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Angiotensin II type 1 receptor antibodies in childhood kidney transplantation

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Abstract: Angiotensin II type 1 receptor antibodies (AT_1RAb) have emerged as non-HLA Ab present in patients with acute AMR and risk of graft loss. Furthermore, AT_1RAb have been shown to increase angiotensin II sensitivity which may play a role in the development of CVD and hypertension. Data on AT_1RAb in stable transplant recipients are lacking. The aim of this study was to analyze the levels of AT_1RAb in a cohort of stable patients after kidney transplantation (tx) in childhood. A cross-sectional study of 30 children (median age 14, range 3–19 yr, median time since tx five yr) and 28 adults who were transplanted in childhood (median age 26, range 20–40 yr, median time since tx 18 yr) transplanted between 1993–2006 and 1983–2002, respectively, was performed. Healthy controls were 51 healthy children (5–8 yr) and 199 healthy donors (median age 56.5 yr, range 42–83 yr). Plasma AT_1RAb were analyzed by immunoassay. Median total AT_1RAb IgG concentration was significantly higher in the pediatric-tx group as compared to the adult-tx group (40.0 and 10.95 U/mL, $p < 0.0001$). For both groups, the tx group showed higher levels: the pediatric-tx group vs. control group (40.0 vs. 13.3 U/mL, $p = 0.0006$) and the adult-tx group vs. adult control group (10.95 vs. 6.5 U/mL, $p < 0.0001$). Age was the strongest indicator of high levels of AT_1RAb IgG ($p = 0.0003$). AT_1RAb total IgG levels are significantly higher in a stable pediatric-tx cohort as compared to adult-tx patients and healthy controls of comparable age groups. The relevance of our findings in relation to age, time since tx, previous or future rejection, and CVD risk merits future studies.

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HLA antibodies (HLA Ab) have well-recognized associations with graft failure in kidney transplantation (1). However, not all cases of graft loss can be explained by the presence of HLA Ab even when there are histological findings consistent with acute AMR. Subsequently, other non-HLA antibodies have emerged as plausible causative agents, including AT_1RAb. These Ab have been found in patients with AMR and vascular rejection (2). The presence of AT_1RAb before transplantation is proposed as a risk factor for graft loss and has a strong association with graft failure (3, 4). Still, the role of these autoantibodies after tx a factor involved in rejection and graft loss is not clear and under investigation (1).

Hypertension, a common complication after renal transplantation (tx), occurs in 30–50% of all kidney transplant recipients depending on the method of blood pressure measurement, definition, and normative data used (5). Hypertension is a risk factor for graft loss and CVD after kidney

Abbreviations: AMR, antibody-mediated rejection; AngII, angiotensin II; AT_1RAb, angiotensin II type 1 receptor antibodies; BMI, body mass index; CAKUT, congenital anomalies of the kidney and urinary tract; CHO, Chinese hamster ovary; CVD, cardiovascular disease; DD, deceased donor; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; GFR, glomerular filtration rate; HENT, health after kidney transplantation; IQR, interquartile range; LD, living donors; MAP, mean arterial pressures; NRR, Norwegian Renal Registry; RAS, renin–angiotensin system; TRPCP6, transient receptor potential cation channel 6.

tx (6). The etiology of hypertension after renal tx is multifactorial and includes the type and degree of native kidney disease, medication such as calcineurin inhibitors and steroids, obesity, vascular malformations, and reduced GFR (5). An activated RAS in the post-tx period is likely to contribute to an increase in blood pressure; however, detailed studies are lacking. Angiotensin II (AngII) is a potent vasoconstrictor and also regulates the water–salt balance through the AT_1 receptor. In addition, AngII acts as a pro-inflammatory cytokine via the AT_1 receptor, increases oxidative stress, and contributes to vascular remodeling and the pathogenesis of atherosclerosis (7). Similar effects have been observed for AT_1RAb, which also activates the AT1 receptor.

Data on AT_1RAb in pediatric kidney transplant recipients are lacking, and, so far, only two publications in children have been published. One case report describes a girl with accelerated acute C4d-positive kidney transplant rejection, malignant hypertension, encephalopathy, and the presence of both AT_1RAb and HLA class II Ab (8). A recent publication describes de novo development of AT_1RAb after kidney transplantation in childhood (9).

The aim of this study was to explore the presence of AT_1RAb in a cohort of tx patients with stable kidney function and transplanted in childhood with predominantly LDs.

Material and methods

Subjects

Transplanted patient cohorts

Ped-tx cohorts were children and adolescents between 3 and 19 yr who underwent transplantation at an age below 16 yr between 1993 and 2006.

