the term non–Stx-HUS to encompass

such variety of forms of HUS related to inherited and acquired complement abnormalities. However, the assignment of patients with HUS to diarrhea-associated (D^+ HUS) and non–diarrhea-associated (D^- HUS) subgroups is no longer valid because approximately 25% of patients with HUS caused by Stx do not have diarrhea (32).

It is generally accepted that renal transplantation is an effective and safe treatment for patients who have Stx-HUS and have progressed to ESRD. In children with Stx-HUS, the incidence of disease recurrence in the graft ranges from 0 to 10% (33,34), and graft survival at 10 yr is better than that in children who receive a transplant for other causes of ESRD (35). In contrast, disease recurrence and transplantation failure are common in patients with non–Stx-HUS (36–38), even though the incidence varies widely in the literature. Most published reports are of single cases or small case series or comprise series that do not distinguish between patients with the different forms of HUS (Stx-HUS *versus* non–Stx-HUS). When only reports with >10 patients who had non–Stx-HUS and underwent renal transplantation are considered (6,34,36,38–41), it emerges that more than half of patients lost the graft for HUS recurrence within the first year after transplant, despite treatment with plasma exchange and/or infusion. Cyclosporine A and FK506 administration was not associated with a higher incidence of HUS recurrence, when compared with regimens that excludes these drugs (34,38,41). Graft failure for HUS recurrence was higher in adults (60%) (34,36,38,41) than in children (20%) (34,38–40). The type of kidney donor, cadaveric or living related, did not modify the outcome (36,40,41). Overall, no clinical prognostic factors that correlate with graft outcome emerge from literature. The aim of our study was to assess whether screening for abnormalities in genes encoding complement regulatory proteins could help in predicting renal transplant outcome in patients with non–Stx-HUS.

Materials and Methods

Search Strategy

To evaluate the effect of the presence of genetic mutations in renal transplant outcome in patients with ESRD secondary to non–Stx-HUS, we performed a literature search in Medline database (National Library of Medicine, Bethesda, MD), using as search terms "hemolytic uremic syndrome" and "kidney transplantation." From the above material, we analyzed data from patients who had been genotyped for mutations in *CFH*, *MCP*, and *IF* genes.

For additional unpublished data, we also contacted authors who have published genetic studies in patients with non–Stx-HUS and examined medical records of patients from the International Registry of Recurrent and Familial HUS/Thrombotic Thrombocytopenic Purpura (HUS/TTP), a network of 100 hematology and nephrology units from Europe, the United States, Canada, Argentina, Israel, Turkey, Saudi Arabia, and South Africa, established in 1996 under the coordination of the Clinical Center for Rare Diseases *Aldo e Cele Daccò*.

Inclusion Criteria and Data Extraction

Two reviewers (E.B. and F.C.) independently assessed all obtained titles and ordered the full text of all potential articles. The two reviewers then examined all of the texts in full and included in the study the patients who had ESRD secondary to HUS; had undergone at least one renal transplant; were described as having diarrhea-negative, atypical, familial, inherited, idiopathic, or recurrent HUS; and had been genotyped for *CFH*, *MCP* and *IF*. Some cases have been reported in different articles. These cases have been considered once; however, all papers that provided clinical, biochemical, and genetic data on the above patients have been quoted. No patient with *S. pneumoniae*–associated HUS has been included in the study, because *S. pneumoniae*–associated HUS is a distinctive rare disorder caused by release of bacterial neuroaminidase (42). All available unpublished data on genotyped patients from the Newcastle cohort (provided by T.H.J.G.) and from the International Registry of Recurrent and Familial HUS/TTP were also included.

Details on demographic characteristics, clinical history, laboratory parameters, genetic tests, and transplant outcome from patients who were genotyped for mutations in *CFH*, *MCP*, and *IF*, were registered in a predesigned data extraction form. As for the outcome of renal transplantation, both definite recurrences (when both clinical and histologic features of HUS reappeared after transplantation) and possible recurrences (when only histologic features consistent with HUS were present) were considered as true recurrences.

