Case Report

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Primary Familial Carpal Tunnel Syndrome with Long-term Follow-up: A Study of Two Families and Review of the Literature

Abstract

Background: Familial carpal tunnel syndrome is a rare hereditary disorder characterized by early onset bilateral carpal tunnel syndrome. A lack of long-term outcome data exists for patients afflicted by this condition. This study examines the long-term subjective outcomes of patients managed with open carpal tunnel release for the diagnosis of familial carpal tunnel syndrome.

Methods and findings: Three patients were diagnosed with familial carpal tunnel syndrome: a 13 y old girl whose maternal family has three consecutive generations of carpal tunnel syndrome, and a 16 y old boy and his 47 y old father whose family has four consecutive generations of carpal tunnel syndrome. All patients completed the Boston Carpal Tunnel Questionnaire at an average of 13.5 y following their initial surgical treatment. Responses revealed onset of new symptoms in the 13 y old girl’s contralateral wrist and symptom recurrence in the 16 y old boy and his 47 y old father. Following carpal tunnel release, the 13 y old girl is now asymptomatic. The 16 y old boy and his father, despite carpal tunnel release, still suffer from moderate and mild functional impairment. The conclusions of our study, along with those of other studies that detail the nature of this syndrome, are limited by the small number of familial carpal tunnel syndrome patients.

Conclusion: In cases of early onset familial carpal tunnel syndrome, carpal tunnel release may prove only partially effective in resolving symptoms. Patients should be counseled that recurrent symptoms may develop despite successful initial carpal tunnel release.

Keywords: Carpal tunnel syndrome; Familial; Familial neuropathy; Median nerve; Pediatric

Abbreviations: BCTQ: Boston Carpal Tunnel Questionnaire; CTR: Carpal Tunnel Release; CTS: Carpal Tunnel Syndrome; EMG: Electromyography; FCTS: Familial Carpal Tunnel Syndrome; HLA: Human Leukocyte Antigen; PMP-22: Peripheral Myelin Protein-22

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Introduction

Carpal tunnel syndrome (CTS) is the most common neuropathy of the upper extremity [1, 2]. When disease is bilateral and family history is positive, one should rule out hereditary neuropathies, inborn errors of metabolism such as mucopolysaccharidosis, and underlying systemic disorders such as endocrinopathies, renal disease, and amyloidosis (Table 1) [1-5]. The absence of more common etiologies should then lead one to consider the primary inherited form of the disease: familial carpal tunnel syndrome (FCTS).

Zabriskie et al. unintentionally reported the first series of patients with FCTS when they documented the symptoms of three sisters in 1935 [6]. Tanzer was the first to describe carpal tunnel syndrome as a familial trait [7]. Since then, a number of case reports and
small FCTS case series have been published. However, essentially all of these studies lack outcome measures beyond five years postoperatively [2, 4, 8-12]. In addition, there are few reports noting outcomes in children afflicted with this condition. Only a small fraction of the less than 1% of CTS patients who present with symptoms prior to age 20 have been diagnosed with FCTS [13]. Longitudinal outcome measures have never been reported for pediatric FCTS patients.

In this case report, we present the members of two families, two of them adolescents, who presented with FCTS. In order to assess the long-term results of their treatment, the two adolescents were followed into adulthood. All patients were administered the Boston Carpal Tunnel Questionnaire (BCTQ) following carpal tunnel release in an effort to investigate treatment results and better counsel patients with this disorder about long-term outcomes [14].

**Case Report**

**Family #1**

A 16 y old Caucasian male (patient #1) presented to our institution with a 10 month history of bilateral carpal tunnel symptoms. He noted that his symptoms were aggravated or precipitated by gripping motions and significantly interfered with his activities and his sleep. Physical examination demonstrated mild thenar atrophy on the right. Bilateral carpal tunnel compression tests were positive and bilateral positive Phalen’s tests were elicited at 10 s. Sensation was remarkable for mildly decreased pin-prick over the volar aspect of the distal right index finger and for mild impairment of vibration sense bilaterally at the wrist. Electromyography (EMG) and nerve conduction studies revealed moderately severe neuropathy of the median nerves at the wrist, bilaterally (median motor nerve latencies measured 6.8 and 5.5 milliseconds on the right and left, respectively; median sensory nerve latencies measured 5.7 and 4.2 milliseconds on the right and left, respectively). Ulnar nerve conduction studies were normal. Family history was remarkable for carpal tunnel syndrome in the father, paternal grandfather, paternal great-grandfather, and a paternal aunt. There was no family history of inborn errors of metabolism, endocrinopathies, or amyloidosis.

