

Vestibular dysfunction in adolescents and young adults after kidney transplant

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Abstract

Introduction: Chronic kidney disease is a slowly progressive disease that causes irreversible loss of renal function and is considered a public health problem worldwide. **Objective:** To evaluate the vestibular behavior in patients with chronic kidney disease undergoing renal transplantation. Methods: A retrospective cross-sectional study was performed. Thirty patients were evaluated, 33.3% female and 66.7% male (mean age 16.9 (\pm 3.6) years old). Patients underwent the following procedures: anamnesis, ENT (ear, nose, and throat) evaluation and vestibular evaluation.

Results: The patients reported dizziness when they were on dialysis. 50% the patients showed an abnormality in the vestibular test, which occurred in the caloric test. The abnormality was more prevalent in the peripheral vestibular system and there was a predominance of deficit peripheral vestibular disorders. **Conclusion:** The dizziness was the most significant symptom for the vestibular test in correlation with neurotological symptoms. Alteration in the vestibular exam occurred in the caloric test, there was a prevalence of alterations for the peripheral vestibular system with a predominance of deficit vestibular dysfunction. We emphasize the need to show professionals involved in patients with chronic kidney disease, those undergoing renal transplant and dialitic treatment the importance of prevention and early identification of otoneurological involvement.

Keywords: electronystagmography, kidney, kidney failure, chronic, kidney transplantation, vestibular function tests.

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INTRODUCTION

Chronic kidney disease (CKD) is a slowly progressive disease that causes irreversible loss of renal function and is considered a public health problem worldwide¹. The prevalence of patients with CKD in Brazil nearly doubled in the last eight years, and the incidence of new cases grows about 8% per year².

In 2006, the Brazilian Society of Nephrology (BSN) reported a prevalence of 383 dialysis patients per million of population in Brazil, 90% in hemodialysis and 10% in peritoneal dialysis³.

Early diagnosis of CKD is related to better prognosis, prevents complications and reduces comorbidities².

Ototoxic drugs, particularly aminoglycoside antibiotics, can cause irreversible damage to hair cells of the spiral organ due to the formation of complex substances derived from the reactivity between the drug and the cell membrane phosphoinositides. The release of oxygen free radicals is also related to the ototoxicity of several drugs⁴. The kidney and the cochlear duct have anatomical, physiological, immunological and pathological similarities. The renal glomerulus and renal tubules have similar characteristics to the stria vascularis. For this reason, many nephrotoxic drugs may also be ototoxic^{5,6}.

Due to the proximity of the structures responsible for hearing and vestibular function, patients often experience changes in both systems. However, complaints of disequilibrium are not observed in all cases⁷.

The vestibular organ is responsible for sensations of body balance, being of fundamental importance in the spatial relationship between organism and environment. For balance to occur appropriately it is necessary a perfect integration between the vestibular organ, auditory and visual system, and proprioceptive sensitivity⁷.

Peritoneal dialysis, hemodialysis and renal transplantation are important procedures in the treatment of patients with chronic renal failure. Both dialysis and transplantation may result electrolyte, osmotic, biochemical, vascular and immune abnormalities in inner ear, causing cochlear and vestibular manifestations such as tinnitus, vertigo and hearing loss⁸.

The aim of this research was to evaluate the vestibular behavior in patients with chronic kidney disease undergoing renal transplantation.

PATIENTS AND METHOD

We analyzed data from 30 patients, 20 (66.7%) male and 10 (33.3%) female, from 13 to 26 years-old (mean age 16.9 (\pm 3.6), with CKD of different etiologies (Table 1), who had undergone a renal transplantation. Patients were evaluated at the Otoneurology Research Center.

Table 1. List of age and base disease of patients subjected to kidney transplantation.

Patient	Age (years)	Base Disease
1	17	Posterior urethral valve
2	19	Hypertensive nephropathy
3	18	Hemolytic uremic syndrome
4	14	Hemolytic uremic syndrome
5	16	Autosomal dominant polycystic kidney disease
6	17	Hemolytic uremic syndrome
7	16	Hemolytic uremic syndrome
8	15	Multicystic kidney
9	20	Posterior urethral valve
10	14	Systemic lupus erythematosus
11	13	Glomerulonephritis
12	13	Posterior urethral valve
13	25	Posterior urethral valve
14	13	Posterior urethral valve
15	16	Neurogenic bladder
16	13	Cystinosis
17	17	Posterior urethral valve
18	20	Glomerulonephritis
19	26	Bladder exstrophy
20	20	Posterior urethral valve
21	24	Reflux nephropathy
22	14	Hemolytic uremic syndrome
23	11	Posterior urethral valve
24	17	Obstructive uropathy
25	19	Glomerulonephritis
26	19	Prune belly syndrome
27	16	Posterior urethral valve
28	16	Unknown
29	17	Posterior urethral valve
30	13	Urogenital sinus

The research was approved by the Human Research Ethics Committee from Pequeno Príncipe Hospital, Brazil (Register Number: 0715-09). All patients or legal responsible signed a consent form.

