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BRIEF REPORT

Successful long-term outcome after renal transplantation in a patient with atypical haemolytic uremic syndrome with combined membrane cofactor protein CD46 and complement factor I mutations

Werner Lukas Pabst · Thomas J. Neuhaus · Samuel Nef · Elena Bresin · Andrea Zingg-Schenk · Giuseppina Spartà

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Abstract
Background Atypical haemolytic uremic syndrome (aHUS) is often associated with a high risk of disease recurrence and subsequent graft loss after isolated renal transplantation. Evidence-based recommendations for a mutation-based management after renal transplantation in aHUS caused by a combined mutation with complement factor I (CFI) and membrane cofactor protein CD46 (MCP) are limited.
Case-diagnosis/Treatment We describe a 9-year-old boy with a first manifestation of aHUS at the age of 9 months carrying combined heterozygous mutations in the CFI and MCP genes. At the age of 5 years, he underwent isolated cadaveric renal transplantation. Fresh frozen plasma was administered during and after transplantation, tapered and finally stopped after 3 years.
Conclusions During the 5-year follow-up after transplantation there have been no signs of aHUS recurrence and graft function has remained good. The combination of heterozygous MCP and CFI mutations with aHUS might have a positive impact on the post-transplant course, possibly predicting a lower risk of aHUS recurrence after an isolated cadaveric renal transplantation

W. L. Pabst · S. Nef · A. Zingg-Schenk · G. Spartà (✉)
Pediatric Nephrology Unit, University Children's Hospital of Zurich, Steinwiesstrasse 75,
8032 Zurich, Switzerland
e-mail: giuseppina.sparta@kispi.uzh.ch

T. J. Neuhaus
Children's Hospital of Lucerne, Lucerne, Switzerland

E. Bresin
Mario Negri Institute for Pharmacological Research,
Clinical Research Center for Rare Diseases,
Ranica, Bergamo, Italy

Introduction

Atypical haemolytic uremic syndrome (aHUS) has a high rate of disease recurrence after renal transplantation [1, 2], with the recurrence dependent on the mutated gene(s) involved in the pathogenetic mechanism. Mutations in membrane cofactor protein CD46 (MCP) are associated with a lower recurrence rate and better renal graft function than mutations in circulating regulators of the complement system, such as complement factor H (CFH) or complement factor I (CFI) [3–5]. Although patients carrying two or more mutations have been described [1], evidence for the management of renal transplantation in patients with aHUS caused by combined CFI/MCP mutations is still limited [4]. Here, we describe a 9-year-old boy suffering from aHUS carrying heterozygous mutations of both CFI and MCP with a favourable 5-year follow-up after isolated cadaveric renal transplantation without aHUS recurrence and good graft function.

Case report

The boy was born with congenital neuroblastoma with spontaneous regression by the age of 7 months. At the age at 9 months anaemia, thrombocytopenia and renal insufficiency led to the diagnosis of aHUS. As these symptoms arose with fever and otitis media, *Streptococcus pneumoniae*-associated HUS was initially suggested and plasmatherapy was not

administered. Peritoneal dialysis was initiated at the age of 10 months due to progressive renal failure. After an initial improvement of both renal function and thrombocytopenia, a first relapse of the aHUS at the age of 11 months led to end stage renal disease (ESRD).

Genetic analysis revealed heterozygous splice site mutation of the *MCP* gene (IVS2-2A>G) [6]. This mutation leads to the skipping of exon 3 causing the loss of amino acids 62–95 with a 3-amino acid change and protein interruption at L99 [5, 6]. The same mutation was found in the healthy father. A previously published functional analysis of IVS2-2A>G demonstrated that heterozygous patients express 50 % of the normal MCP level [5]. Our patient also carried the aHUS *MCPggaac* risk haplotype [7] since he was heterozygous for the c.2232T>C polymorphism. The genetic analysis also revealed a heterozygous 5-bp deletion of *CFI*, delTTCAC(1446–1450), in the boy and the healthy mother; this deletion causes a frameshift and introduction of a premature stop codon (W486Stop) [6], resulting in an abnormal protein that is not secreted [8]. The CFI levels measured in the serum of our patient were consistently at the lower range (77 %; normal range 70–130 %) [6]. The genetic screening of thrombomodulin, *CFH* as well as the levels of CFH were normal. However, the patient was also heterozygous for the −257 T, 2,089 G and 2,881 T CFH polymorphisms targeting the aHUS disease risk haplotype H3 [9]. Homozygous deletion of CFHR1-R3 and autoantibodies to CFH were excluded. Genetic screening for C3, CFB and CFHR5 was not performed.

