ECM REMODELING CAUSES CARPAL TUNNEL SYNDROME

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Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy and its occurrence in the general population is estimated at 1% with occasional symptoms noted as many as 3.7% of adults. The syndrome refers to the constellation of symptoms resulting from median nerve compression within the carpal tunnel. Recent studies using MRI have demonstrated findings such as increased distance between the tendons and volar vowing of the transverse carpal ligament indicating that increased tenosynovial volume is the underlying pathogenesis of the idiopathic CTS. Most of the previous histological studies of tenosynovium have demonstrated that inflammatory changes are extremely rare and edema and nonspecific fibrous changes are predominant findings. The purpose of the present study is to carry out immunohistochemical study to demonstrate extracellular matrix alterations in the tenosynovium removed during open carpal tunnel release and correlate them with clinical and radiological findings.

Materials and Methods

All patients signed an informed consent document, and the study was approved by the local Institutional Review Board. The study group consisted of 26 patients (3 men and 23 women) who were treated surgically for idiopathic carpal tunnel syndrome. The mean age of patients was 51.2 years (range, 29 to 82). The criteria for the diagnosis of CTS included a history of paresthesias in the median-nerve distribution, nocturnal hand pain, positive findings on physical examination, and a positive electrophysiological study. The work-up also included standard radiographs of the hand and wrist to rule out bone abnormalities responsible for median nerve compression. Patients with a history of diabetes mellitus, inflammatory arthritis, autoimmune disorders, thyroid abnormalities, renal failure, acromegy or tumors including myeloma were excluded from participation.

Electrodiagnostic studies were performed preoperatively on all patients. The criteria for the positive electrophysiological test were a distal motor latency of >4.5 ms and a median sensory nerve conduction velocity of <35 m/s across the carpal tunnel. A standard open carpal tunnel release was then performed through a 5 cm longitudinal palmar incision. After open release, the tenosynovium was removed by pulling the flexor tendons into the wound with care taken not to damage the median nerve. The tenosynovium specimens were fixed in 10% formalin immediately and sent to the pathology department. The specimens were embedded in paraffin, cut into 5-μm-thick sections, and stained with hematoxylin and eosin (HE) and alcian blue. The histological appearance of the tenosynovium was evaluated with regard to inflammation, edema, fibrosis, and hypertrophy.

Immunohistochemical studies were performed with a polyclonal rabbit anti-Tenascin C antibody, monoclonal anti-versican antibody, monoclonal anti-proliferating cell nuclear antigen (PCNA), and monoclonal anti-type III collagen antibody. Expression of tenascin C and versican were quantified by an image analyzer system using 5 randomized fields for each specimen.

Results

The patients were divided based on the period from the onset of the symptoms to the surgery as follows: early group <3 month, intermediate group 4< <6 month, advanced group >7 month. H & E, alcian blue, and immunohistochemical staining with anti-type III collagen and anti-PCNA show that histological findings of the tenosynovium change with progression of the disease. Edema is the distinctive feature in the early phase. With regard to collagen contents in the tenosynovium, type I and II collagen are predominant in early to intermediate phase with scarce to mild deposition of type III collagen. In advanced phase, tenosynovium shows extensive fibrosis with diffuse deposition of type III collagen. Throughout the phases, cell proliferation stays at a low level and lacking inflammatory cell infiltration, indicating that tenosynovial tissue reaction in CTS is predominantly an extracellular matrix remodeling rather than inflammatory or degenerative/regenerative one. Both tenascin C and versican did not show uniform expression pattern but expression level tends to vary from area to area. In the case of tenascin C, diffuse expression is predominant in the early group and perivascular expression is prevailing in the late group. Versican expression is generally very low in the early phase, increases gradually and is maintained even during the late phase. Figure 1 shows the results of quantitative analysis of tenascin C and versican, which clearly demonstrates that ECM components changes sequentially with progression of tenosynovial pathology in CTS.

Discussion

The present study clearly demonstrates that CTS is associated with drastic ECM remodeling. The sequential changes in ECM composition suggest that different components could play distinct roles in a cascade of biological events during the progression of the disorders. Tenasin C is a glycoprotein abundantly expressed in embryo, but is not expressed in most adult normal tissues. Tenasin-C transiently reappears during inflammation, tissue repair/regeneration or tumor invasion. As shown in the present study, tenasin-C may be involved in edema formation at the early phase of ECM remodeling. There have been several reports showing that chondroitin sulfate proteoglycans including versican bind to members of tenasin family. The early deposition of tenasin-C may thus provide a scaffold for subsequent accumulation of versican. Versican is a large chondroitin sulfate proteoglycan belonging to the hyaluronan-binding proteoglycans. The molecule shows high interactive nature and has been shown to play significant roles in key events in development and diseases as a structural molecule to create loose and hydrated matrices and by interacting with cells or other molecules to regulate cell phenotypes. It also involves in remodeling of ECM. Since tenasin C has been shown to be an ECM component directly regulated by mechanical stress, repetitive strain can exaggerates tenosynovial thickening through upregulation of tenasin C expression. So, inhibition of tenasin C may block the subsequent biological events causing tenosynovial thickening and be a new approach for prevention of CTS.

Figure 1. Type III collagen expression

Early phase Intermediate phase Late phase

Figure 2. Sequential changes of tenasin C and versican


50th Annual Meeting of the Orthopaedic Research Society
Poster No: 1217