Adult-tx cohort: Adults (20–40 yr) having a renal transplant during childhood (<16 yr of age undergoing first renal tx between 1983 and 2002), aged >19 yr, were identified from the NRR.

The transplanted patients were invited to participate in a cross-sectional study, the HENT study, performed in 2008–2010.

Inclusion criteria for the HENT study were a functioning graft for at least one yr and no ongoing signs of rejection. Written informed consent was obtained from patients and/or their parents (if younger than 16 yr) prior to study start. The HENT study protocol of the transplanted patients was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway, and the study was carried out according to the Declaration of Helsinki. Details from the HENT study have previously been published (10–12).

Control groups

Healthy children control group: Blood samples from a healthy group of fasting children aged 5–8 yr were used as background control group for the transplanted child study group. These healthy Norwegian children were included as part of a longitudinal pregnancy follow-up study of mother and children after pregnancy complications. Details from this study have previously been published (13).

Adult healthy control group: A total of 199 healthy controls were recruited at the University Hospitals of Goettingen, Berlin, and Erlangen after informed consent was obtained.

Clinical information from the transplant groups

Causes of ESRD (pediatric-tx group and adult-tx group)

Causes of ESRD were CAKUT (n = 18), glomerulonephritis (n = 9), nephronophthisis (n = 9), hemolytic uremic syndrome (n = 2), FSGS/congenital nephrotic syndrome (n = 6), metabolic causes (n = 4), and other or unknown (n = 10). For more detailed information, see Table 1.

Blood pressure

Hypertension in participants <19 yr of age was defined as a blood pressure above the 95th centile for age, height, gender, and/or using antihypertensive medication. Hypertension in adults was defined as a blood pressure >140/90 mmHg and/or using antihypertensive medication.

Rejection

Data up to and including 2014 were retrieved retrospectively and prospectively in regard to the HENT study through medical charts and from the NRR concerning kidney transplant rejection.

Acute rejection episodes were defined by an elevation in serum creatinine of at least 20%, accompanied by antirejection therapy and/or accompanied by positive histological findings. Rejections were not categorized further into acute cellular, vascular, or AMR.

Angiotensin II type 1 receptor antibodies (AT_1RAb) measurement by ELISA

Concentrations of AT_1RAb were measured by a sandwich ELISA using a kit (CellTrend GmbH, Luckenwalde, Germany) from EDTA plasma according to the manufacturer's protocol. Extracts from transfected CHO cells overexpressing the human AT1R were coated on microtiter 96-well polystyrene plates. Conformational epitopes of the receptor were maintained by addition of 1 mM calcium chloride to every buffer. Samples were analyzed in duplicate in a 1:100 serum dilution after incubation at 48 °C for two h. After washing steps, plates were incubated for 60 min with a 1:20 000 dilution of horseradish peroxidase-labeled goat anti-human IgG (Jackson, Bar Harbor, ME, USA) used for detection. To obtain a standard curve, plates were incubated with test sera from an anti-AT_1RAb-positive index patient. When compared to the neonatal cardiomyocyte bioassay used in the first study (4), the solid-phase assay had 96% specificity and 88% sensitivity. The interassay variability was 8%; the intra-assay variability was 5%. All Oslo samples were sent anonymously to Berlin for anti-AT_1RAb assessment, without information regarding the patients' clinical characteristics. The detection threshold of anti-AT1R-Abs was set at 2.5 U/mL and maximum value was given as 40.0 U/mL, which was the upper cut off limit.

Statistical analyses

Data were reported as median, range values with IQRs, or as proportions and percentages (for the categorical

Table 1. Clinical characteristics of the participants

	Ped-tx (n = 30)	Adult-tx (n = 28)	Ped controls (n = 51)	Adult controls (n = 199)
Median age at blood sampling (range)	14 (3–19) yr	26 (20–40) yr	6.7 (4.8–8) yr	56.5 (48–83) yr
Male/female	19/11	17/11	20/31	140/59
Age at Rtx (yr)	7 (1–16)	13 (1–16)	–	–
Median time since Rtx years (range)	5 (2–14)	18 (7–27)	–	–
LD/DD (n, %) 1 Rtx	26/4; 87/13	23/5; 82/18	–	–
2 Rtx	1/1	8/6	–	
3 Rtx	1/1	0/3		
Hypertension (n, %)	16/30, 53	23/28, 82	None	None
Acute rejection (n, %)	5/30, 17	14/28, 50	–	–
Median GFR (mL/min/1.73 m^2)	50 (22–95)	56 (20–120)*	–	–
Etiology of ESRD (n)			–	–
CAKUT	11	7	–	–
Glomerulonephritis	2	7	–	–
Nephronophthisis	3	6	–	–
HUS	1	1	–	–
FSGS/CNF	4	2	–	–
Metabolic†	4	–	–	–
Other diagnosis/unknown	5	5	–	–