The duration of dialysis prior to renal transplantation ranged from one to 13 years (mean 6.7 (\pm 3.8)). Eight patients were treated with peritoneal dialysis, 17 with hemodialysis, and five with both.

The mean length of hospitalization in males and female ranged from 5 to 120 days. The follow-up post-transplant in males ranged between 0.5 and 9 years and females ranged from 2 to 8 years (mean 4.4 \pm 2.2 years).

Regarding the type of donor for renal transplantation, 21 were from living donors and nine from deceased

donors. All patients had undergone renal transplant, regardless the underlying renal disease, time and type of previous treatment, and donor type.

Patients with mental, visual, musculoskeletal impairments, with ear diseases were excluded. The patients had kidney transplant for a minimum of five months and a maximum of 13 years.

A questionnaire to obtain otoneurological symptoms and personal and family information was applied (protocol developed by the Department of Otoneurology, Tuiuti University of Paraná).

Patients undertook a special diet, starting 72 hours before the otoneurological exams (abstaining from the intake of coffee, any kind of soda or caffeinated tea, chocolate, smoke, or alcohol). Analgesics, tranquilizers, and antihistaminic and antivertigo medications were suppressed during this period to minimize possible interferences with the test results. Three hours of fasting was recommended prior to the exam.

Vestibular function evaluation is composed of many labyrinthine function and ocular tests. The first part of our patients' evaluation was simply clinical and consisted of a systematic search for spontaneous, gaze, and positional nystagmus. The second part consisted of interpretation of the ENG test results, which is the objective register of the variations in the corneoretinal potentials, captured by sensitive electrodes. The ENG test is composed of: calibration of the ocular movements, search for spontaneous and gaze nystagmus, the oscillatory tracking test, optokinetic nystagmus search, and rotatory and caloric tests.

Clinical Evaluation

The search for positional nystagmus and vertigo was verified through Brandt and Daroff's maneuver⁹. Patients were requested to remain seated with the head and neck bent and the body tilted to the side, which evokes the vertigo; the head was then positioned 45 degrees in the opposite direction, and the neck rested on a horizontal plane at the final position. Patients returned to the first position and repeated the procedure toward the opposite side. The clinician searched for nystagmus for 30 seconds in each position.

The search for spontaneous nystagmus occurred without specific stimulation, with open and closed eyes. We searched for horizontal and vertical gaze nystagmus with 30-degree deviations (right, left, up, and down).

ENG Registers

We performed ENG with three-channel equipment (Berger Eletromedicina, model VN316, made in São Paulo, SP, Brazil). We cleaned the periorbital region with alcohol and placed the electrodes with electrolytic paste at the lateral angle of each eye and in the midpoint of the

frontal line, forming a triangle and enabling the register of horizontal, vertical, and oblique ocular movements.

We performed tests with a rotating chair (Ferrante, model COD 14200, made in São Paulo, SP, Brazil), a visual stimulator (Neurograff Eletromedicina, model EV VEC, São Paulo, SP, Brazil), and an air caloric stimulator (Neurograff Eletromedicina, model NGR 05, São Paulo, SP, Brazil).

We made the following eye and labyrinth tests at ENG:

(a) calibration of eye movements to assess the regularity of the trace; (b) analysis of spontaneous nystagmus (eyes open and closed) and semi-spontaneous (eyes open) to evaluate the occurrence, direction, inhibiting effect of ocular fixation (IEOF) and the maximum slow component angular velocity (MSCAV) of the nystagmus; (c) pendular eye tracking test to assess occurrence of nystagmus and its curve type; (d) evaluation of optokinetic nystagmus at a velocity of 60° per second, in counterclockwise and clockwise in the horizontal direction. We evaluated the occurrence, direction and maximum MSCAV of the nystagmus; (e) search pre-rotatory and post-rotatory nystagmus by decreasing pendular rotation test, with stimulation of the lateral semicircular canals. For stimulation of the lateral semicircular ducts (horizontal) the head is flexed 30° forward. For evaluation of the anterior (or superior) semicircular ducts the head was positioned 60° backward and 45° to the right and for evaluation of the posterior semicircular ducts the head was positioned 60° backward and 45° to the left. It was observed the occurrence, direction, frequency of the nystagmus; (f) analysis of nystagmus pre-caloric and post-caloric, was performed with the patient tilted 60° backwards for adequate stimulation of the lateral semicircular ducts. The irrigation time of each ear with air at 42 °C, 18 °C and 10 °C lasting 80 seconds and the responses were recorded with open and closed eyes to observe the IEOF. We evaluated the direction, the absolute values of MSCAV of the nystagmus and the calculation of the ratio of directional preponderance (DP) and labyrinth predominance (LP) of post-caloric nystagmus¹⁰.

