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Brief report

Early diagnosis of systemic amyloidosis by means of a transverse carpal ligament biopsy carried out during carpal tunnel syndrome surgery☆

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ABSTRACT

Introduction and objective: The systematic analysis of a carpal transverse ligament (CTL) sample obtained during routine carpal tunnel syndrome (CTS) surgery may constitute a method of early diagnosis for systemic amyloidosis.
Material and methods: Prospective study carried out on 147 consecutive CTL samples collected from patients intervened for CTS at the University Hospital of León from April 2006 to May 2007. In those cases in which amyloid deposition was observed in the CTL sample, the study was completed with a *fine needle aspiration biopsy* (FNAB) of the subcutaneous fascia, using the Red Congo stain in both cases. Positive cases were referred to the Internal Medicine and/or Hematology departments, and their evolution was monitored for up to 8 years.
Results: CTL amyloid deposition was observed in 29 patients (19.7%), with a FNAB only being performed in 19 of them (65.5%). The test was positive in 11 cases (57.9%), and 4 patients in this subgroup (3% of the total) developed events attributable to amyloidosis over the following 3 years.
Conclusions: A CTL routine biopsy carried out during CTS surgery may anticipate the systemic amyloidosis diagnosis.

Diagnóstico precoz de amiloidosis sistémica mediante biopsia de ligamento transverso del carpo durante la cirugía del síndrome del túnel carpiano

Palabras clave:
Síndrome del túnel del carpo
Amiloidosis
Diagnóstico precoz

RESUMEN

Introducción y objetivo: Planteamos la posibilidad de que el análisis sistemático de una muestra de ligamento anular anterior del carpo (LAAC) obtenida durante la cirugía rutinaria de síndrome del túnel carpiano (STC) pueda constituir un método de diagnóstico precoz para la amiloidosis sistémica.
Material y métodos: Estudio prospectivo en el que se recogieron las muestras consecutivas de LAAC de 147 pacientes intervenidos por STC en el Hospital Universitario de León entre abril de 2006 y mayo de 2007. En aquellos en los que se observó depósito de amiloide en la muestra de LAAC, se completó el estudio con la realización de punción-aspiración con aguja fina (PAAF) de grasa abdominal subcutánea, utilizando en ambos casos la tinción de Rojo Congo. Los casos positivos fueron derivados a los servicios de Medicina Interna y/o Hematología, observando su evolución durante 8 años.

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Resultados: Se observó depósito de amiloide en LAAC en 29 pacientes (19,7%), y pudo realizarse PAAF de grasa abdominal en 19 de ellos (65,5%), resultando positiva en 11 (57,9%); de ellos, 4 pacientes (3% del total) desarrollaron en los 3 años posteriores episodios atribuibles a la amiloidosis.
Conclusiones: La biopsia rutinaria de LAAC durante la cirugía de STC podría adelantar el diagnóstico de la amiloidosis sistémica.

Introduction

Amyloidosis is a disease of unknown etiology characterized by the depositing of an amorphous substance (amyloid) in the extracellular spaces of various organs and tissues, conditioning functional and structural abnormalities, depending on the location and the intensity of the deposit. This can be localized or systemic. The most common types of the disease are primary, secondary to chronic infections or inflammation, chronic hemodialysis-associated amyloidosis and familial amyloidosis. The symptomatology depends on the location of the amyloid deposit, which can affect practically every organ of the body, which usually leads to a delay in the diagnosis of the disease. This is confirmed by Congo Red staining of abdominal subcutaneous fat obtained by the fine needle aspiration biopsy (FNAB). The treatment varies depending on the type of amyloidosis and its prognosis depends on the severity of the disease at the time of diagnosis and the progression of the amyloid deposits. As both factors worsen with the lack of known screening methods and with the frequent delay in clinical suspicion, this prognosis is often wrong, especially in primary forms.

One of the most frequent examples of amyloid neuropathies is carpal tunnel syndrome (CTS), consisting of the compression of the median nerve as it travels through the wrist. It is the most frequent focal peripheral neuropathy in the general population, with a prevalence ranging from 1 to 5%,[1] and it responds to several causes (including amyloidosis), although the most common is idiopathic. Its treatment is usually based on the surgical release of the median nerve through the section of the covering structure (transverse carpal ligament [TCL]).

