UNEXPECTEDLY HIGH PREVALENCE OF RARE GENETIC DISORDERS IN KIDNEY TRANSPLANT RECIPIENTS WITH AN UNKNOWN CAUSAL NEPHROPATHY

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BACKGROUND and AIM

Up to 30% of patients reach end stage renal disease without diagnosis of their nephropathy. A confirmed diagnosis is possible in less than 50% of candidates for renal transplantation, leading to a situation in which relapse on the transplant is not predictable.

Moreover some genetic nephropathies have a multiorgan involvement that could be in some cases very severe.

Since genes remain the same throughout the all life, even after developing ESRD and receiving a transplant, several undiagnosed rare disorders could be recognized after renal transplant (Tx) through genetic analysis.

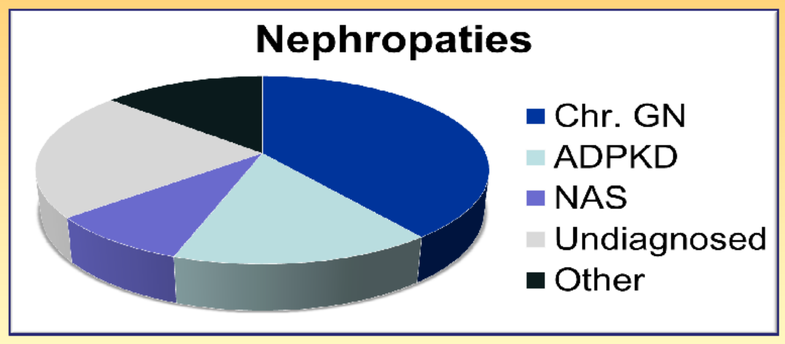
Aim of this study was to check the prevalence of genetic disease causing ESRD in a population of patients receiving a kidney trasnplant

PATIENTS and METHODS

Study period: 1998-2012

Overall Population: 911 Kidney Tx (43 dual; 37 living donor)

Study population: 278 (31%) KTR without a definte diagnosis



Investigated Diseases: Uromodulin-associated nephropathy; HNF1ß-associated nephropathy; Fabry disease; Nephronophthisis; Adenine phosforibosil-transferase (APRT) deficiency; Inverted Formin 2 FSGS.

RESULTS - 1

A rare genetic disease was diagnosed in 12 patients after KTx (Table), representing 1.31% (12/911) of KTx patients in the observation period. The **prevalence of a rare genetic disorders was 12/278 (4.32%) among patients without a definite diagnosis** of causal nephropathy.

Usual disease presentation and disease characteristics

Disease	Altered Protein	Transmission	Renal phenotype	Relapse after KTx?	Extrarenal manifestations?
APRT Deficit	Adenine-phosphoribosil transferase	AR	2,8 DHA Crystal nephropathy	Yes (up to graft loss)	No
UMOD	Uromoduline	AD	Interstitial nephritis	No	Gout
HNF-1β	Hepatocyte Nuclear Factor 1β	AD	Interstitial nephritis	No	NODAT, pancreatitis, malformation
INF2	Formin 2	AD	FSGS	No	No
Fabry	α-galactosidasis	X-link	Lysosome accumulation	No	Neuropathy, CardioMyoP
Senior-Loken	unknown	AR	Nephronophthisis	**No**	Retinitis pigmentosa (Blindness)

Study population characteristics

Disease	n	Preval.	Age of ESRD	Relapse after KTx?	Extrarenal manifestations?	Therapy / Outcome
APRT Deficit	2	0,72%	67; 48	2/2 (AKI from crystal nephrop.)	No	Allopurinol, bicarbonate: recovery of renal function. One pt died of breast cancer with a functioning graft.
UMOD	5	1,79%	57; 69; 67; 41; 65	No (6 yrs mean f/up)	None	Alive with functioning graft
HNF-1β	2	0,72%	48; 47	No (4 yrs mean f/up)	Pancreas enzyme elevation (both)	Alive with functioning graft
INF2	1	0,36%	24	No (12 yrs f/up)	No	Alive with functioning graft; has an affected son
Fabry	1	0,36%	61	No (6 yrs f/up)	Sick sinus, hypertophic CMP, stroke, vascular dementia	Enzyme replacement therapy: still progressive vascular disease Stable renal function (Cr = 1,5 mg/dL)
Senior-Loken	1	0,36%	30	No (21 yrs of KTx)	Blindness	First KTx lost after 16 years (Chr. Rej.); alive with functioning graft