We compared results with normal standards, obtained from epidemiological studies for the Brazilian population¹¹⁻¹³. Table 2 shows the criteria used to analyze each test as well as to distinguish central from peripheral vestibulopathy.

The diagnosis of peripheral vestibulopathy is achieved by comparison with normal standards and the absence of pathognomonic signs of central vestibular alterations.

The data were analyzed by Fisher's exact test and Chi-square, searched for a statistically significant difference in ENG results, comparing the affected patients with those in the control group ($p < .05$).

Table 2. Normal standards and criteria used to analyze the vestibular tests and distinguish central from peripheral.

	Normal Vestibular Exam	Peripheral Vestibular Exam	Central Vestibular Exam
Position nystagmus (Brandt & Daroff's maneuver)	Absent	Present (rotatory, horizontal rotatory, and oblique) with latency, paroxysm, weariness, and vertigo	Present (vertical inferior, superior, rotatory, horizontal rotatory, and oblique), without latency, paroxysm, weariness, and vertigo
Calibration of the ocular movements	Regular	Regular	Irregular (alterations in latency, accuracy, and velocity of the saccadic movements)
Spontaneous nystagmus	Present (< 7degrees/sec) with closed eyes; absent with open eyes	Present (> 7 degrees/sec) with closed eyes; absent with open eyes	Present with open eyes (vertical inferior, superior, rotatory, horizontal rotatory, oblique, cyclic, dissociated, and retractor)
Gaze nystagmus	Absent	Absent	Present, unidirectional, bidirectional, or mixed; presents a variety of nystagmus types
Oscillatory track	Types I and II	Type III	Type IV (pathognomonic); alterations of morphology and gain
Optokineticnystagmus	Symmetrical, < 20 degrees/sec	Asymmetrical, > 20 degrees/sec, having superposed spontaneous nystagmus with open eyes that justifies this alteration	Asymmetrical, > 20 degrees/sec, absent and reduced
Rotation test	< 33%, after stimulation of the lateral and superior semicircular ducts	> 33%, after stimulation of the lateral and superior semicircular ducts	> 33%, after stimulation of the lateral and superior semicircular ducts and absence of induced oblique nystagmus
Air caloric test	Absolute value: between 2 and 24 degrees/sec Relative values: Labyrinth preponderance < 41% Nystagmus directional preponderance < 36%	Absolute value: < 2 degrees/sec (hyporeflexia), > 24 degrees/sec (hyperreflexia) and areflexia Relative values: Labyrinth preponderance > 41% Nystagmus directional preponderance > 36% (Jongkees formula)	Absolute value: < 2 degrees/sec (hyporeflexia), > 24 degrees/sec (hyperreflexia) and areflexia Relative values: Labyrinth preponderance > 41% Nystagmus directional preponderance > 36% (Jongkees formula). Different nystagmus types may be observed: dissociated, inverted, perverted, and absence of the fast component of the nystagmus
Inhibiting effect of ocular fixation	Present	Present	Absent

Based on Padovan & Pansini¹¹, Mangabeira-Albernaz et al.¹², and Ganança et al.¹³.

RESULTS

The patients showed no vestibular complaints during the anamnesis. They mentioned dizziness only when they were performing the dialysis.

The studies on positional/positioning nystagmus, eye movement calibration, investigation of spontaneous nystagmus with eyes open and closed, semi-spontaneous nystagmus, pendular tracking tests and optokinetic nystagmus showed no alterations.

For the caloric test, fourteen cases (46.7%) of labyrinthine hyporeflexia and one case (3.3%) of LP altered.

Fifteen cases (50%) had peripheral vestibular system and there was a predominance of deficit peripheral vestibular disorders, with seven bilateral cases (23.3%) and eight unilateral cases (26.7%).