A hereditary predisposition to compressive neuropathies was suspected. Complete sequencing of peripheral myelin protein 22 (PMP-22) was performed and was normal. Thyroid studies were normal, as were antimitochondrial antibodies. Urine heavy metal and organic acid analyses were within normal limits, and studies for inborn errors of metabolism were negative.

Conservative measures, including splinting, non-steroidal anti-inflammatory drugs (NSAIDs), and activity modification provided temporary relief. Bilateral carpal tunnel releases (CTR) were performed without complications. Intra-operatively, the transverse carpal ligament measured approximately 3.0 mm at its thickest point bilaterally [15]. No abnormalities of the median nerve were appreciated. A sample of synovium was sent to Pathology for histologic examination and demonstrated non-inflammatory dense fibrous tissue. Congo red stains for amyloid were negative. The patient was seen in our clinic six weeks postoperatively. He had no complaints of numbness or tingling. On physical examination, two-point discrimination was 3-4 mm in all fingers. Tinel’s sign was positive bilaterally. Phalen’s test was positive at the most
proximal margins of the previous incisions. Electrodiagnostic testing demonstrated moderately severe median motor and sensory neuropathy at the right wrist, and mild median motor neuropathy at the left wrist (median motor nerve latencies measured 4.9 and 4.5 milliseconds on the right and left, respectively; median sensory nerve latencies measured 3.8 and 3.3 milliseconds on the right and left, respectively). EMG results, while still abnormal, showed meaningful improvement relative to the EMG performed prior to the patient’s first CTRs.

Magnetic resonance imaging revealed fusiform focal enlargement of both median nerves, suggestive of nerve entrapment in areas of postoperative scarring. High T2 signal within the thenar muscle compartment bilaterally was consistent with denervation, but no associated atrophy or fatty replacement was appreciated. The patient underwent bilateral re-release of his carpal tunnels without complication. Bilateral vascularized hypothenar fascia was used to cover the nerves.

Patient #1 completed the Boston Carpal Tunnel Questionnaire 11.9 yr after his initial carpal tunnel release. Results of patient #1’s BCTQ are summarized in (Table 2). Using Storey’s suggested scoring system, the patient’s BCTQ responses demonstrate ongoing mild symptom severity and moderate functional difficulties due to recurrence of CTS symptoms despite two nerve releases [16].

The father of patient #1 (patient #2), a 47 y old Caucasian male, accompanied his son to our clinic. He complained of longstanding intermittent, bilateral (right>left) numbness and tingling most bothersome at night, and progressive right hand weakness and clumsiness. Carpal tunnel compression tests were positive bilaterally. A provisional diagnosis of bilateral carpal tunnel syndrome was made. Splinting offered temporary relief. Following informed consent, the patient underwent right carpal tunnel release. Intra-operatively, an hourglass-shaped compression at the proximal portion of the carpal tunnel was noted, as was a thickened transverse carpal ligament of 3-4 mm [15]. No gross abnormalities of the median nerve were noted. The patient was seen six weeks post-operatively, at which point his numbness had resolved completely and his pain had markedly improved. The patient elected to use a gel sleeve and not have his other side released due to relatively mild left-sided symptom severity.

Patient #2 completed the Boston Carpal Tunnel Questionnaire 12 y after his carpal tunnel release, the results of which are summarized in (Table 2). Despite near-complete resolution of right-sided symptoms following treatment, he currently experiences mild symptom severity bilaterally and mild functional impairment [16].

