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Carpal tunnel syndrome in hemodialysis patients as a dialysis-related amyloidosis manifestation – incidence, risk factors and results of surgical treatment

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Carpal tunnel syndrome (CTS) is the most common complication of dialysis-related amyloidosis (DRA) developing in patients on long-term dialysis therapy. The aim of this study was to evaluate the incidence of CTS and identify factors influencing the development of CTS in patients on maintenance hemodialysis, as well as results of its surgical treatment.

Material/Methods: The study included 386 patients, among whom CTS was diagnosed in 40 patients (10.4%) on the basis of signs and physical symptoms, as well as by nerve conduction. The group of patients with CTS and the group of patients without CTS were compared according to age (mean 54.50 *vs.* 56.48 years) and duration of dialysis treatment. Initial analysis of CTS incidence by sex, presence of anti-HCV antibodies, and location of arterio-venous fistula (AV fistula) was undertaken.

Results: Duration of dialysis treatment was the statistically significant risk factor for the development of CTS (16.05 *vs.* 4.51 years; $p<0.0001$). Among patients treated for a long period on hemodialysis (20–30 years), 100% required surgical release procedures, while 66.66% of those treated for 15–19 years, 42.1% of those treated for 10–14 years, and 1.6% of those treated for less than 10 years. CTS was diagnosed more often in anti-HCV-positive patients as compared with anti-HCV-negative patients (47.5 *vs.* 6.9%; $p<0.0001$). No significant differences were found when comparing CTS incidence by sex or between the development of CTS requiring surgical release intervention and location of the AV fistula.

Conclusions: Surgical release procedure of the carpal tunnel gave good treatment results in patients with CTS.

key words: **carpal tunnel syndrome (CTS) • dialysis-related amyloidosis (DRA) • arterio-venous fistula (AV fistula)**

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Background

Dialysis-related amyloidosis (DRA) diagnosed in patients with advanced renal insufficiency on maintenance hemodialysis often manifests as signs and symptoms of carpal tunnel syndrome (CTS), chronic arthropathy, presence of subchondral cysts and pathological fracture tendency. Increased levels of beta-2-microglobulin (BMG) in the plasma of dialyzed patients plays an essential role in the pathogenesis of DRA. Prevalence of DRA increases with duration of dialysis therapy. CTS is the most common complaint in DRA, caused by pressure on the median nerve from complexes of amyloid, the main component of which is BMG. Diagnosis of CTS is based on signs and symptoms verified by nerve conduction [1–4].

The aim of this study was to evaluate the incidence of CTS and identify factors influencing the development of CTS in patients on maintenance hemodialysis, as well as results of its surgical treatment.

Material and Methods

The study included 386 patients (285 patients from the Department of Nephrology, University Hospital, Cracow, and 101 patients from the Dialysis Unit, St. Lukasz Hospital, Tarnow) on maintenance hemodialysis during the years 2005–2008. Patients were hemodialysed 3 times per week, for 4–5 hours each time, using cuprophane membranes; while in the last 10 years cellulose or polysulphone, low-flux type dialyzers were used. Patients with CTS requiring surgical release procedure were distinguished from this group. Diagnosis of CTS was initially based on signs and physical symptoms verified by nerve conduction examination. Clinical CTS diagnosis was based on numbness, nocturnal pain in the median nerve distribution, and positive stimulating tests, particularly the Tinel sign. A prolonged sensory and/or motor latency from the wrist to digits innervated by the median nerve was the electrophysiological diagnostic criterion of CTS. The following parameters were evaluated: patient age, sex, duration of dialysis therapy, etiology of renal insufficiency, presence of anti-HCV antibodies, localization of AV fistula, and presence of cysts and joint pain. Concentrations of urea and creatinine before and after dialysis and potassium, calcium, and phosphorus were measured monthly. Statistical analysis using the non-parametric Mann-Whitney test for unassociated variables compared age and duration of dialysis therapy for the groups of patients with CTS and without CTS. Initial analysis of CTS by sex, presence of anti-HCV antibodies and location of AV fistula were verified using the Chi-square test. Risk factor evaluation of CTS incidence underwent logistic regression analysis.