Statistical Analyses

χ^2, Fisher exact test, and Kaplan-Meier analysis with log rank test statistics were applied as appropriate. The time variable was defined as the duration in months from the first transplantation until return to chronic dialysis for patients with transplantation failure (event) or the last available follow-up visit for successful transplantations (nonevent). Statistical analyses were done with the SPSS software (version 11.5; SPSS, Inc., Chicago, IL).

Results

CFH, MCP, and IF Mutations and Transplant Outcome in Patients with ESRD Secondary to Non–Stx-HUS

A total of 78 patients who had non–Stx-HUS and had received a total of 100 kidney transplants were identified (Table 1). For 40 patients, detailed clinical information was reported. Sixty-seven percent of patients had at least one graft failure: In 81.5% of them, the graft loss was attributed to HUS recurrence, and in the remaining 18.5%, it was secondary to acute or chronic rejection. The percentage of graft failure for recurrence was 42.8% in children and 62.5% in adults (Fisher exact test $P = 0.3176$). The time between renal transplantation and graft loss for recurrence ranged from 3 d to 2 yr, with 82.6% of grafts lost within the first year. In addition, two patients manifested HUS recurrence between 3 and 5 mo after transplantation but maintained functioning renal grafts. The overall incidence of disease recurrence in these 40 patients was 60.0%, with 91.6% resulting in failure of the graft. Initial immunosuppressive therapy was specified for 25 renal transplants. Cyclosporine A and FK506 (13 of 20 grafts; 65.0%) administration was not associated with a higher incidence of HUS recurrence, when compared with regimens that excluded these drugs (two of five grafts; 40.0%; Fisher exact test $P = 0.3577$).

Twenty-seven had *CFH* mutations (*CFH* positive) and received a total of 36 kidney grafts. The localization and the effect of *CFH* mutations are shown in Figure 1. The relevant clinical data of the *CFH*-positive group are summarized in Table 2. Among them, 12 patients (six children, four adults, two unspecified) had familial HUS, whereas nine (four children, five

Table 1. Outcome of renal transplantation in patients with non–Stx-HUS[a] genotyped for factor H (*CFH*)

