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A 10-year monitoring of the eyesight in patients after kidney transplantation

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Abstract

A pilot study of a 10-year analysis of the eyesight characteristics in patients after renal transplantation with a view to a later wider study of the same population.

The study encompassed 50 eyes in 25 patients who underwent renal transplantation in the years 2007 and 2008. All patients underwent: visual acuity measurement, tonometry, slit lamp examination, and spectroscopic optical coherence tomography.

Changes in the eyes observed during the 10-year observation period included mostly: cataract (48%), hypertensive angiopathy (28%), diabetic macular edema (16%), and glaucoma (16%). Ten years after the renal transplant visual acuity declined in 15 patients (60%). In 67% of those with eyesight deterioration the cause was cataract, while in patients with no changes in the eyesight (n = 10) cataract was diagnosed only in one. Patients with cataracts had been more often treated with cyclosporine, and that difference was statistically significant (73% vs 21%; $P < .05$). Comparing patients with hypertensive angiopathy with controls has shown that in the first group creatinine levels were statistically significantly higher (1.6 vs 1.16 mg/dL; $P < .05$). Patients with angiopathy had been also longer on renal replacement therapy before transplant (57 vs 26 months, $P > .05$), and this group included also statistically more persons after retransplantation (43% vs 5%, $P < .05$).

Most frequent ophthalmological diagnoses in patients after a kidney transplant include cataract, diabetic retinopathy, and hypertensive angiopathy. Visual acuity deterioration was seen in 60% of patients and was mainly the effect of cataract progress. The effect of cyclosporine on cataract progress was significant. The diagnosis of hypertensive angiopathy corresponded with poorer function of the transplanted kidney.

Abbreviations: 4p MDRD = 4point Modification of Diet in Renal Disease abbreviated formula, ADPKD = adult dominant polycystic kidney disease, AR = acute rejection, ATG = polyclonal antithymocyte globulin, CsA = cyclosporine, DGF = delayed graft function, DN = diabetic nephropathy, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, F = female, GN = glomerular disease, HD = hemodialysis, KTx = kidney transplantation, M = male, MMF = mycophenolate mofetil, NODAT = new onset diabetes mellitus after transplantation, P = prednisone, PD = peritoneal dialysis, PRA = panel reactive antibodies, PREE = pre-emptive kidney transplantation, PREE RET = pre-emptive kidney retransplantation, TAC = tacrolimus, TIT = total ischemia time, UTI = urinary tract infection.

Keywords: cataract, cyclosporine, diabetic macular edema, diabetic retinopathy, glaucoma, hypertensive angiopathy, kidney transplant

1. Introduction

Renal transplant (KTx) is considered the best therapeutic option for patients with end-stage chronic renal disease (ESRD). The largest benefits are seen in young people and in those with diabetic nephropathy in the course of type 1 diabetes. According to the estimates, every year worldwide about 80,000 kidney transplants are being performed. In Poland, the number of transplants in the last decade stays within the range of 900 to 1150 per year.[1,2]

Transplants would not have been possible without immunosuppression (IS). Unfortunately, the same drugs that prevent transplant rejection cause several adverse effects. The gold standard in the IS post-transplantation is therefore to use several drugs with different mechanisms of action, and in the minimum effective doses. Higher doses are recommended in the post-operative period, and should be decreased thereafter. In some patients it is possible to decrease the number of IS drugs, for example, by withdrawing steroids. After a kidney transplant, the most widely used immunosuppressives are: steroids (prednisone, prednisolone, metyloprednisolon), calcineurin inhibitors (CNI): cyclosporine (CsA), tacrolimus (TAC), proliferation signal

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inhibitors (mTOR inhibitors): sirolimus, everolimus, and inhibitors of cell division: azathioprine, mycophenolate mofetil/sodium (MMF/MPA). In some patients, an induction with polyclonal or monoclonal antibodies is being used.[3]

A patient with ESRD after KTx has usually many comorbidities such as hypertension, diabetes, or glaucoma. Moreover, ESRD often presents in the elderly, in whom eyesight deteriorates with age (e.g., because of cataract). That is why ophthalmological care is so important: because of progression of the pre-existing eye diseases, and because of the new ailments connected with the IS.