"TEACHING" IMAGES

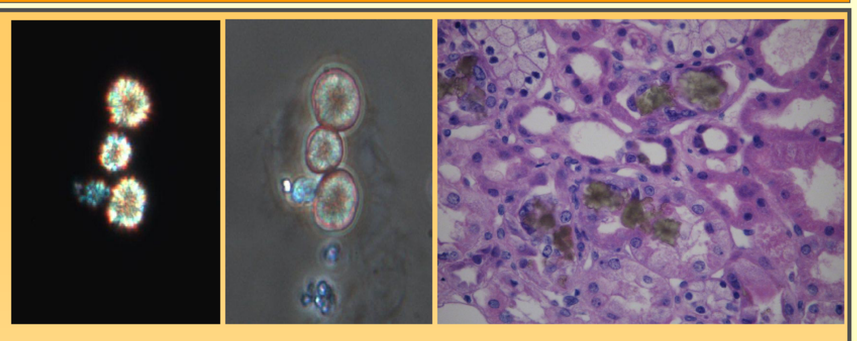


Figure 1: *DHA crystal nephropathy relapse on a transplanted kidney. The outcome was good (recovery of renal function) since specific therapy was started (allopurinol)*

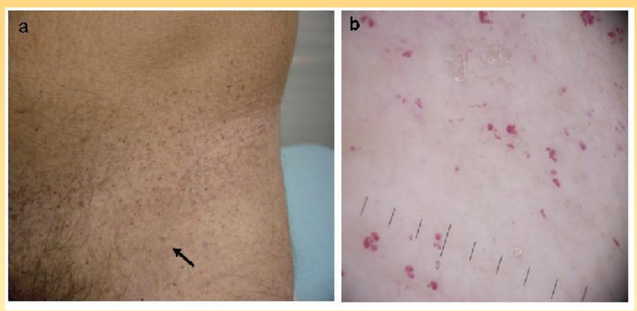


Figure 2: *Angiokeratomas of the patient #10, affected by Anderson-Fabry disease (alpha galactosidase A deficiency).*
a) Angiokeratomas are pointed by the arrow: there are diffuse angiokeratomas, with however the typical "swimsuit" distribution of the lesions.
b) b) *Dermoscopic examination of the lesions: multiple angiokeratomas represented by a small, warty, red to red-blue, non-itchy papules.*

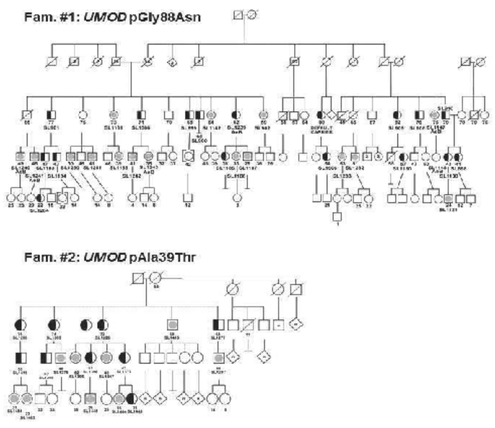


Figure 3: *Family trees of UMOD-associated nephropathy (medullary cystic kidney disease type 2 – MCKD2). This is a clear example of AD transmitted disease with complete penetrance: each affected patient has an affected parent*

CONCLUSIONS

1. ***The prevalence of rare genetic disorders might be as high as 4.3% if considering only KTx recipients without a definite diagnosis of causal nephropathy.***
   - APRT deficiency has an estimated prevalence 1:50000-1:100000 newborns: prevalence ratio in our sample would be 720-1440
   - UMOD-associated nephropathy has a prevalence of 1.67 pmp in the GP and 0.073% among dialysis patients; prevalence ratio in our sample would thus be 59.2 if compared with dialysis patients.
2. ***This missing diagnosis can have a serious impact on graft survival*** –such as in the case of 2,8DHA– ***and in general on management KTx patient and on other affected family members*** (such as HNF1B and Anderson-Fabry disease).
3. A high index of suspicion is needed in the transplant physician to detect key-signs and symptoms –sometimes "hidden" in patient history– which suggest the presence of a genetic nephropathy.

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