Results

Carpal tunnel syndrome was diagnosed and verified using nerve conduction examination in 40 patients, who comprised 10.4% of the studied patient population on maintenance hemodialysis. Causes of terminal renal insufficiency in CTS patients were as follows: glomerulonephritis (45%), degenerative polycystic kidney disease (12.5%), chronic pyelonephritis (10%), diabetic nephropathy (5%), amyloidosis nephropathy (2.5%), lupus nephritis (2.5%), hypertensive nephropathy (2.5%), and renal cirrhosis of unknown origin (20%). Patients with CTS were aged between 36 and 83 years (mean 54.5 years), while the asymptomatic patient group was aged 18 to 100 years (mean 56.48 years) (Figure 1, Table 1). Dialysis therapy in the patient group with CTS ranged from 4–30 years (mean 16.05 years); while dialysis duration among patients without CTS ranged from 0.2–16.4 years (mean 4.51 years) (Figure 2, Table 1). Statistical analysis showed that patients with CTS were hemodialysed significantly longer ($p<0.00001$) (Mann-Whitney test).

Surgical release procedure was required in 5 patients (100%) with CTS on maintenance dialysis treated for a long period (from 25–30 years). In patients hemodialysed from 20–24 years, CTS developed in 5 patients (100% of the sub-group). In the group of patients hemodialysed from 15–19 years, patients with CTS comprised 66.66% (10 patients). Less than half of the patients hemodialysed from 10–14 years were operated on due to complaints in the course of CTS; they comprised 42.1% of this subpopulation (16 patients). Four patients dialyzed for fewer than 10 years were found to have CTS (1.6%) (Table 2).

Biopsies performed at the time of CTS surgery confirmed DRA. Histological examination of biopsy specimens was performed in 21 out of 40 patients (52.5%), and all of these 21 biopsied patients presented with signs of amyloid deposits.

Among patients with CTS, the majority were males (M:F, 2:1) (27 males, 13 females), which did not reflect the ratio of both sexes in the studied population (229 males, 157 females).

No statistically significant differences in incidence of CTS by sex (Chi-square test, p=NS) was noted. In the studied population, 43 patients were found to have positive anti-HCV antibodies. In the group of patients with CTS, 19 patients were found to have positive anti-HCV antibodies, which equaled 47.5% of patients of this subgroup. In the group of 346 patients without CTS, 24 patients were found to have positive anti-HCV antibodies (6.9%). Incidence of CTS was statistically significantly higher in patients with positive anti-HCV antibodies (Chi-square test, $p<0.00001$) (Table 3).

All patients with CTS complained of numbness, tingling and pain in the first 3 radial digits. The symptoms of paresthesia were more pronounced at night, causing insomnia and frequent waking. In 21 patients, these problems increased during dialysis. In some cases the diagnosis of CTS was supported by positive Tinel sign. In a number of patients muscle weakness, hypoesthesia and thenar hypotrophy were observed. Nerve conduction studies showed prolonged distal sensory and motor latencies from the wrist to digits, innervated by the median nerve (Table 4). After surgical release procedure, patients clinically improved. Pain and paresthesia disappeared after 24–48 hours in every case. Regression of sensory and motor deficiencies was much slower and took 4–6 months. In 14 patients, CTS developed in the wrist where the AV fistula was located; in 3 patients on the opposite side, and bilaterally in 23 patients (57.5%). No statistical differences were noted between the development of CTS requiring surgical release procedure and location of the AV fistula (Chi-square test, p=NS). A total of 72 surgical procedures of the median nerve release were performed in 40 patients with CTS, in 9 patients due to recurrence of CTS, and 23 on the opposite hand. The traditional surgical

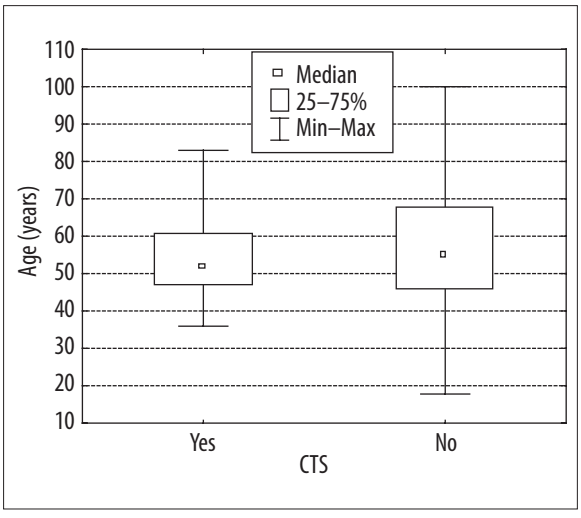

Figure 1. Incidence of CTS and age of patients.