Changes in the eyesight, diagnosed after a kidney transplant, are mostly related to the eye status before the operation. The ophthalmologist should therefore examine the visual acuity, intraocular pressure, check the eye fundus, and perform spectroscopic optical coherence tomography (SOCT). These tests are important for the therapeutic process, and noninvasive (as opposed to the contrast examinations, such as fluorescein angiography), a thing particularly important in the case of nephropathies. It is important to evaluate the eye condition before transplant (at baseline) and then monitor it thereafter, especially for such diseases as diabetic retinopathy, which may be present before KTx (patients with type 1 diabetes), but may also develop as a result of new onset diabetes after transplantation (NODAT). Retinopathy risk factors include: duration of diabetes, acute nephropathy, unsuccessful metabolic control, pregnancy, hypertension, obesity, hyperlipidemia, anemia. For the doctor it is also important to distinguish between non-proliferative (NPDR) and proliferative (PDR) retinopathy. In the latter, when there is a membrane growth, neovascularisation and bleeding into the vitreous—the prognosis is poorer. Such patients require more frequent control visits, and sometimes—surgical intervention. NPDR is less risky, however the patient may still require focal laser therapy and should undergo periodic, ophthalmologic check-ups.[3] It is worth mentioning that at every stage of the diabetes progress, patients may develop diabetic macular oedema (DME), markedly hampering eyesight, and requiring both systemic and local treatment. Most importantly, however, KTx by itself can stabilise retinopathy.[4,5] Another frequent comorbidity is hypertension (HT), that may damage retinal vessels. That is why fundoscopy is important, particularly with evaluation of retinal vessels. HT changes in the back of the eye are at first very discrete (functional narrowing only) and limited to arteries. Only with time visible damage both to retinal arteries and veins could be seen, leading to the collapse of the blood-retina barrier. As a result small bleedings, "micro-strokes" in the retina (giving the symptom of cotton balls) or hard exudates appear, and in advanced cases it may lead to oedema, both of the retina itself, and of the optic nerve.[6] Results of the studies showing that hypertension retinopathy symptoms withdraw after kidney transplant should be perceived as the cause for optimism.[7] Primary, open-angle glaucoma (POAG) is an eye disease that might be precipitated by IS. High-risk groups include patients diagnosed with glaucoma, intraocular hypertension, and those with family history of glaucoma.[8] Other conditions predisposing to POAG include: age (more frequent after 65 years of age), race (more frequent in people of African origin), myopia, retinal diseases (e.g., thrombi in retinal vessels). Moreover, in patients after KTx one can see the progress of a slow optic nerve neuropathy, that is, a decrease in retinal nerve fiber layer (RNFL) thickness.[9] Persons after KTx are also more prone to cataracts. Risk factors predisposing to cataract development after KTx include: age, diabetes, HD, and use of large doses of steroids. At present many types of cataract are diagnosed in patients after KTx.[10] Optic nerve neuropathy is a rare but severe adverse effect of the tacrolimus treatment, manifesting with sudden, marked deterioration of the eyesight.[11] Neurotoxicity of cyclosporine and tacrolimus is the result of inhibition of the calcium calmodulin-dependent protein phosphatase and calcineurin.[12] Because of IS patients after KTx are also prone to opportunistic infections. IS treatment also predisposes patients to limbal stem cell deficiency (LSCD). Normally, these cells are responsible for the regeneration of corneal epithelium. Their depletion causes epithelial damage, marginal corneal ulcerations, conjunctivalization, and corneal vascularisation.[13]

Taking into consideration the fact that KTx recipients are in the high-risk group of progression of any co-existing eye diseases, and of development of new ones, we have undertaken the study to evaluate the eyesight of patients within the 10-year period after kidney transplant. We have also prepared the study design for further trials on a larger group of kidney transplant recipients.