Study (First Author, Year)	Patient	Gender	Familial HUS	Age at HUS Onset	Time between HUS and Dialysis[b]	*CFH* Mutation	Donor Type	Initial Immunosuppressive Treatment	TR Failure	Reason for Failure	Duration from TR until Chronic Dialysis	Follow-Up of Functioning Grafts
Caprioli, 2001,	1	M	Yes	8 mo	No recovery	Yes	?	?	Yes	Recurrence of HUS	5 mo	
2003	2	F	No	31 yr	15 yr	Yes	Cadav	CsA, Pred, MMF	Yes	Recurrence of HUS	3 mo	
	3	F	Yes	25 yr	No recovery	Yes	Cadav	CsA, Aza, Pred	Yes	Recurrence of HUS	5 mo	
	4[c]	F	Yes	3 wk	No recovery	Yes	Cadav	Tac, Aza, Pred	Yes	Recurrence of HUS	1 mo	
	5	M	No	36 yr[d]	No recovery	Yes	Cadav	Tac, MMF, Pred	Yes	Recurrence of HUS	7 d	
	6	F	No	25 yr	No recovery	No	Cadav	?	No			9 yr
	7	F	No	34 yr	No recovery	No	Cadav	Tac, ATG, Pred	Yes	Acute rejection	1 mo	
	8	M	Yes	26 yr	?	No	TR1: Cadav	TR1: Aza, Pred	TR1: Yes	TR1: Chronic rejection	TR1: 10 yr	
							TR2: ?	TR2: ?	TR2: Yes	TR2: Acute rejection	TR2: <1 wk	
							TR3: ?	TR3: ?	TR3: Yes	TR3: Chronic rejection	TR3: 1 yr	
	9	F	No	26 yr	7 mo	No	Cadav	CsA, Pred, MMF	No			4 yr
	10	M	No	6 mo	?	No	Cadav	?	Yes	Recurrence of HUS	3 d	
	11	F	Yes	31 yr	No recovery	No	?	?	Yes	Recurrence of HUS	1 mo	
	12	M	Yes	31 mo	No recovery	No	TR1: Cadav	TR1: ?	TR1: Yes	TR1: Acute rejection	TR1: 1 mo	
							TR2: Cadav	TR2: CsA, Pred	TR2: Yes	TR2: Acute rejection	TR2: 1 mo	
	13	F	No	4 yr	4.5 yr	No	?	?	No			2 yr
International	14	F	Yes	Adulthood	?	No	?	?	No			5 yr
Registry	15	F	No	30 yr	No recovery	No	LRD	Tac, MMF, Pred	No			2 yr
(unpublished)	16	M	No	9 yr	?	No	?	?	No			10 yr
Newcastle cohort[e]	17	F	Yes	?	?	Yes	?	Tac, MMF, Pred	No			6 yr
(unpublished)	18	F	Yes	Adulthood	No recovery	Yes	Cadav	?	Yes	Recurrence of HUS	1 mo	
	19	F	Yes	Adulthood	No recovery	Yes	Cadav	?	Yes	Recurrence of HUS	1 mo	
	20	F	Yes	?	?	Yes	TR1: ?	?	TR1: Yes	TR1: Rejection	TR1: 3 mo	TR2: 13 yr
							TR2: ?	?	TR2: No			
	21	F	Yes	Adulthood	?	Yes	?	?	TR1: Yes	TR1: Recurrence of HUS	TR1: 22 mo	
							?	?	TR2: Yes	TR2: Chronic rejection	TR2: 10 yr	
	22	F	No	22 yr	No recovery	Yes	LRD	Tac	Yes	Recurrence of HUS	52 d	
	23	M	No	6 yr	No recovery	Yes	Cadav	CsA, ATG, Pred	Yes	Recurrence of HUS	4 mo	
Richards, 2003[f]	24	M	Yes	27 yr	No recovery	No	Cadav	CsA, Pred	No			16 yr
	25	M	Yes	31 yr	No recovery	No	Cadav	Aza, Pred	No			23 yr
	26	M	Yes	35 yr	No recovery	No	Cadav	CsA, Aza, Pred	No			13 yr
Perez Caballero,	27	M	No	Adulthood	?	Yes	?	?	TR1: yes	?	?	
2001							?	?	TR2: ?			
	28	?	Yes	Childhood	?	Yes	?	?	TR1: yes	?	?	
							?	?	TR2: ?			
	29	?	No	Childhood	?	No	?	?	Yes	?	?	
Donne, 2002	30	F	Yes	4 mo	No recovery	No	LRD	CsA, Aza, Pred	Yes	Recurrence of HUS	7 wk	
	31	M	Yes	30 yr[d]	No recovery	No	Cadav	CsA, Aza, Pred	Yes	Recurrence of HUS	3 mo	
	32	M	Yes	30 yr	No recovery	No	TR1: Cadav	TR1: CsA, Aza, Pred	TR1: Yes	TR1: Recurrence of HUS	TR1: 2 yr	
							TR2: LRD	TR2: CsA, Aza, Pred	TR2: Yes	TR2: Recurrence of HUS	TR2: 6 mo	
	33	F	Yes	31 yr[d]	No recovery	No	LUD	MMF, Sir	Yes	Recurrence of HUS	10 d	
Dragon-Durey,	34	M	Yes	11 mo	12 mo	Yes	?	?	No			18 mo
2004	35	M	No	6 mo	No recovery	Yes	?	?	No			10 yr
	36	M	No	16 mo	No recovery	Yes	?	?	No			4 yr
	37	F	No	9 mo	No recovery	Yes	?	?	Yes	Recurrence of HUS	25 d	

adults) had no familial history; for the remaining six patients, a family history was not available. In 16 patients, a heterozygous mutation was found, indicating an autosomal dominant transmission of the disease, whereas an autosomal recessive transmission was demonstrated in five cases, two with a homozygous mutation (and consanguineous parents) and three with compound heterozygous changes (Figure 1, bottom). For six patients (6), the type of *CFH* mutation was not specified. HUS