**Family #2**

A healthy, 13 y old, right-hand-dominant Caucasian female (patient #3) presented with a one year history of CTS. Symptoms began insidiously and initially presented in only the patient’s left hand; however, severe symptoms in her dominant, right hand promptly followed. Minor activities induced parenthesis and numbness, which progressed to pain if the activity was continued. Symptoms were relieved when the patient stopped inciting activities. Painful, bilateral nighttime dysesthesias disturbed the patient’s sleep. Family history was remarkable for carpal tunnel syndrome in the mother and maternal grandmother, both of whom were healthy otherwise. There were no obvious signs of connective tissue or skeletal diseases. Usual presenting symptoms of familial amyloid neuropathy, including generalized neuropathy at the left wrist (median motor nerve latencies measured 4.9 and 4.5 milliseconds on the right and left, respectively; median sensory nerve latencies measured 3.8 and 3.3 milliseconds on the right and left, respectively). EMG results, while still abnormal, showed meaningful improvement relative to the EMG performed prior to the patient’s first CTRs.

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Patient #2 completed the Boston Carpal Tunnel Questionnaire 12 y after his carpal tunnel release, the results of which are summarized in (Table 2). Despite near-complete resolution of right-sided symptoms following treatment, he currently experiences mild symptom severity bilaterally and mild functional impairment [16].

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**Table 2 Results of Boston Carpal Tunnel Questionnaire (BCTQ)a.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time Between Initial Therapy and BCTQ Completion (yr)</th>
<th>Symptom Severity</th>
<th>Symptom Characteristics</th>
<th>Functional Status Severity</th>
<th>Functional Status Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient #1</td>
<td>11.9</td>
<td>Mild</td>
<td>• Moderate loss of sensation</td>
<td>Moderate</td>
<td>• Difficulty with:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mild weakness and tingling</td>
<td></td>
<td>◊ Writing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mild daytime pain lasting 1-2 minutes per episode</td>
<td></td>
<td>◊ Buttoning clothes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Mild nighttime numbness</td>
<td></td>
<td>◊ Gripping a telephone handle</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Difficulty with the use of small objects</td>
<td></td>
<td>◊ Household chores</td>
</tr>
<tr>
<td>Family #1</td>
<td>12.0</td>
<td>Mild</td>
<td></td>
<td></td>
<td>◊ Carrying grocery bags</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>◊ Bathing and dressing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Changed positions at work due to CTS symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Missed 3 days of work during the past month due to CTS symptoms</td>
</tr>
<tr>
<td>Patient #2</td>
<td>16.7</td>
<td>Asymptomatic</td>
<td>-</td>
<td>Asymptomatic</td>
<td>• Difficulty with:</td>
</tr>
<tr>
<td>Family #2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>◊ Buttoning clothes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>◊ Holding a book while reading</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>◊ Gripping a telephone handle</td>
</tr>
</tbody>
</table>

a (BCTQ) Symptom Severity Scale is reported based on the following scores: Asymptomatic (11), Mild (12-22), Moderate (23-33), Severe (34-44), and Very Severe (45-55). Functional Status Scale is reported based on the following scores: Asymptomatic (8), Mild (9-16), Moderate (17-24), Severe (25-32), and Very Severe (33-40) [16]
neuropathy and cardiomyopathy, were not present in the patient or her family members. There was no evidence for any associated systemic disorder. Laboratory studies were within normal limits, including a sedimentation rate, chemistry group, and studies checking for collagen vascular disease. Physical examination demonstrated positive Tinel's sign, Phalen's test, and carpal tunnel compression test on the right. EMG showed moderately severe median neuropathies at the wrist bilaterally.

Splitting provided nocturnal relief, but symptoms remained unchanged during the day. A steroid injection at the right carpal tunnel resulted in complete resolution of symptoms. No numbness, tingling, or dysesthesias were present at three-month follow-up. Phalen's test, carpal tunnel compression test, and Tinel's sign were negative bilaterally. Two-point discrimination remained 4 mm on both borders of all digits.

Although the right hand symptoms resolved completely, the patient was later diagnosed with CTS in her left wrist at an outside institution. A left CTR was performed 14 y after her initial right-sided release. Patient #3 completed the Boston Carpal Tunnel Questionnaire 16.7 y following steroid injection into the right carpal tunnel and remains asymptomatic with respect to symptoms of CTS (Table 2).