2. Materials and methods

2.1. Recipient characteristics

Study participants were recruited from among the patients of Department of Nephrology, Transplantology and Internal Diseases, Medical University of Gdańsk, after KTx in the years 2007 and 2008. The studied group consisted of 25 patients (14 males, 11 females) aged between 23 and 69 (mean 47.88 ± 11.3) years. Ophthalmological studies encompassed 50 eyeballs.

The underlying renal diseases included chronic glomerulonephritis (36%), diabetic nephropathy (16%), adult dominant polycystic kidney disease (16%), not known and others (32%).

The modality of renal replacement therapy (RRT) before transplantation was hemodialysis (68%), peritoneal dialysis PDP (20%), in 12% of participants kidney transplantation was performed pre-emptively before starting dialysis. Four patients had their second transplantation. Before KTx 20 patients were diagnosed with hypertension, and 7 with diabetes. Patients' characteristics are presented in Table 1. All patients received kidneys from deceased donors. Postoperatively, 14 patients were on tacrolimus, and 11 on cyclosporine. All patients were maintained on glucocorticosteroids and mycophenolate mofetil/sodium. Induction with polyclonal antibody ATG was used in 4 patients.

2.2. Donor characteristics

The kidney donors (9 males, 16 females) were between 23 and 69 (mean 47.9 ± 15) years of age. Their mean eGFR (Cockroft–Gault) and plasma creatinine levels were 105.65 ± 34 mL/min/$1.73\,m^2$ and 0.94 ± 0.36 mg/dL, respectively. In 32% of the donors the cause of death was external trauma. Cerebrovascular incident was a cause of death in 52% of cases and other factors accounted for 16% of the deaths.

2.3. Statistical analysis

Categorical data were expressed as values and percentages. Continuous data were expressed as means and SD. Categorical data were compared with the Fisher exact test, whereas continuous data were compared with the Student t test or the Mann–Whitney U test (when variances were not homogeneous, the Levene test was used). Statistically significant variables in the univariate analysis were introduced in a multivariate model based

Table 1

Characteristics of the studied group of patients after kidney transplantation.

Variables	
Mean age—years mean (min–max)	47.88 (23–69)
Blood type	A—13, 0—6, B—6
Gender (M/F)	14/11
Dialysis modality before KTx	17—HD, 5—PD, 2—PREE, 1—PREE RET
Mean duration of dialysis before KTx—months (min–max)	34.96 (0–150)
Cause of ESRD	GN—9 DN—4 ADPKD —4 Other—3 Not known—5
Hypertension n (%)	20 (80%)
Diabetes mellitus n (%)	7 (28%)
2nd KTx n (%)	4 (16%)
Number of HLA mismatches mean (min–max)	3 (0–4)
PRA mean (min–max)	
Last	1 (0–22)
Historical	4 (0–33)
TIT mean (min–max)	649 (239–1133)
Immunosuppressive protocols (n)	MMF, CsA, P (11) MMF, TAC, P (10) MMF, TAC, P, ATG induction (4)

ADPKD = adult dominant polycystic kidney disease, ATG = polyclonal antithymocyte globulin, CsA = cyclosporine, DN = diabetic nephropathy, ESRD = end-stage renal disease, GN = glomerular disease, HD = hemodialysis, HLA = human leukocyte antigens, KTx = kidney transplantation, MMF = mycophenolate mofetil, PRA = panel reactive antibodies, PRA = panel reactive antibodies, PD = peritoneal dialysis, PREE = pre-emptive kidney transplantation, PREE RET = pre-emptive kidney retransplantation, TAC = tacrolimus, TIT = total ischemia time,

on forward stepwise logistic regression. All analyses were performed using Statistica software for Windows (Statsoft version 12). The limit of significance was set at 0.05.