Table 1. Continued

Study (First Author, Year)	Patient	Gender	Familial HUS	Age at HUS Onset	Time between HUS and Dialysis[b]	*CFH* Mutation	Donor Type	Initial Immunosuppressive Treatment	TR Failure	Reason for Failure	Duration from TR until Chronic Dialysis	Follow-Up of Functioning Grafts
	38	M	No	41 yr	?	Yes	?	?	Yes	Recurrence of HUS	18 mo	
Olie, 2004	39	F	Yes	3 yr	No recovery	Yes	TR1: Cadav	TR1: CsA, Aza, Pred, ATG	TR1: Yes	TR1: Recurrence of HUS	TR1: 3 d	
							TR2: ?	TR2: MMF, Pred, Bas	TR2: Yes	TR2: Recurrence of HUS	TR2: 3 mo	
Fremeaux-Bacchi,	40	F	No	26 yr	?	No	?	?	TR1: Yes	TR1: Recurrence of HUS	?	
2004							?	?	TR2: Yes	TR2: Recurrence of HUS	?	
Johnson, 2004	41	M	Yes	5 mo	3 yr	Yes	Cadav	Aza, Pred	Yes	Acute rejection	11 d	
Kavanagh, 2005	42	F	No	32 yr	No recovery	No	Cadav	CsA, Pred	Yes	Recurrence of HUS	2 mo	
	43	M	No	33 yr	No recovery	No	LRD	CsA, Aza, Pred	Yes	Recurrence of HUS	22 mo	
Neumann, 2003	$n = 6$	?	?	?	?	Yes	1 TR: LRD	?	8 TR: Yes	8 TR: Relapse and	8 TR: <1 yr	2 TR: ≥1 yr
							9 TR: Cadav	?	2 TR: No	acute rejection		
	$n = 29$	?	?	?	?	No	8 TR: LRD	?	20 TR: Yes	20 TR: Relapse and	20 TR: <1 yr	17 TR: ≥1 yr
							29 TR: Cadav	?	17 TR: No	acute rejection		

[a]non–Stx-HUS, non–Shiga toxin–associated hemolytic uremic syndrome; TR1, first renal transplantation; TR2, second renal transplantation; TR3, third renal transplantation; Cadav, cadaveric graft; LRD, graft from living-related donor; LUD, graft from living-unrelated donor; CsA, cyclosporine A; Pred, prednisone; MMF, mycophenolate mofetil; Tac, tacrolimus; ATG, anti-thymoglobulin; Sir, sirolimus; Bas, basiliximab.
[b]Irreversible loss of renal function during the acute phase = No recovery.
[c]*CFH* mutation described even in Buddles *et al.* (18).
[d]HUS onset after nephrectomy.
[e]*CFH* mutations described in Warwicker *et al.* (12) and Richards *et al.* (14).
[f]Family described in Warwicker (12).

Table 2. Characteristics and outcome after transplantation in patients with non–Stx-HUS and mutations of factor H

Patients	27
Gender	
male	9
female	11
unspecified	7
Disease onset	
childhood (<16 yr)	10
adulthood (≥16 yr)	9
unspecified	8
Type of HUS	
familial	12
sporadic	9
unspecified	6
Transplanted kidneys	36
Type of donor	
cadaver	18
living related	2
unspecified	16
Kidney failures	
no. of patients	21
no. of grafts	29

manifested during childhood in 10 patients and during adulthood in nine (for eight patients, the age of onset was not available), with no recovery after the first episode in overall 80.0%. The mean number of transplants per patient was 1.33 ± 0.48, with seven patients receiving two kidney grafts and one patient receiving three grafts. The type of donor was documented for 20 grafts: 90.0% were from cadaveric donors, and 10.0% were from living-related donors (Table 2). The incidence of graft failure was high; overall, 77.8% of these patients had at least one graft failure. In 15 of them, the cause of graft loss was available and in 13 (86.7%) was attributed to HUS recurrence. Similar results were obtained when the number of grafts was considered. Overall, 80.6% of graft failures occurred in these patients. For 17 grafts, the cause of failure was available and in 14 (82.3%) of them was attributed to HUS recurrence. The time between renal transplantation and graft loss for recurrence ranged from 3 d to 22 mo, with overall 12 (85.7%) grafts lost within the first year and two (14.3%) lost between 18 and 22 mo (Figure 2). One additional patient (patient 17, Table 1) manifested two episodes of HUS recurrence after transplantation but maintained a functioning graft at 6 yr of follow-up. The overall incidence of disease recurrence was 73.7% in the patients with *CFH* mutations. Avoidance of calcineurin inhibitors did not prevent recurrence of HUS and graft loss. The incidence of graft failure was not influenced by the type of *CFH* mutation (missense 70.0%, nonsense 66.7% failures; Fisher exact test $P = 1.0000$) and by the position (SCR 19 to 20: 75.0%, all of the other SCR 57.1% failures; Fisher exact test $P = 0.6169$). Likewise, the incidence of graft failure was 66.7% in patients with lower-