Discussion

The majority of CTS cases with a positive family history are likely due to polygenic factors [17]. However, when onset of disease occurs at an early age in a patient with a strongly positive family history and/or bilateral symptoms, a hereditary condition such as FCTS should be excluded [1-4, 13]. FCTS is a rare disorder characterized by early onset CTS, presenting at an average age of 27 [1-3, 8, 13, 18] Symptoms typically begin on one side, but ultimately progress to bilateral involvement in 96% of patients [13]. Clinical features are those of classic CTS: numbness and tingling in the radial three and a half digits, clumsiness of the affected hand, and pain, frequently disruptive of sleep [1-4, 13]. The diagnosis of FCTS is by exclusion and requires that other, more common causes of bilateral CTS be ruled out (Table 1) [4]. Laboratory studies, including thyroid stimulating hormone, creatinine, glucose, and growth hormone assays are normal, as are genetic studies [1-4, 13]. Electrodiagnostic testing reveals the typical median nerve neuropathy [1, 2, 19]. Intra-operatively, a narrow carpal tunnel and/or thickened transverse carpal ligament are frequently observed, as was seen in our first two patients [2, 4, 10, 15, 18, 20-22]. Histologically, Congo red stains are negative for the presence of amyloid.2

Since Tanzer's 1959 proposition that CTS may follow a familial pattern, numerous case reports and small FCTS case series have been published [2-4, 7, 9-12, 18-21, 23-31]. Gray et al., in 1979, were the first to explicitly suggest an autosomal dominant inheritance pattern with incomplete penetration after identifying early-onset, bilateral CTS in 19 of 43 family members [18]. Subsequent authors have since constructed FCTS pedigrees supporting such a pattern [2, 4, 10-12, 19, 25, 28, 31]. Other authors submitted that since the disease appears to have a predilection for women inconsistent with purely autosomal dominant inheritance, additional genetic factors should be considered [17, 29]. Elistner et al. later suggested that the disease's female predilection may be the result of X-linked dominant transmission lethal in hemizygous males [28].

Attempts have been made to identify diagnostically relevant associations between FCTS and various biomarkers. Shinohara et al. discovered the presence of human leukocyte antigen (HLA)-A2 in four female FCTS patients from one family [29]. Mochizuki also identified a preponderance of HLA-AW33 and HLA-B12 antigens in a family affected by FCTS. However, subsequent investigations into links between FCTS and specific HLA types have not confirmed their association, nor have they identified other reliable disease markers [11, 18]. Genetic linkage analysis between FCTS and polymorphic blood markers has also proven unfruitful [28, 32].

Early authors noticed a frequent associated between FCTS and trigger finger symptoms, which has been documented in as many as 63% of FCTS patients in some studies [12, 18]. In conjunction with the higher incidence of thickened transverse carpal ligaments among FCTS patients, these findings have been used to suggest that the disease may represent an inherited connective tissue diathesis [13, 20]. The pathophysiology underlying FCTS remains unknown, but a connective tissue etiology would account for many of the similarities between the presentations of FCTS and CTS due to storage diseases known to affect connective tissue structures [1].

Because median neuropathy is usually bilateral in CTS, bilateral electrodiagnostic testing should be considered when the diagnosis of FCTS is suspected, even if one side is asymptomatic. This is especially important in children, who may not complain of symptoms but have electrodiagnostic evidence of nerve damage [1, 4, 8, 9, 33]. Patient #3's initially unilateral presentation, but ultimate need for contralateral CTR, illustrates how FCTS can progress to involve both upper extremities, increasing the risk for permanent nerve damage if not appropriately addressed. Vadasz and Stoll both noted that FCTS patients in their studies followed a presentation suggestive of genetic anticipation; if this anticipatory pattern is not merely the result of ascertainment bias, it would further justify the need for early screening studies [4, 25]. Swoboda suggests that clinical examination and electrodiagnostic testing should also be carried out in parents and siblings of affected patients, regardless of whether signs and symptoms are present [9].