2.4. Ophthalmological patients characteristics

The examination included: ophthalmological history, visual acuity testing on ETDRS tables (BCVA-best corrected visual acuity), applanation tonometry, slit-lamp examination, and spectroscopic optical coherence tomography (SOCT). Full evaluation was done twice: at baseline (up to 1 month after KTx) and after 10 years from the transplant. SOCT evaluated basic parameters such as: foveal retinal thickness and macular morphology. The baseline apparatus was OCT Stratus (Carl Zeiss), and re-evaluation after 10 years was done on 3D SOCT 2000 (Topcon). The only criterion excluding a patient from the examination was a cataract present at the time of the first (baseline) visit.

3. Results

3.1. Post-transplant disease course

Complications diagnosed in the post-transplant period are listed in Table 2. In 8 patients the graft function was delayed (DGF), and in 2 cases acute rejection (AR) was diagnosed and treated successfully with prednisolone boluses. Other complications included: UTI (2 patients) and NODAT (3 patients). At present all transplanted kidneys work well—the average creatinine level is 1.3 mg/dL (Table 3).

Table 2

Complications in the studied group of patients after kidney transplantation.

Complications after KTx	N (%)
AR n (%)	2 (8%)
DGF n (%)	8 (32%)
UTI n (%)	2 (8%)
NODAT n (%)	3 (12%)

AR = acute rejection, DGF = delayed graft function, KTx = kidney transplantation, NODAT = new onset diabetes mellitus after transplantation, UTI = urinary tract infection

3.2. Results of the ophthalmological examination

Ophtalmological diagnoses at baseline and after 10 years from KTx are presented in Table 4. Ten years from KTx 12 patients developed cataracts and that weighed on the statistical worsening of the eyesight in the whole study group (60%).

In 14 patients there had been visual disturbances at baseline. In 13 of those the damage progressed; and in 1 sight problems were initially so advanced that it has been difficult to observe further worsening. Only 1 patient in the study group had normal eyesight at baseline, and experienced worsening in the course of study. Hypertensive angiopathy (I and II grade in the Scheie grading system) was diagnosed in 7 of the participants (including *de novo* 3 cases) and in patients with diabetes (both diagnosed before and after KTx) we have seen 2 cases of epiretinal membrane (ERM) and 4 cases of macular oedema (including 2 *de novo*). A total of 2 patients experienced retinal detachment, and 1—optic neuropathy in 1 eye. Among newly observed sight problems we have seen OAG in 2 patients.

Comparison of patients after kidney transplantation with, and without cataract is presented in Table 5. Patients with, and without cataracts were similar in all but 1 of the analysed parameters. Namely, significantly more patients suffering from cataract, were receiving CsA ($P < .05$).

In univariate analysis CsA was significantly associated with cataract. It was also the independent predictor upon multivariate analysis.

Comparison of patients after kidney transplantation with, and without, hypertensive angiopathy is presented in Table 6. Patients with angiopathy had significantly higher creatinine concentration at the end of follow-up ($P < .05$). Significantly more patients after second transplantation suffered from hypertensive angiopathy, as compared with patients after first transplantation ($P < .05$).

On univariate analysis, risk factors significantly associated with hypertensive angiopathy were, among others: induction therapy, AR, kidney function after 10 years, second transplantation, male gender, but none of them was the independent predictor in multivariate analysis.

Table 3

Graft function (eGFR and serum creatinine concentration) in kidney transplant patients.

Time after KTx	eGFR (4p MDRD), mL/min	Creatinine concentration, mg/dL
1 month	60.1	1.3
10 years	59.2	1.26

4p MDRD = 4point Modification of Diet in Renal Disease, eGFR = estimated glomerular filtration rate, KTx = kidney transplantation.

Table 4

Ophthalmological diagnosis in studied group of patients after kidney transplantation.