CNF, congenital nephrotic syndrome Finnish type.
*n = 27.
†Metabolic = cystinosis and primary hyperoxaluria type 1.

variables). Comparisons between the groups were analyzed using an unpaired *t*-test, Mann–Whitney *U*-test (for variables with skewed distribution). The strength of crude associations between normally distributed continuous variables was measured using Spearman's correlation coefficient, as the variables had a skewed distribution. Associations between age, time since tx, donor source, rejections, and GFR were analyzed by multivariate regression. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. All statistical analyzes were performed using SPSS Statistics 18 (IBM company, Hong Kong).

Results

Table 1 presents a summary of clinical data from the two transplanted cohorts as well as from the two control cohorts. The cross-sectional study of the 30 children (ped-tx) had a median age of 14 yr at HENT study inclusion (range 3–19 yr), with a median time since tx of five yr (range 2–14 yr) (Table 1). All were transplanted between 1993 and 2006. Mean age of the control group of healthy of children (n = 51) was seven yr (range 5–8 yr) (Table 1). Regarding the control subjects, there were no significant differences in time since delivery for blood sampling between the group of children with a mother from a hypertensive pregnancy or from a non-hypertensive pregnancy, nor differences in offspring gender, BMI, systolic or diastolic blood pressure, or MAP (13).

The group of 28 adults who were transplanted at the age >16 yr (adult-tx) participated in the HENT follow-up study at a median age of 26 (range 20–40 yr), with a median time since tx of 18 yr. All subjects in the adult-tx group were transplanted between 1983 and 2002 (Table 1). The adult control group consisted of 66 men (33.3%) and 132 female (66.7%) subjects and had a median age of 56.5 yr (range 42–83 yr).

The pediatric-tx group had a significantly higher median total AT_1RAb IgG concentration, 40.0 U/mL (IQR 14.48–40.0), compared with the pediatric control group median 13.3 U/mL (IQR 7.49–38), p = 0.0006. Median total AT_1RAb IgG concentration was significantly higher in the ped-tx group 40.0 U/mL (IQR 14.48–40.0) as compared to the adult-tx group 10.95 U/mL (IQR 8.2–25.53), p < 0.0001. In contrast, the adult transplanted group had a significantly higher median total AT_1RAb IgG levels 10.95, (IQR 8.2–25.53) U/mL than the adult control group 6.5 U/mL (IQR 2.5–9.3), p < 0.0001 (Fig. 1). Sixteen of 30 patients in the pediatric-tx group (53.3%) had levels >40.0 U/mL, in contrast to 21.6% in ped control, 17.8% in adult-tx group, and none in the adult control group, respectively (Fig. 1).

The healthy pediatric control group had similar median total IgG concentration as the adult-tx group, 13.3 vs. 10.95 U/mL, p = 0.3 (Fig. 1). There was no AT_1RAb IgG level gender difference in the ped-tx group between girls (n = 11) and boys (n = 19) (40.0 (9–40.0) U/mL vs. 40.0 (11–40.0) U/mL). Similar to the ped-tx group, there was no gender difference for the adult transplanted group (women 9 (2.5–40.0) U/mL (n = 9) and men 11.9 (2.5–40.0) U/mL (n = 19)).

There was no difference in AT_1RAb IgG levels depending on the donor source, living-related

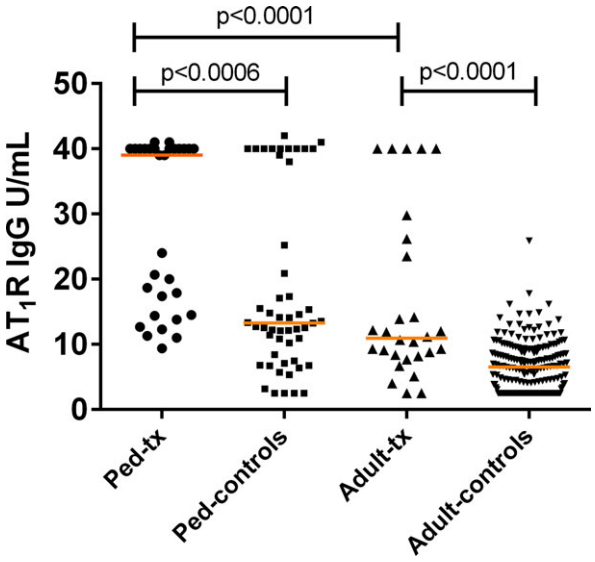

Fig. 1. Individual AT_1RAb IgG levels for the four study groups: pediatric transplanted group (ped-tx), n = 30; pediatric control group (ped-controls) n = 51; adult transplanted group (adult-tx), n = 28; and adult control group (adult-controls), n = 199. Bars indicate median levels. Highest cutoff level is 40 U/mL.

donor (LD, n = 47) vs. DD (n = 11), median 18.7 U/mL, ([IQR 11.2–40.0] U/mL) vs. median 12.7 U/mL, ([IQR 6.7–40.0] U/mL), p = 0.183. Donor source was considered as DD when more than one transplantation was performed with either LD or DD.