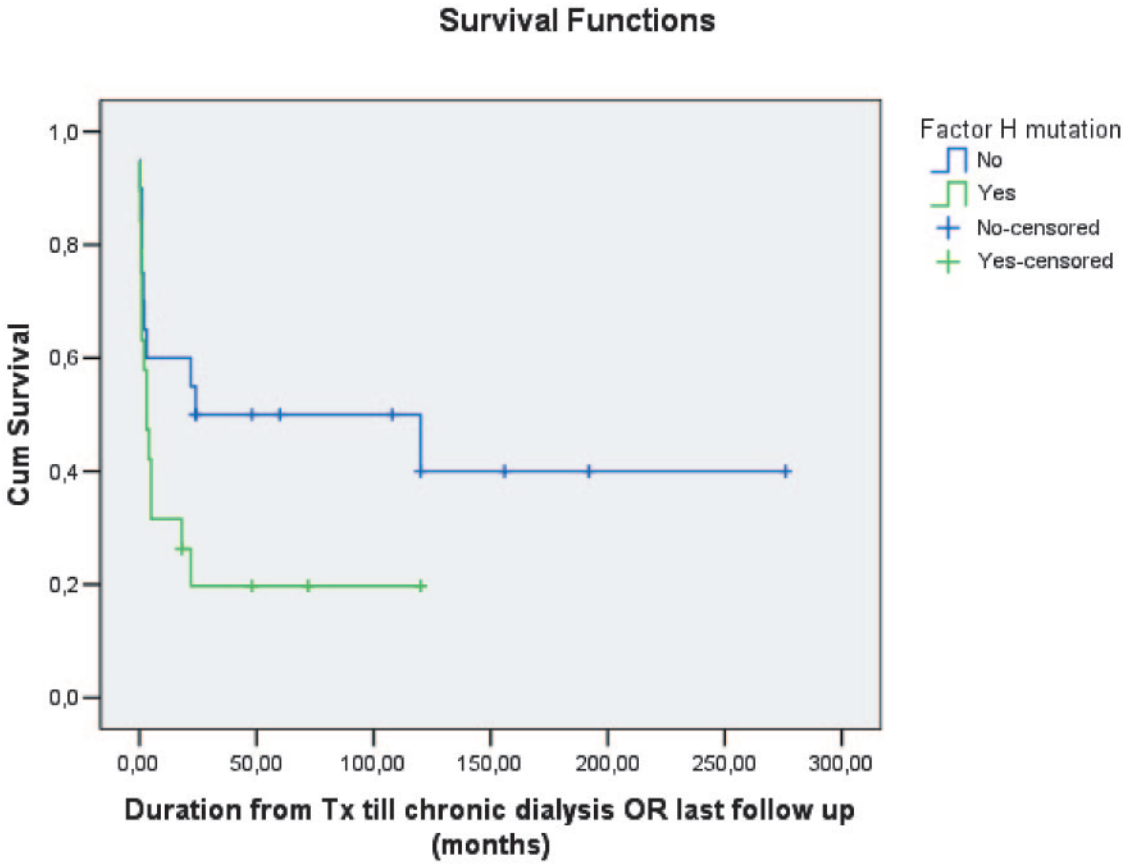

Figure 2. Cumulative graft survival in patients with non–Stx-HUS and factor H mutations (*CFH*-positive) and in patients without factor H mutations (*CFH*-negative; Kaplan-Meier analysis, $P = 0.078$).

than-normal CFH levels (CFH antigen serum levels as determined by Radial immunodiffusion or ELISA assays) and 90.9% in those with normal or high CFH levels (Fisher exact test $P = 0.2848$; Figure 1, Table 1). However, normal CFH levels do not suggest normal function, because it has been shown that most *CFH* mutations in patients with HUS result in a normal protein secretion but cause loss of the capability of CFH to bind C3b and endothelial cells.