Ophthalmological diagnosis	Output examination early after KTx n (%)	Examination 10 years after KTx n (%)
Cataract	0	12 (48)
Glaucoma	2 (8)	4 (16)
Proliferative diabetic retinopathy proliferative	2 (8)	2 (8)
Nonproliferative diabetic retinopathy	4 (16)	8 (32)
Diabetic macular oedema	2 (8)	4 (16)
Epiretinal membrane	0	2 (8)
Retinal detachment	0	2 (8)
Hypertensive angiopathy	4 (16)	7 (28)
Reduced visual acuity	14 (56)	15 (60)
Optic neuropathy	0	1 (4)

KTx = kidney transplantation.

4. Discussion

Despite being conducted on a relatively small group of patients, our study has detected numerous ophthalmological diseases. Some patients already at baseline were having comorbidities, such as: NPDR and PDR, DME, HA (hypertensive angiopathy). In those patients (especially the ones with PDR or/and DME) visual acuity had been diminished already before the start of the study.

After 10 years ocular problems were detected in 72% of patients. Of course that was also resulting from advancing age, and related complications such as progressing cataracts, decreasing retinal thickness, or RNFL (retinal nerve fiber layer) thinning.[14]

Most frequent ocular complications were cataracts (48%), for many years linked with steroids[15] (Fig. 1). Our study, however, has additionally shown that another factor predisposing for cataracts was cyclosporine use ($P = .028$). Similar were the conclusions of Nakamura et al.[16] It is assumed that CsA decreases steroids' clearance, and as a result the latter may act longer on the lens.[17] Additionally CsA is known to inhibit the action of P-glycoprotein (a cellular membrane protein).[18] P-glycoprotein has the ability to remove foreign substances (including drugs) from within the cells preventing their accumulation. That is why blocking it favors cataract progression.

Around 60% of patients experienced a decrease in visual acuity, and in most cases the cataract was responsible. Other diseases that in our observation predisposed to the decrease in visual acuity were: optic nerve neuropathy, diabetic macular oedema (DME), diabetic retinopathy, ERM, and retinal detachments.

Hypertensive angiopathy was present in 28% of patients, of whom in 16%—at baseline. For years, in the clinical evaluation of HA, Scheie classification has been useful, where: grade 0 = nothing, grade 1 = barely detectable arterial narrowing, grade 2 = obvious arterial narrowing with focal irregularities, grade 3 = as in grade 2 with the addition of retinal hemorrhages or exudates, grade 4 = as in grade 3 with the addition of disk swelling. In our study group, we have seen mostly grades 1 and 2 in Scheie classification. No patient progressed to advanced hypertensive angiopathy. Observed changes were mostly mild. HA was statistically more often seen in patients after retransplantation. It was probably the effect of longer duration of hypertension, and possibly also of an IS treatment after the first KTx. We have also observed statistically significantly higher serum creatinine concentrations in patients with HA, most probably resulting from vascular changes induced by hypertension, present also in microcirculation of the transplanted kidney.[19]

One patient developed primary open-angle glaucoma (POAG) and another—a silicone oil glaucoma after treatment for retinal

Table 5

Comparison of patients after kidney transplantation with, and without, cataract.

Variables N (%)	Cataract N = 12	Without cataract N = 13	Fisher test *P* value
CsA use	8 (67%)	3 (23%)	0.028
Male gender	7/12 (58%)	7/13 (54%)	$P > .05$
DGF	3 (25%)	5 (38%)	$P > .05$
Death	4 (33%)	2 (15%)	$P > .05$
HA	10 (83%)	10 (77%)	$P > .05$
2nd KTx	1 (8%)	3 (23%)	$P > .05$
HD	8 (67%)	9 (69%)	$P > .05$
AR	1/(9%)	1 (8%)	$P > .05$
Variables mean ± SD	**Cataract N = 12**	**Without cataract N = 13**	**Student *t* test *P* value**
Age, years	52.4 ± 11.2	43.7 ± 12.2	$P > .05$
Months of dialysis	26.6 ± 22,5	42.7 ± 45.5	$P > .05^*$
TIT	628.0 ± 205	668.8 ± 293	$P > .05^*$
Age of the donor, years	43.7 ± 13	39.2 ± 16	$P > .05$
Creatinine concentration 1 month after KTx, mg/dL	1.28 ± 0.4	1.34 ± 0.3	$P > .05$
GFR 1 month after KTx, mL/min	62.2 ± 21	58.1 ± 17	$P > .05$
Creatinine concentration 10 years after KTx, mg/dL	1.28 ± 0.2	1.25 ± 0.4	$P > .05^*$
GFR 10 years after KTx, mL/min	55.2 ± 15	62.7 ± 22	$P > .05$

CsA = cyclosporine, GFR = glomerular filtration rate, KTx = kidney transplantation.
* Mann–Whitney *U* test.