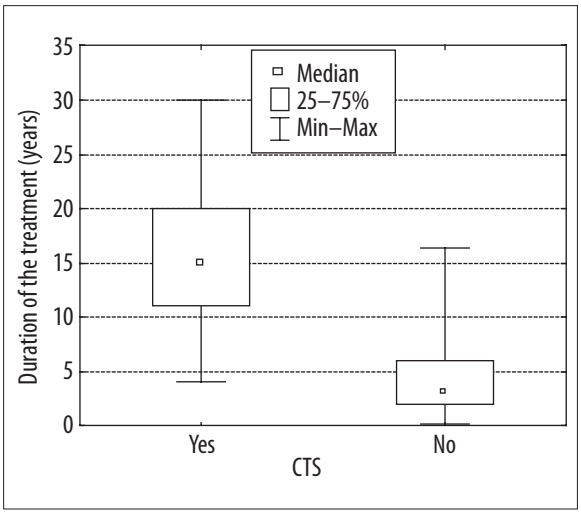

Figure 2. Incidence of CTS and duration of dialysis treatment.

Table 1. Age and duration of dialysis treatment of patients with CTS and without CTS.

CTS	Mean	Median	Min.	Max.	Interquartile range	SD
Age	54.10	52.00	36.00	83.00	14.00	10.30
Dialysis duration (years)	16.05	15.00	4.00	30.00	8.95	6.85
Without CTS	**Mean**	**Median**	**Min.**	**Max.**	**Interquartile range**	**SD**
Age	56.48	55.00	18.00	100.00	22.00	15.21
Dialysis duration (years)	4.51	3.20	0.20	16.40	4.05	3.68

Table 2. Duration of dialysis therapy among patients with CTS.

Dialysis duration (years)	Patients with CTS	Percentage of population
25–30	5	100.00
20–24	5	100.00
15–19	10	66.66
10–14	16	42.10
<10	4	1.60

Table 3. Frequency of positive anti-HCV antibodies in the study population.

	Patients	Anti-HCV positive	Percentage
All patients	386	43	11.1
Patients with CTS	40	19	47.5
Patients without CTS	346	24	6.9

Table 4. Mean latency values in sensory and motor fibers of median nerve.

Sensory median nerve	Recomended values* <3.7 msec	Motor median nerve	Recomended values* <4.0 msec
Latency (msec)	4.56±0.97	Latency (msec)	5.32±0.87

* According Davson DM [22].

method was implemented where the transverse carpal ligament was severed, which later released the median nerve. During the surgical procedure, tumor-like changes were found in tendons and synovial membranes; sometimes fibrotic adhesions, segmental tendon fragmentation of the finger flexors, or deep changes in the synovial membrane were also found. In 24 patients, subchondral cysts were visualized during radiological examination, computer tomography or magnetic resonance imaging. Such changes were found in the acetabulum of the hip joint, in the head of the femoral bone, radial and humeral bone, patella and the wrist bone. Six patients had hip replacement performed (endoprosthesis implantation). In patients with signs and symptoms of CTS, nerve conduction and electromyography were performed to verify pre-surgical CTS. Sensory-motor neuropathy was diagnosed in 11 patients. No statistically

significant differences were noted in concentrations of the following biochemical parameters: urea, creatinine, potassium, calcium, phosphorus, sodium and liver parameters in patients with CTS and the group of patients without CTS.

Discussion

As survival time of dialysis patients lengthens, late complications begin to appear. Dialysis-related amyloidosis is one of them. The most common symptom of DRA is CTS. The frequency of clinical symptoms of CTS in patients on chronic hemodialysis ranges between 2% and 31%. This is probably due to the number and characteristics of the evaluated patient group; and to the degree to which diagnostic criteria is employed. Most patients require surgical release procedure [5–8]. Among the studied group of 386 patients on maintenance hemodialysis, CTS was diagnosed in 40 patients who required surgical release procedure of the wrist. This group equaled 10.4% of the studied population. In this study, the mean age of patients with CTS was lower (54.5) than the mean age of patients without CTS (56.48 years). Patients with CTS were younger but this was not statistically significant. Others investigators noted statistically significant dependence between the age of hemodialysed patients and the occurrence of CTS [5,7].