When analyzing the association of age with elevated levels of AT_1RAb IgG, there was a negative correlation between elevated levels and age (r = −0.46, p = 0.0003). At the same time, the longer the time since transplantation, the lower the levels (r = −0.29, p = 0.04) (Fig. 2a,b).

In a multivariate linear regression of the transplanted groups adjusting for age at the HENT study, LD vs. DDs, previous rejections, gender, GFR, and time from tx to the HENT study, age at tx was the only significant predictor for elevated AT_1RAb IgG levels at the HENT study inclusion time (β = −1.063, p = 0.006).

Fifty-three percent in the ped-tx group and 82% in the adult-tx group were hypertensive at the HENT study inclusion time, as defined above. We found a tendency toward higher AT_1RAb IgG levels and hypertension (p = 0.13).

Data on exposure to previous rejections before inclusion in the HENT study showed that there was a difference in rejection rates between the groups. The adult-tx group had by far more rejections than the pediatric cohort, 50% as compared to 17%. A previous rejection was poorly associated with AT_1RAb IgG levels (p = 0.11) in the adult-tx group. Rejection events in the pediatric group were rare so that statistical analysis was not performed.

The AT_1RAb IgG levels in the transplant cohorts were spread evenly between the various subgroups of transplant indication, with no correlation with any diagnostic group (data not shown).

Discussion

To our knowledge, this is the first report of AT_1RAb in a cohort of stable kidney recipients transplanted in childhood. In this retrospective study, our main findings were that the AT_1RAb levels were significantly higher both in children and in adults transplanted in childhood compared with healthy controls. Moreover, tx

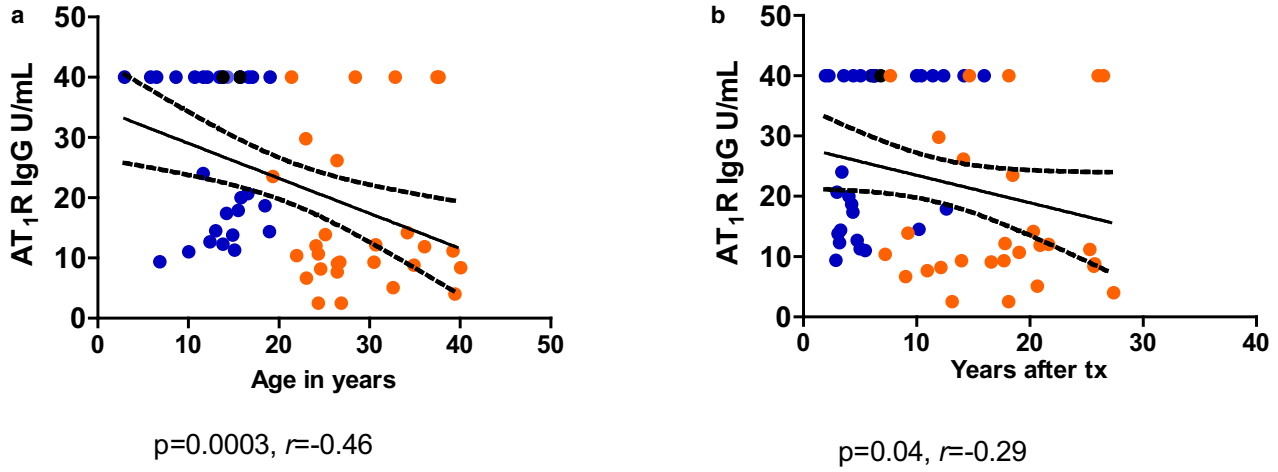

Fig. 2. (a) Individual AT_1RAb IgG levels in relation to age. Blue spots indicate the pediatric-tx group; red spots indicate the adult-tx group. (b) Individual AT_1RAb IgG levels in relation to time since tx. Blue spots indicate the pediatric-tx group; red spots indicate the adult-tx group.

children had significantly higher AT_1RAb levels compared to the adult-tx group. Age at tx was the only significant predictor for elevated AT_1Rab levels.