The test was normal in 15 cases (50%). Although not as significant in the statistical study, 50% of patients showed abnormalities in vestibular exam and this result was important.

The relationship between gender (Table 3), age (Table 4) or time of dialysis (Table 5) and ENG was not statistically significant. The relationship between the type of dialysis or the time after renal transplantation and ENG is described in Tables 6 and 7 respectively.

There was no statistically significant relationship between the donor type (living or deceased) and ENG ($p = 0.0543$). There was no relationship between length of hospital stay after transplantation (less or more than 20 consecutive days) and ENG ($p = 0.4561$).

The relationship between the duration and cause of the renal disease with the result of the ENG testing are described in Tables 8 and 9, respectively.

There was no statistical significance between disease duration and the results of the ENG ($p = 0.2320$).

DISCUSSION

Clinical manifestations of vestibular disorders are relatively frequent in patients with CKD on dialysis.

Table 3. Relationship between sex and electronystagmography in patients subjected to kidney transplantation.

Exam and Sex	Exam Result		p	Test
	Hyporeflexia	Normorreflexia		
CT				
Male	10	4	0.4500	Fisher
Female	10	6		
	NVE	DPVD	p	TEST
ENG				
Male	10	10	1.0000	Chi-square
Female	5	5		

CT: Caloric test; ENG: Electronystagmography; NVE: Normal vestibular exam; DPVD: Deficit peripheral vestibular dysfunction.

Table 4. Relation between the age and the electronystagmography in patients subjected to kidney transplantation.

Exam and Age (years)	Exam Result		p	Test
	Hyporeflexia	Normorreflexia		
CT				
Under 17	7	7	1.0000	Chi-square
17 or above	8	8		
	NVE	DPVD	p	Test
ENG				
Under 17	8	7	0.7150	Chi-square
17 or above	7	8		

CT: Caloric test; ENG: Electronystagmography; NVE: Normal vestibular exam; DPVD: Deficit peripheral vestibular dysfunction.

Table 5. Relation between the amount of time under dialysis and the electronystagmography in patients subjected to kidney transplantation.

Exam and Treatment Duration (years)	Exam Result		p	Test
	Hyporeflexia	Normorreflexia		
CT				
Under 7	7	7	0.7321	Chi-square
7 or above	7	9		
	NVE	DPVD	p	Test
ENG				
Under 7	7	7	1.0000	Chi-square
7 or above	8	8		

CT: Caloric test; ENG: Electronystagmography; NVE: Normal vestibular exam; DPVD: Deficit peripheral vestibular dysfunction.

However, in our research the complaints of dizziness were reported only during the dialysis treatment. In the 1960, Yassin et al.¹⁴ reported that 47.6% of dialysis patients complained of vertigo. Several authors from the mid-1970s demonstrated that CKD patients often had otological symptoms such as tinnitus, dizziness and

Table 6. Relation between the type of dialysis and the electronystagmography in patients subjected to kidney transplantation.

Exam and type of treatment	Exam Result		p	Test
	Hyporeflexia	Normorreflexia		
CT				
Peritoneal dialysis	5	3	0.2860	Fisher
Hemodialysis	7	10		
Hemodialysis/ Peritoneal dialysis	3	2		
	NVE	DPVD	p	Test
ENG				
Peritoneal dialysis	5	3	0.2860	Fisher
Hemodialysis	7	10		
Hemodialysis/ Peritoneal dialysis	3	2		

CT: Caloric test; ENG: Electronystagmography; NVE: Normal vestibular exam; DPVD: Deficit peripheral vestibular dysfunction. For applying Fisher test, only two categories of results were considered: peritoneal dialysis and hemodialysis (the most frequent).

Table 7. Relation between the amount of time of kidney transplantation and electronystagmography.

Exam and Transplantation Time (years)	Exam Result		p	Test
	Hyporeflexia	Normorreflexia		
CT				
Under 5	6	8	0.5104	Chi-square
5 or above	5	11		
	NVE	DPVD	p	Test
ENG				
Under 5	5	6	0.7048	Chi-square
5 or above	10	9		

CT: Caloric test; ENG: Electronystagmography; NVE: Normal vestibular exam; DPVD: Deficit peripheral vestibular dysfunction.

Table 8. Relationship between duration of illness and electronystagmography in kidney disease patients with renal transplants.

Duration of Illness (years)	Exam Result		p	Test
	Abnormal	Normal		
Less than 5				
Less than 5	3	6		
5-9	9	4	0.2320	Chi-square
9 or more	3	5		

hearing loss^{5,15}. In the 2010s, Terra et al.¹⁶ reported that 41.3% of hemodialysis patients complained of dizziness and 2011s, Caplin et al.¹⁷ reported vertigo in 63%.