The group of patients with CTS was characterized by a 2-fold higher number of males (27 males, 13 females), which did not reflect the ratio of both sexes in the study population (229 males, 157 females). This data differs from the results of other authors (ratio of M:F=1:1) or relates to other studies (67% of males in the group with CTS) [5,9]. In the non-dialyzed patient population, CTS is definitely more frequently diagnosed in females (F:M=3:1) [10]. The decreased percentage of females with CTS in hemodialysed patients is supposedly due to common abnormalities that accompany terminal renal failure or to the fact that these patients do not perform as much movement of the wrist due to decreased physical activity. In the analyzed group of patients, no difference was noted between incidence of CTS and patient sex. Among the 40 patients with CTS, half of them had diagnosed chronic glomerulonephritis. Explanation of this interrelationship is difficult. To date, no connections have been found between the etiology of terminal renal failure and incidence of CTS in dialyzed patients, except for Schwarz et al, who found an increased incidence of CTS in dialyzed patients after analgetic nephropathy [11].

Duration of dialysis therapy in the group of patients with CTS was significantly longer (mean 16.05 years) in comparison with dialysis duration among patients without CTS (mean 4.51 years). This correlates with observations of other authors [2,3,12,13]. All patients dialyzed for more than 20 years underwent surgical release procedure of the wrist; whereas surgical procedures in CTS patients dialyzed for less than 10 years were very rare. Duration of dialysis therapy was the only statistically significant risk factor for CTS.

In the analyzed population of 386 hemodialysed patients, 43 were found to be anti-HCV positive (11.1%); whereas in the subgroup of patients without CTS only 24 patients were found to be HCV positive (6.9%). There were 19 patients with CTS that had anti-HCV antibodies, which is 47.5% of this subgroup. Hemodialysed patients with CTS were found to have anti-HCV antibodies significantly more often. Such a correlation has not been commonly noted by researchers, and is probably due to the fact that the percentage of patients with positive anti-HCV antibodies depends on the duration of dialysis therapy [14,15]. The longer a patient is dialyzed, the higher the probability of HCV infection. One can speculate that this relationship may be due to stimulation of the liver by the inflammatory process to produce beta-2-microglobulin, and this in turn plays an essential role in the pathogenesis of dialysis-related amyloidosis. In the "pre-erythropoietin era", hepatitis C infection was common in chronic dialysis patients when blood transfusions were routine [7].

CTS developed in 14 patients in the wrist with the AV fistula, in 3 patients that had the AV fistula on the opposite side, and in 23 patients bilaterally (57.5%). Prevalence of CTS in the wrist where the AV fistula was located did not fulfill the criteria for statistical significance. A relationship between CTS and the AV fistula location has been postulated in many publications [6,13,16–18]. The pathomechanism of CTS in hemodialysed patients appears to be complicated. Vascular factors associated with the AV fistula and mechanisms due to amyloid deposition must be considered, along with the substantial increase in venous pressure in the region of the AV fistula, which, together with periodic patient water overload, generates pressure on the median nerve. Clinical signs and symptoms such as paresthesia, increasing pain during the night and during dialysis, insomnia, and frequent waking during the night decrease patient quality of life. Pharmacological therapy as symptomatic treatment only transiently decreases complaints. In 40 patients with CTS, 72 surgical release procedures were performed; 9 were due to recurrences after using the traditional surgical procedure (surgically severing the transverse carpal ligament), and in 23 patients due to second hand localization.

After the operative procedures, rapid relief of paresthesia and pain symptoms were observed; return of sensory and motor deficits took 3–4 months longer. These results is in agreement with the findings of other authors, and indicate that recurrences of CTS in dialyzed patients are more common in comparison to the non-dialyzed population. In the treatment of CTS recurrences, excluding synovectomy, resection of the thickened tendinous sheaths of the finger flexor is recommended [12,17,19–21].

Conclusions

CTS is a common complication of long-term dialysis therapy. Duration of dialysis therapy is an independent and statistically significant risk factor in the development of CTS. CTS occurs significantly more often in anti-HCV-positive patients, which may be related to the longer period on dialysis. CTS incidence does not significantly depend on sex or location of the AV fistula. Surgical release procedure of the wrist is an effective treatment method.

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