The incidence of graft failure was lower in the 51 patients without *CFH* mutations (*CFH* negative; 28 of 51; 54.9%), as compared with patients with *CFH* mutations (*CFH* positive; 21 of 27; 77.8%; Fisher exact test $P = 0.0533$, $\chi^2 = 3.96$, $P = 0.0467$). In this group, graft outcome was variable, with some patients experiencing a disease recurrence within a few days after transplantation and others retaining a well-functioning graft until 10 to 20 yr posttransplantation (Table 1, Figure 2). Of interest, two patients with no familial history of the disease and no *CFH* mutation received a living-related renal transplant, one from a sibling and the other from the father. Both recipients (patients 30 and 32) lost the graft for HUS recurrence, 7 wk and 6 mo after transplantation, respectively, and both donors (patients 31 and 33) developed HUS within 1 yr after donation. The donors underwent renal transplantation and experienced graft loss for HUS recurrence at 10 d and 3 mo after transplantation, respectively (43). These data underline the risk for disease recurrence in non–Stx-HUS recipients of living-related kidney graft and suggest that living-related donors may be at risk for developing a *de novo* disease after kidney donation to a family member with non–Stx-HUS.

Three *CFH*-negative patients (patients 40, 42, and 43) had a mutation in the *IF* gene (Table 3). All three had no familial history of HUS and lost the kidney graft for disease recurrence. Patient 40 was hospitalized at the age of 26 yr for recurrence of HUS (confirmed by renal biopsy) after a second renal transplant. She had already lost her first kidney transplant as a result of HUS recurrence coinciding with acute rejection. Patient 42 developed ESRD after an episode of HUS, during the third trimester of her first pregnancy. She received a cadaveric renal transplant that was lost for disease recurrence after 2 mo. Patient 43 received a live related transplant from his brother at the age of 35 yr. Twenty months after transplantation, the disease recurred, as documented by renal biopsy. Despite treatment with 23 plasma exchanges, renal function continued to deteriorate and the patient returned to dialysis.

For 16 *CFH*-negative patients (patient 6 to 16, 24 to 26, 42, and 43), information on the results of *MCP* gene screening was available, with four of them having *MCP* mutations (Table 4). Three patients are brothers from the same family (patients 24,

Table 3. Outcome after renal transplantation in patients with non–Stx-HUS associated to a mutation of factor I (*IF*)

Study (First Author, Year)	Patient	Gender	Familial HUS	Age at HUS Onset	Time between HUS and Dialysis[a]	*IF* Mutation	Effect of Mutation	HUS Recurrence after TR	Outcome after Transplantation
Fremeaux-Bacchi, 2004	40	F	No	26 yr	?	G1666A	Trp528Stop	Yes[b]	Graft failure secondary to HUS recurrence[b]
Kavanagh, 2005	42	F	No	32 yr	No recovery	G463A	Trp127Stop	Yes	Graft failure secondary to HUS recurrence
	43	M	No	33 yr	No recovery	922delC	Premature stop	Yes	Graft failure secondary to HUS recurrence

[a]Irreversible loss of renal function during the acute phase = no recovery.
[b]Disease recurrence and graft failure for recurrence after both the first and the second transplant.

25, and 26) and show an autosomal dominant transmission, whereas the fourth patient is a woman without a familial history (patient 6). HUS occurred in adulthood in all patients with ESRD as a consequence of a single episode. As shown in Table 4, kidney transplant outcome was favorable in all four patients with an *MCP* mutation, with none experiencing a disease recurrence in the graft. Among the three brothers, one died from hepatic failure of unknown cause after 13 yr of a functioning graft, one developed Waldenström's macroglobulinemia, and the other remains well with a functioning graft. Patient 6 had an uneventful pregnancy 7 yr after transplantation with 9 yr of disease-free follow-up.