Little has been suggested regarding appropriate treatment for patients with FCTS. Numerous authors report remission of FCTS symptoms following carpal tunnel release. However, the vast majority of these studies limit follow-up to the period between intervention and three years after treatment, with only the occasional study following patients for five years. In our study, patients #1 and #2 both experienced symptom recurrence near or after their 5 y post-operative date. It remains unknown whether the progressive nature of FCTS predisposes patients to delayed symptom recurrence following CTR. Results of long-term follow-up will be important to determine the natural history of the disease and the duration of relief FCTS patients can expect after release. Until now, only a study by Elistner et al. describes...
FCTS patient outcomes beyond five years [28]. Elstner provides longitudinal follow-up on three patients, one of whom is a 70 y old woman who presented for evaluation 18 y following her initial CTR. In the interim, symptoms had recurred twice (both times more than five years after release), prompting two re-releases of the carpal tunnel. The patient continued to suffer from CTS symptoms at the date of follow-up examination. We are unable to draw definitive conclusions about FCTS due to the rarity of the disease and the consequently small size of our study population, but the recurrence of debilitating CTS symptoms in three (patients #1 and #2 in our study, and patient II: 1 in Elstner’s study) of the six FCTS patients ever followed for more than five years after CTR raises concerns regarding the disease’s potential for lifelong recurrence. The recurrence of CTS symptoms in the wrists of patient #1 and #2 may also suggest that in addition to a predisposition for development of CTS, certain families with histories of FCTS might also have genetic predispositions to CTS recurrence. In these families, it may be prudent to modify treatment and initiate regular follow-up to minimize or prevent the return of symptoms. Future studies would benefit from examining whether the rate of recurrence among FCTS patients is different among patients who present in childhood, such as patients #1 and #3 in our study, and those who present later in life, such as Elstner’s patients.

Potentially increased recurrence rates also beg the question of whether CTR is the best initial treatment for FCTS. Very few reports detail the use of conservative therapies such as splinting, activity modification, NSAIDs, or steroid injection in FCTS patients. This may be due to authors’ failure to mention employment of these modalities. More likely, however, it represent practitioners’ reflexive progression to CTR given CTR’s established effectiveness in treating CTS caused by other heritable conditions (e.g. mucopolysaccharidosis or mucolipidosis) [1, 34]. Several studies, including our own, demonstrate examples where conservative therapy provided partial or lasting CTS symptom relief. Leifer et al. reported on three patients, from a family with eight individuals affected by FCTS, who experienced complete symptom resolution with splitting [19]. Vadasz and Stoll both mentioned significant symptom improvement in FCTS patients following cessation of videogame playing [4, 25]. Danta also presented an FCTS patient who received repeated relief from steroid injections [20]. Patient #3 in our study has enjoyed symptom resolution for greater than 16 y from a single steroid injection. Practitioners may therefore wish to initiate therapy for FCTS with conservative measures. In patients for whom conservative treatment is ineffective or only temporarily helpful, CTR represents a viable next step. Should future long-term follow-up show that FCTS patients are likely to experience symptom recurrence following CTR (as discussed above), conservative therapies may play an even greater therapeutic role because of their potential to relieve symptoms (at least temporarily) while avoiding complications inherent to surgery.

In our study, disease was documented in four of four consecutive generations in family #1 and three of three consecutive generations in family #2. Extensive work-up failed to reveal evidence of an underlying disorder other than familial carpal tunnel syndrome. Conservative therapy, followed by carpal tunnel release was performed upon patient #1 and #2, and both responded well initially. Corticosteroid injection was performed upon patient #3 and her symptoms resolved completely, though they later presented in the contralateral wrist.

The conclusions of our study, along with those of other studies that detail the nature of this syndrome, are limited by the small number of FCTS patients. Study results are also limited by recall bias, as identification of family members with CTS is often retrospective and unconfirmed by medical records. However, when symptoms present in childhood and patients are accompanied by parents who are able to reliably describe their own symptoms and the symptoms of their immediate family members (as occurred in both families presented here), recall bias is minimized for at least three generations and sufficient family history is obtained to suggest an FCTS diagnosis.

To our knowledge, our average follow-up of 14.3 y for the two FCTS patients treated in adolescence is the longest yet described in this patient population. Our average overall follow-up of 13.5 y for all three FCTS patients also represents one of the longest in the literature. This information may enhance the ability of clinicians who treat these patients to appropriately counsel individuals regarding expected outcomes and the potentially higher likelihood of recurrent symptoms over time [35-40].
References