At the age of 5 years, the patient underwent isolated cadaveric renal transplantation with two donor-HLA-matches. Fresh frozen plasma (FFP; i.e.Octaplas®; Octapharma Plasma,Charlotte, NC) (20 ml/kg) was administered immediately before and after transplantation, followed by daily doses for 19 days and then a gradual tapering of the FFP infusions—three times a week for 2 weeks, twice a week for 7 weeks, once a week for 8 weeks, once every other week for 4 months, once every 3 weeks for 3 months and once every 4 weeks for 1 year. Two years after transplantation, FFP infusions were given once every 2 months for a further year and finally stopped 3 years after transplantation. Initial immunosuppression therapy consisted of cyclosporine A (10 mg/kg/day), mycophenolate mofetil (1,200 mg/m^2/day) and prednisolone (2 mg/kg/day) and resulted in good primary renal graft function. Eleven days after transplantation, cyclosporine A was switched to tacrolimus (0.4 mg/kg/day, aiming at a trough level of approx. 10–15 μg/l for 4 weeks, 3–7 μg/l thereafter) and intravenous methylprednisolone was administered (500 mg/m^2 once daily for 6 days) based on a biopsy-proven cellular graft rejection (Banff IIA). Volume overload required transient hemofiltration; in addition, one single plasma exchange was performed with FFP (40 ml/kg) as a preventive measure. Consistent with the benign clinical course, renal biopsy showed no evidence of thrombotic microangiopathy. Twenty-nine days after transplantation, a second graft rejection was diagnosed on renal biopsy (Banff IIB) and the patient was treated again with 4 doses of daily intravenous methylprednisolone. Renal protocol biopsy 6 months after transplantation was normal without evidence of thrombotic microangiopathy (TMA) or complement deposition. No complement depositions were seen in the previous two biopsies.

After transplantation, the patient suffered from several viral and bacterial infections, including esophagitis (human herpesvirus type 1), enteritis (*Clostridium difficile* toxin), reactivation of cytomegalovirus, viral meningitis and urinary tract infections. These were treated with the appropriate antiviral or antimicrobial drugs, but without intensifying FFP administration.

Neither clinical nor laboratory signs of aHUS recurrence appeared during the 5-year follow-up after transplantation with maintenance of a good glomerular renal function (Table 1), normal blood pressure and no proteinuria. Additionally, the child's general development and growth are normal (within the 10th and 25th centile).

Discussion

We describe a 9-year-old boy (current age) suffering from aHUS who carries combined heterozygous mutations in the MCP and CFI genes. He presented with the first episode of aHUS at the age of 9 months followed by a first relapse at 11 months that led to ESRD. Genetic analysis revealed that the boy had inherited the MCP and CFI mutations from his healthy father and mother, respectively [6]. This observation suggests that these specific mutations on the MCP and the CFI gene do not necessarily lead to aHUS if present as a single, isolated mutation. It is possible, however, that the combination of any trigger (e.g. infection, but often unknown) with the presence of a heterozygous mutation (e.g. that of the parents) might result in aHUS.

The performance of an isolated transplantation was controversial as, at that time, no data were available on patients with combined heterozygous MCP/CFI mutations. The presence of the CFI mutation in our patient would have argued against an isolated transplantation, as graft failure due to aHUS recurrence had been reported in patients with heterozygous CFI mutations [10, 11]. The difficult course of the patient, the unknown risk of a combined liver–kidney transplantation, the lack of specific antibodies against complement proteins at that time (e.g. eculizumab) and the reduced long-term life expectancy on dialysis finally led to the decision to perform an isolated renal transplantation. Both parents were excluded as potential donors, based on the increased risk of developing aHUS relapse in the recipient and