Table 6

Comparison of patients after KTx with, and without, hypertensive angiopathy.

Variables mean ± SD	With angiopathy N = 7	Without angiopathy N = 18	*t* Student test *P* value
Age, years	48.8 ± 7.9	47.5 ± 13.8	$P > .05^{*}$
Months of dialysis	57.3 ± 54.6	26.3 ± 23.4	$P > .05^{*}$
Number of HLA mismatches	2.0 ± 1	2.8 ± 0.7	$P > .05$
PRA current (%)	0.833 ± 2	1.7 ± 5.4	$P > .05$
PRA historical (%)	5.7 ± 7.2	3.6 ± 8.5	$P > .05$
TIT, minutes	706.4 ± 219	626.9 ± 264	$P > .05$
Age of the donor, years	44.7 ± 15.4	40.1 ± 15	$P > .05$
Creatinine concentration, mg/dL 1 month after KTx	1.41 ± 0.2	1.27 ± 0.4	$P > .05$
GFR 1 month after KTx, mL/min	49.39 ± 15.1	62.16 ± 20.3	$P > .05$
Creatinine concentration 10 years after KTx, mg/dL	1.61 ± 0.34	1.16 ± 0.24	0.009
GFR 10 years after KTx, mL/min KTx	49.39 ± 11.4	62.16 ± 19.8	$P > .05$

Variables N (%)	With angiopathy N = 7	Without angiopathy N = 18	Fisher test *P* value
CsA	3 (43%)	8 (44%)	$P > .05$
Male gender	6/7 (86%)	8/18 (44%)	$P > .05$
DGF	3 (43%)	5 (28%)	$P > .05$
Death	3 (43%)	3 (17%)	$P > .05$
HA	6 (86%)	14 (78%)	$P > .05$
2nd KTx	3 (43%)	1 (5%)	$P < .05$
HD	5 (71%)	12 (67%)	$P > .05$
AR	1 (14%)	0/(0%)	$P > .05$

AR = acute rejection, CsA = cyclosporine, DGF = delayed graft function, DN = diabetic nephropathy, eGFR = estimated glomerular filtration rate, ESRD = end-stage renal disease, F = female, GN = glomerular disease, HA = hypertensive angiopathy, HD = hemodialysis, KTx = kidney transplantation.

* Mann–Whitney *U* test.

detachment, which—because of a different pathomechanism was excluded from further analysis. In all patients with POAG (also if present at baseline) local hypotensive treatment was introduced, and visual acuity remained stable within 10 years of observation in all but 1 patient (diagnosed with DME).

Even after 10 years of monitoring, patients with nonproliferative diabetic retinopathy (NPDR) did not progress to the proliferative form of the disease (PDR). Diabetic macular edema (DME) had been seen at baseline in 2 patients with (100%) recurring throughout the observation period. It has to be stressed however that those patients had been treated for ocular complications (hemorrhages into the vitreous body, retinal laser therapy) already before KTx. Among 9 patients with NPDR, 2 also had DME. Cataract developed in 45% participants with diabetic retinopathy. Epi-retinal membrane (ERM) was seen only in 1 patient in the NPDR group, and 1 in the PDR group. No patient with diabetic retinopathy had to be hospitalized because of the progress of the disease within the 10-year observation period. As in the Chow et al[20] study, in the post-transplant follow-up period, most of our patients with diabetes (73%) had a stable retinopathy.