Fifteen (50%) of our patients showed abnormalities on examination of the vestibular system. These results are consistent with several other researches that showed vestibular disorders in patients with CKD treated with

Table 9. Relationship between cause of kidney disease and the result of electronystagmography in patients with renal transplants.

Cause of Illness	Exam result		Total
	Abnormal	Normal	
Posterior urethral valve	4	6	10
Hypertensive nephropathy	-	1	1
Hemolytic uremic syndrome	5	-	5
Autosomal dominant polycystic kidney disease	-	1	1
Multicystic kidney	1	-	1
Systemic lupus erythematosus	1	-	1
Glomerulonephritis	1	2	3
Neurogenic bladder	-	1	1
Cystinosis	1	-	1
Bladder extrophy	-	1	1
Reflux nephropathy	-	1	1
Obstructive uropathy	1	-	1
Prune belly syndrome	1	-	1
Unknown	-	1	1
Urogenital sinus	-	1	1

renal transplantation or dialysis for a long time. The frequency of vestibular disorders in CKD, with or without renal transplantation, ranges from 1.9% to 100%, with cases of central and peripheral disorders, with hyporeflexia and hyperreflexia^{8,17,18-22}.

The evaluation of the vestibular system is essential in the investigation of body balance, and caloric testing is very important, because it assesses the labyrinth separately.

In the present study, we observed an alteration in the peripheral vestibular system, identified in the caloric test, with a predominance of deficit dysfunction. Yassin et al.¹⁴ demonstrated the presence of spontaneous nystagmus in five patients with CKD undergoing hemodialysis and kidney transplantation, and Guerrigues & Clemente²¹ reported 63.1% of central vestibular disorders in individuals with CKD.

Deafness and balance disorders are directly related to the level of uremia¹⁹. The intensity of the clinical and histopathological findings is directly proportional to the time and type of treatment. Treatment for a long time can induce electrolyte, biochemical, vascular, osmotic and immune abnormalities. The longer the time on dialysis, the higher the risk of ear and vestibular disease¹⁵.

In our research there were 15 (50%) cases of normal vestibular exam, 14 (46.7%) of labyrinth hyporeflexia and one case (3.3%) of LP altered. These values are consistent with other studies that found that hyporeflexia is more frequent than hyperreflexia^{18,22}. Discordant results were observed by Yassin et al.¹⁴.

The relationship between the gender of the patients and the results of ENG showed no significant values. There is no comparing data in the literature. The relationship between the age of the patients and ENG was not statistically significant.

There was no statistically significant correlation between the duration of the kidney disease, type and duration of dialysis treatment with vestibular tests. Yassin et al.¹⁴ reported that 37.5% of patients with chronic kidney disease who performed over 264 sessions of dialysis or were transplanted had vestibular dysfunction. Regarding the duration of kidney disease, we did not find this comparison in the accepted literature so that we could compare our findings.

The relationship between the time of renal transplantation and ENG was not significant. However, post-transplant patients need otologic follow-up, because the immunosuppressive drugs (cyclosporine and corticosteroids) can cause change in plasma viscosity inside the inner ear²³.

Sazgar et al.²⁴ performed the examination of vestibular evoked myogenic potentials (VEMP) in 22 patients undergoing hemodialysis and observed alteration in creatinine level and absence of waves when compared to a control group.

In accordance with the authors in the accepted literature, we observe an uncertainty with respect to the cause of labyrinthine dysfunction since they formulated several hypotheses. Among these reasons are the duration of kidney disease, type and prolonged use of dialysis, use of ototoxic medications pre- and post-renal transplant, high levels of urea and/or serum creatinine, and even unknown causes. Perhaps one or more of these factors may be the explanation of the labyrinthine alterations evidenced in the present study. Therefore, we suggest monitoring this type of population so that we can do deeper future clinical research.

CONCLUSION

Dizziness was the most significant symptom for the vestibular test in correlation with neurotological symptoms.

Alteration in the vestibular exam occurred in the caloric test, there was a prevalence of alterations for the peripheral vestibular system with a predominance of deficit vestibular dysfunction.

We emphasize the need to show professionals involved in patients with CKD, those undergoing renal transplant and dialytic treatment the importance of prevention and early identification of otoneurological involvement. These patients should periodically perform labyrinth exam to prevent future abnormalities of the vestibular system.

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