HLA antibodies (HLA Ab) have well-recognized associations with graft failure in kidney transplantation (14). However, not all cases of graft loss can be explained by the presence of HLA Ab even when there are histological findings consistent with AMR, and subsequently, other antibodies have emerged as plausible causative agents. Several reports of elevated AT_1RAb have recently been published in connection with kidney transplant rejection (3, 4). However, the role of these autoantibodies in rejection and graft loss following tx is not clear and under investigation (1). The mechanism of autoantibody development is probably multifactorial and not well understood. One hypothesis is that patients develop autoantibodies to AT_1 polymorphisms via the usual routes of allosensitization, both as a consequence of blood transfusion and as a transplantation (15) To what extent they are responsible for injury to the microcirculation and further amplification of cell damage still has to be clarified (16).

The pathophysiological role of AT_1RAb is unknown, but in a rat model, purified AT_1RAb from patients with vascular rejection induced renal artery muscular contractions after renal ischemia and allogeneic transplantation. Pretreatment with a pharmacological ATR1 blocker only partially inhibited the AT_1RAb-mediated contraction, which was almost completely abolished by neutralizing peptides targeting epitopes on the ATR_1 receptor (17). In addition, it is known that the autoantibodies stimulate the receptor in an agonistic way and contribute to vascular and perivascular inflammation (18). According to *in vitro* studies, the AT_1Rab may contribute to inflammation, endothelial dysfunction, and atherosclerosis (7).

The human gene for AT_1R is located on chromosome 3 and so far several polymorphisms have been identified, either mediating "loss of function" or "gain of function." Among these, the A1166C polymorphism is associated with increased responsiveness to AngII and various cardiovascular and renal pathologies (2). In the previously described pediatric case, the child was homozygote for the AGTR1 gene A11166C polymorphism (8).

Among other interesting observations, renal podocytes have been shown to express the AT_1 receptor, and AngII regulates and enhances the expression of TRPCP6, which leads to FSGS in animal models (19). In the previously published case of a child with AMR, the child had new-onset collapsing FSGS. There has been another published case in an adult with AMR, elevated levels of AT_1RAb and biopsy findings of focal collapsing glomerulopathy. The detected elevated levels of AT_1RAb were successfully removed by plasmapheresis and the condition improved (20, 21).

Autoantibodies to AT_1R have been associated with other diseases, such as preeclampsia, systemic sclerosis, and malignant hypertension (22, 23). A common feature of these diseases is the dysfunction of diseased vessels with marked inflammation and high thrombotic potential. Women with a history of preeclampsia, and their offspring, have an increased risk of CVD later in life, and increased levels of biomarkers for CVD have been shown to persist up to eight yr after birth (13, 24). The relation between this long-term health risk and presence of autoantibodies to AT1R in pregnancy is not known. Current hypotheses include the proposal that the presence of AT1Rab in pregnancy may mediate increased sensitivity to AngII and the development of pregnancy-related hypertension despite unaltered levels of AngII in preeclampsia (22). The presence of AT_1RAb has also been found to be associated with intrauterine growth restriction (25). The presence of AT_1RAb in pregnancy has been shown by us to be present both in the mother and in the fetus in preeclampsia (22). Whether these autoantibodies also induce or accelerate vascular dysfunction and could contribute to atherosclerotic processes and increased future cardiovascular risk, either for the mother and/or for the offspring, is not known.

There are some limitations to our study. First, this is a retrospective cross-sectional study, with blood sampling at different time points after transplantation. Second, data were not collected at the time of rejection and information about rejection was sampled from the NRR and from searches in medical reports and journals. As some data regarding rejections were historical, not all rejections episodes could be clinically categorized in details. None the less, even if the rejection rate in the adult group was significantly higher than in the pediatric group (50% vs. 17%, resp), the AT_1RAb levels in adults were significantly lower than in the ped-tx cohort at HENT inclusion. The longer interval from rejection may be a plausible explanation for the adults having lower IgG levels than the children with rejections previously, but even so, the levels in the pediatric control group were similar to the adult-tx group, suggesting that the time from tx was not the only relevant factor. Third, our samples sizes were

small and the groups were heterogeneous with respect to causes of end-stage disease and medical history. In addition, our control and patient groups were not perfectly age matched.

Conclusion

AT_1RAb total IgG levels were significantly higher in a stable pediatric-tx cohort compared to adult-tx patients and healthy controls of comparable age. The role of AT_1RAb after renal transplantation is still not defined. The relevance of our findings in relation to age and time since tx and the relation to rejection and CVD merits future longitudinal studies.

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