Discussion

Children with Stx-HUS rarely progress to ESRD, but when they do, renal transplantation results in a good prognosis with a very low recurrence rate, ranging from 0 to 10% (33,34). In contrast, >50% of patients with non–Stx-HUS—most of them are children or young adults—progress to ESRD and need renal replacement therapy. However, whether kidney transplantation is an appropriate treatment in these patients is debatable. Previous reports detailing kidney graft outcome indicate a poor prognosis with >50% of graft lost for recurrence (6,34,36,38–41).

The results of our review of published and unpublished cases genotyped for *CFH*, *MCP*, and *IF* confirm the overall poor outcome of renal transplantation in patients with non–Stx-HUS, with recurrence occurring in 60.0% of patients and graft failure developing in 91.6% of them despite treatment. Recurrence occurred within the first year after transplantation in 82.6% of patients. Overall 1-yr kidney graft survival in patients with non–Stx-HUS was 32% for cadaveric transplants and 50% for living donor transplants. For comparison, data reported to the UNOS Renal Transplant Registry showed that in the 1990s, the overall 1-yr graft survival rate for cadaveric kidney transplants was 87%, whereas for living donor transplants was 93% (44). Similar to previous published studies (33,34), we found that the percentage of graft failure for HUS recurrence was higher in adults. Avoidance of calcineurin inhibitors did not prevent recurrence of HUS and graft loss. No clinical prognostic factors could help to distinguish patients who were at high risk for graft failure from those who could benefit from transplantation. However, we found that screening for mutations is important as it may help to define graft prognosis. First, we examined the effect of *CFH* mutations. We found that the presence of a *CFH* mutation was associated with a poor outcome after renal transplantation. The incidence of graft failure was higher in patients with a *CFH* mutation than in those without.

Table 4. Outcome after renal transplantation in patients with non–Stx-HUS associated with mutation of *MCP* gene

Study (First Author, Year)	Patient	Gender	Familial HUS	Age at HUS Onset	Time between HUS and Dialysis[a]	*MCP* Mutation	Effect of Mutation	HUS Recurrence after TR	Outcome after Transplantation
Present article	6	F	No	25 yr	No recovery	C218T	Arg25Stop	No	Functional graft at 9 yr
Richards, 2003	24	M	Yes	27 yr	No recovery	6bp del	Loss of 237Asp and 238Ser	No	Functional graft at 16 yr
	25	M	Yes	31 yr	No recovery	6bp del	Loss of 237Asp and 238Ser	No	Functional graft at 23 yr
	26	M	Yes	35 yr	No recovery	6bp del	Loss of 237Asp and 238Ser	No	Functional graft at 13 yr, death

[a]Irreversible loss of renal function during the acute phase = no recovery.

Interpretation of these results is facilitated by the knowledge that CFH is a plasma protein that is produced mainly by the liver. Thus, a kidney transplant will not correct the *CFH* genetic defect in these patients (11,12). Expression and functional studies have demonstrated that mutant CFH has a severely reduced capacity to interact with both polyanions on endothelial cells and surface-bound C3b; this results in diminished complement regulatory activity on the cell membrane (31,45). Renal transplantation is a condition of complement activation, which may be triggered by ischemia reperfusion damage, immune insult, and infectious complications (46,47). In patients who carry a *CFH* mutation, regulation of complement activation and C3b deposition on graft vascular endothelium is impaired as a result of the loss of polyanion-binding capacity of mutant CFH, thus predisposing to recurrence of the disease in the graft.

Simultaneous kidney and liver transplant was performed recently by our group in two young children with non–Stx-HUS and *CFH* mutations, with the objective of correcting the genetic defect and preventing disease recurrences (20,48). However, both patients who were treated with this procedure were complicated by premature irreversible liver failure. The reasons for this are currently under evaluation but may include increased susceptibility of the transplanted liver to ischemic or immune injury related to uncontrolled complement activation. In the first patient, humoral rejection of the liver graft manifested by the 26th day after transplantation, and in a few days, the child developed hepatic encephalopathy and coma. She underwent a second, uneventful liver transplantation (20). The second case was complicated by primary nonfunction of the liver graft followed by multiorgan failure and the patient's death (48). Thus, despite the potential to correct the genetic defect, combined kidney and liver transplant for non–Stx-HUS associated with *CFH* mutations should not be performed unless a patient is at imminent risk for life-threatening complications.