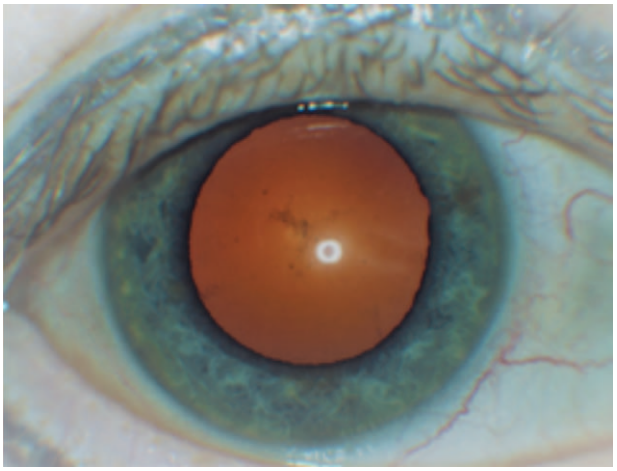

Figure 1. Initial subcapsular cataract.

Two patients experienced retinal detachment requiring operative treatment: 1 was post-traumatic and another was rhegmatogenous. Optic neuropathy developed in 1 patient (1 eye) and was probably linked with tacrolimus therapy. During treatment, there was progressive vision loss with concentric narrowing of the visual field. SOCT revealed marked decrease of the RNFL and ganglion cell + inner plexiform layer (GCL-IPL) thickness (Fig. 2). It is been suspected that tacrolimus, as well as cyclosporine (calcineurin inhibitors) may have a toxic effect on oligodendrocytes—glial cells forming myelin sheets in the CNS.[21]

5. Conclusions

To sum up, we would like to stress that for such severely diseased patients as persons after KTx, a 10-year monitoring period is a long time. And that time was also an adverse factor, apart from ophthalmological conditions that were present at baseline. According to our observations of the study group, most frequently seen ocular complications were: cataracts, diabetic retinopathy, and hypertensive angiopathy. Eyesight worsening was seen in 60% of patients and resulted mainly from cataract

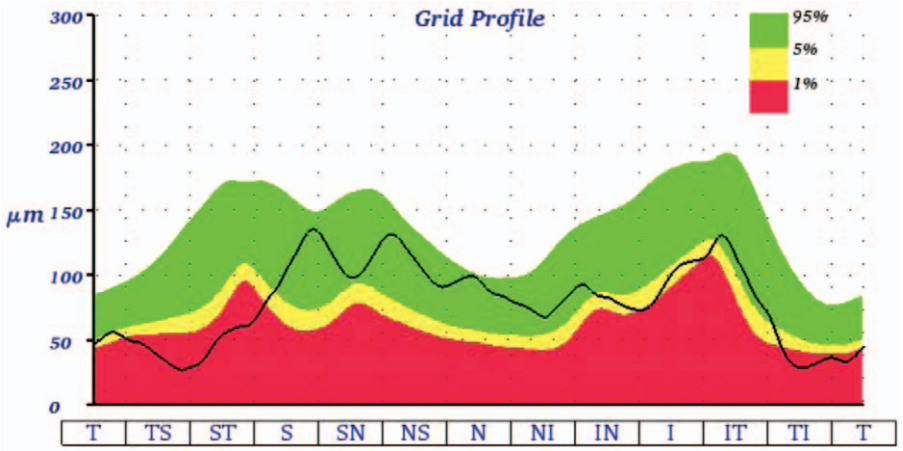

Figure 2. Neuropathy of the optic nerve after tacrolimus therapy. Retinal nerve fiber layer thickness (RNFL) loss. RNFL = retinal nerve fiber layer thickness.

progression. It seems that this progression was affected by cyclosporine use. Hypertensive angiopathy was also linked with worse transplant function, which might be the symptom of microcirculation damage in the transplanted kidney as well. Several limitations of this study deserve mention. Generalization of the results may be limited, as the study was restricted to a single centre. This study had limited power to identify statistically significant differences, because of the small number of cases included.

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