The approximate incidence of amyloidosis in the general population is 8 patients per million inhabitants per year, and it is estimated that 10–30% will be diagnosed with a CTS and 20–25% may start with this.[2] With these data and lacking a method of early diagnosis of systemic amyloidosis, the purpose of our study is to evaluate the systematic collection of a TCL sample during the routine surgical procedure of CTS to screen for possible systemic amyloidosis in initially asymptomatic patients.

Material and methods

Prospective, interventional, longitudinal follow-up cohort study. After approval by the Ethics Committee of our hospital, we studied 152 TCL samples obtained from patients with a clear diagnosis of CTS and surgically operated consecutively in the services of Orthopedic Surgery and Traumatology, Neurosurgery and Plastic Surgery of the same center during the period ranging from 1 April 2006 to 31 May 2007. Every patient had a clinical and electromyographic diagnosis compatible with CTS and their previous conservative treatment had failed. Patients operated on the same disease more than once during the mentioned period (5 patients) were excluded. Therefore, the study sample included 147 patients. To perform the final statistical analysis, in order to prevent selection biases, other patients ruled out were those who were previously operated their TCL sample was positive for amyloid deposits and could not be located or refused to continue the study (10 patients).

The surgical intervention involved the release of the median nerve through longitudinal section of the TCL, taking a segment approximately half centimeter wide of the ligament. The specimen was immediately sent to the Pathological Anatomy Service and processed using Red Congo staining to identify the presence of amyloid substance. Patients with positive staining and giving their consent, subsequently underwent an FNAB of subcutaneous abdominal fat, and the positive cases were referred to the Internal Medicine and/or Hematology services, being studied and reviewed for a mean time of 8.1 years (SD 0.7, 95% CI 7.7–8.4), which we consider sufficient after reading the literature related to the natural evolution of the disease. All tissue samples were evaluated by the same pathologist.

Patients were classified into four groups: without amyloidosis, with amyloidosis focused on TCL and with asymptomatic or symptomatic systemic amyloidosis (amyloid deposit also present in abdominal fat). Only in the latter, definitive classification was performed by immunohistochemistry.

Statistical analysis was performed with the SPSS program (v15, SPSS, Inc., Chicago, IL, USA) after collecting the data in a database using the Excel 2010 program. Initially, we calculated the theoretical sample size required to perform the study, obtaining a final sample size (adjusted for losses) of 126. In order to verify the normal variable distribution, the Kolmogorov–Smirnov normality tests were applied in samples with n over 50 or Shapiro–Wilk in the samples below that number. The statistical tests were chosen in each case depending on the results: Student's *t*, Mann–Whitney *U*, ANOVA, Kruskal–Wallis, Chi-square. The probability of severe disease episodes was calculated using a Kaplan–Meier survival curve. The results with $p < 0.05$ values were accepted as statistically significant.

Results

Of the 147 patients in the study, 31 (21%) were males and 116 (79%) were females. The mean age of the group was 58 years (SD 14). 29 patients had amyloid deposits in TCL (19.7%, 95% CI 12.9–26.5), the latter being statistically significantly positive in women (χ^2 (1) = 4.3, $p = 0.03$), in patients with hypertension (35% vs 14%, $p = 0.009$) and in hypertensive women (43.3% vs 16.3% $p = 0.005$).

Abdominal fat FNAB was performed in 19 of the 29 patients with positive TCL biopsy, that is 65.5% patients (6 could not be found and 4 refused to continue), being positive in 11 (57.9%, 95% CI % 33.5–79.7), being diffuse deposit in 6 (54.5%) and focal deposit in 5 (45.5%). There were no significant differences between the groups with and without amyloid positivity in subcutaneous abdominal fat, except in patients with thyroid disease (33.3 vs 5.6%, $p = 0.008$).

During the follow-up of the 19 patients with positive TCL biopsy, the 8 patients with negative abdominal fat FNAB did not develop any severe amyloidosis-related events. Four of the 11 patients with positive abdominal fat FNAB developed amyloidosis-induced episodes for 3 years following CTS surgery: multiorgan failure and death (one case), amyloid neuropathy in the lower limbs (one case), dizziness and paresthesia in the lower limbs (one case) and amyloid heart disease (one case). All with general syndrome with asthenia, polyarthralgias and weight loss (Table 1). In all 4 cases the amyloid deposit in the abdominal fat was described as dispersed, without