Forty-five percent of patients with non–Stx-HUS and no evidence of a *CFH* mutation, when given a kidney transplant, lose the graft within 1 yr. Of note, two patients who had no familial history of the disease and no *CFH* mutation and received a living-related renal transplant experienced HUS recurrence in the allograft. Both donors developed HUS after nephrectomy. Thus, the decision to offer a living-related renal transplant to patients with non–Stx-HUS should take into account the risk for a *de novo* disease in the donor. Unilateral nephrectomy and renal mass reduction could cause endothelial damage, triggering the disease in the donor, if the latter is genetically predisposed by a disease-associated mutation. This hypothesis is supported by the case of one of the patients with *CFH* mutation in this report (patient 5), who developed the disease after nephrectomy as a result of trauma caused by a motor vehicle accident.

IF, like CFH, is synthesized by the liver; therefore, it is expected that patients with an *IF* mutation would have a similar outcome posttransplantation as those with a *CFH* mutation. Indeed, graft failures for HUS recurrence were recently reported in three patients with a heterozygous *IF* mutation (28,29). The remarkable exception were patients with *MCP* mutation. Indeed, four of these patients underwent successful transplantation, with no disease recurrence. At variance with CFH and IF, which are circulating soluble regulators, MCP is a transmembrane protein that is highly expressed in the kidney. Transplantation of a kidney that expresses normal MCP therefore should correct the defect in patients with an *MCP* mutation.

CFH mutations have been found in approximately 30% of patients with non–Stx-HUS. Very recent published data in two different cohorts (49) that included 75 and 77 patients, respectively, and unpublished results from our International Registry (155 patients) indicate that the frequency of *MCP* mutations in non–Stx-HUS ranges from 5 to 14% and that the frequency of *IF* mutations ranges from 4 to 10%. Thus, overall genetic screening before renal transplantation would be of help to predict graft outcome for approximately 40 to 50% of patients with non–Stx-HUS. The number of patients with *CFH*, *MCP*, and *IF* mutation that have been reported until now is small. Multicenter trials and registries are required to get enough numbers to characterize better the predictive value of these mutations to graft outcome. *CFH*, *MCP*, and *IF* genotyping requires the analysis of the whole coding region of the genes because mutations that have been found in patients with non–Stx-HUS are located in different exons. We recognize that not all transplant centers are equipped for *CFH*, *MCP*, and *IF* genotyping. This hurdle could be overcome by centralizing the analyses in a few referring centers with proven experience in the field.

This study has important clinical implications. We suggest that genotyping for *CFH*, *MCP*, and *IF* is performed in all patients who have ESRD secondary to non–Stx-HUS and are being considered for transplantation. Genetic testing should be particularly recommended before living-related donation to avoid the risk for *de novo* disease in the donors. It is difficult to justify renal transplantation in patients with a *CFH* mutation because of the high risk for graft failure, and the same applies to patients with an *IF* mutation. Combined liver and renal transplantation in these patients theoretically could correct the genetic abnormality and prevent disease recurrence. However, this procedure is not recommended at present because it may be complicated by fatal primary liver nonfunction. In contrast, graft outcome seems to be good in patients with *MCP* mutations.

Despite these recent advances, the underlying genetic abnormality, if any, remains unknown in almost half of patients with non–Stx-HUS. Alterations in other genes encoding for complement regulatory proteins could be involved in determining predisposition to the disease. However, evidence is emerging that in some patients, the disease is caused by an acquired autoimmune event that leads to the formation of anti-CFH antibodies (25). Further advances in our understanding of the molecular pathogenesis of the disease are needed to enable more accurate prediction of the risk for recurrence and allow the development of tailored therapeutic approaches.

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