Table 1 Post-transplant course of haemolysis parameters and plasma creatinine

Haemolysis parameters and plasma creatinine	Day of transplantation	Days/months/years after transplantation						
		Day 2	Day 9	Day 28	Month 5	Month 12	3 years	5 years
Platelets (G/l)	214	255	464	338	505	510	223	317
Hematocrit (l/l)	0.27	0.33	0.25	0.24	0.27	0.34	0.33	0.41
Lactate dehydrogenase (U/l)	201	250	351	195	274	255	205	194
Schistocytes	None	None	None	None	None	None	None	None
Creatinine (μmol/l)	950	66	146	82	81	65	45	49[a]
Biopsy	–	–	Banff IIA rejection No TMA	Banff IIB rejection No TMA	Normal biopsy No TMA	–	–	
Fresh frozen plasma infusion	Daily	Daily	Daily	Three times a week	Every 2 weeks	Monthly	–	–

TMA, Thrombotic microangiopathy

[a] Normal range for plasmatic creatinine: <60 μmol/l. Estimated glomerular filtration rate by the Schwartz formula with k = 0.4: 80 ml/min/1.73 m^2

the devastating possibility of triggering aHUS in the heterozygous donor by removing one kidney [12].

To our knowledge, only one case report has described a successful isolated renal transplantation in a patient with aHUS carrying mutations in both CFI and MCP—in this case, a 36-year-old man [13]. The patient received daily FFP infusions during the first 10 days after transplantation. Follow-up 9 months after transplantation showed acute humoral graft rejection, but no aHUS recurrence.

Kidney graft outcome seems to be favourable in patients with isolated *MCP* mutations without disease recurrence in the renal graft, taking into account that MCP is a transmembrane protein highly expressed in the kidney [14]. Normal MCP in the kidney graft may have prevented the recurrence of aHUS in our patient as multiple hits in complement genes are involved in the pathogenesis of aHUS, as reported by Cruzado et al. [13]. However, Frémeaux-Bacchi et al. reported that vascular microchimerism, in which the mutated protein is produced in the kidney graft by endothelial cells originating from the recipient, may favour aHUS recurrence [15].

In our patient, measures to prevent recurrent aHUS after transplantation included the administration of FFP and one session of plasma exchange. We observed neither clinical nor laboratory signs of aHUS recurrence despite multiple potential triggers, such as repeated graft rejection and multiple infections necessitating pharmacologic treatment. Even 2 years after stopping FFP infusions, no aHUS recurrence occurred. The frequency of FFP administration was chosen empirically due to lack of data on aHUS patients with a combined MCP/CFI mutation. The half life of CFI is about 29–45 h. Effective levels of CFI have been maintained after a single infusion of 27–40 ml/kg FFP in homozygous CFI-deficient patients for 8 days, and the effects on C3d/C4d formation have lasted up to a maximum of 16 days [16]. In addition, it cannot be excluded that there are other mutations in circulating complement proteins not yet defined. The fact that the above-mentioned patient with combined CFI/MCP mutations [13] required only 10 days FFP treatment may suggest that a shorter treatment time with FFP in our patient could also have been sufficient.

Other combinations of mutations in complement regulatory genes with different outcomes after renal transplantation have been reported [3, 17–19]. Seitz et al. [17] described adult patients, two with combined MCP/CFH mutations and one with three mutations involving MCP, CFH and CFI; all developed aHUS recurrence after transplantation, and two successfully treated with plasma exchange. Sellier–Leclerc et al. [3] reported one child carrying mutations in both CFH and CFI with no aHUS recurrence after renal transplantation during a 3 year-follow-up.

Although a favourable course has been observed in our patient to date, the risk of aHUS recurrence may still remain due to potential exposure to unknown environmental triggers in combination with this specific genetic background [20].

Regular screening for signs of haemolysis and the immediate initiation of the appropriate treatment when required are indispensable in the case of aHUS recurrence (e.g. plasma exchange/infusion, complement blockers). The currently available complement blockers (e.g. eculizumab) may reduce the risk of aHUS recurrence in renal transplant without the need of long-term plasma therapy. This may be relevant if only isolated renal transplantation is performed, such as in a patient with aHUS with a combined CFI/MCP mutation, where the underlying CFI mutation carries a high risk for a poor outcome, including graft loss [10]. However, the combination of heterozygous MCP and CFI mutations with aHUS may also predict a lower risk of aHUS recurrence after an isolated renal transplantation.

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