Research Article

Correlation Analysis between Referring Service, Pathologic and Clinical Outcomes of Peripheral Nerve Biopsy

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Abstract

Introduction: Peripheral nerve biopsy has diagnostic utility in certain conditions but comes with inherent procedural risks. We investigated the relationship between referring service and peripheral nerve biopsy outcomes.

Methods: Retrospective chart review of nerve biopsies examining the relationship between referring service and diagnostic yield of the biopsy and alterations in clinical treatment based on biopsy results.

Results: A total of 76 nerve biopsies were referred from neurology, rheumatology and internal medicine. Definitive pathology was returned for 57.7%, 75% and 100% of biopsies, respectively. Therapeutic implications occurred in 78.9%, 75% and 0% of biopsies, respectively. No statistically significant relationship is identified between referring service and definitive pathology result (p = 0.7857) or referring service and therapeutic implications (p = 0.2504).

Conclusion: A correlation between the referring service for a peripheral nerve biopsy and diagnostic yield of the biopsy could not be identified in our data set. Pathologic results, even non-diagnostic results, had an appreciable impact on alterations of treatment plan.

Keywords: nerve, biopsy, referring service, pathology

Introduction

Nerve biopsy is a procedure typically used as part of the evaluation of peripheral nerve disorders after less invasive evaluation has been performed and further clarification of diagnosis is needed. Several publications have discussed the utility of nerve biopsy, usually sural nerve biopsy, and the diagnostic and therapeutic impact of these biopsies [1-5]. These are referred to and performed by a surgeon, typically a neurosurgeon [6]. As with any procedure, complications arise and although very rarely life-threatening, may have an impact on overall quality of life. Commonly encountered issues post-biopsy are persistent dysesthesia and sensory loss in the area innervated by the biopsied nerve, typically the lateral foot if the specimen was the sural nerve [2,4-7]. In addition, the biopsy may be non-diagnostic or may not alter management while subjecting the patient to possible unnecessary risks and costs [1-6].

The evaluation of peripheral nerve pathology prior to biopsy identifies several factors which may be analyzed in an attempt to increase the likelihood of a “meaningful” biopsy [8]. This dilemma is obvious as several publications
attempt to address pre-biopsy factors [1,9,10]. These factors include the role of electromyelography (EMG) prior to biopsy [1], simultaneous muscle and nerve biopsy to decrease the possibility of a non-diagnostic procedure [10], and simply communicating between providers to ensure agreement on pre-biopsy evaluation and appropriate biopsy site [9]. The latter topic raises a largely unaddressed pre-biopsy factor: who are the referring or requesting providers? Is there a difference of biopsy yields, clinically and pathologically, between the various biopsy referring specialties? The literature notes primary providers may request the biopsy [11] while others identify neurology as the service performing evaluation prior to biopsy [5,12]. We set out to identify if the requesting service for a nerve biopsy had an influence on the pathologic or clinical result of the biopsy.

Materials and Methods

Chart review

We performed a single-institution retrospective chart review of patients age 19 years and older who were charted for Current Procedural Terminology (CPT(R) AMA) code 64795 (nerve biopsy) between January 1, 2012 and July 1, 2016. Each chart matching the search criteria was abstracted to identify the referring service, results from the pathology report of the nerve biopsy, and any therapeutic consequences of the nerve biopsy by the referring service based on the pathology report.

Pathology examination was performed at a quaternary pathology department for the biopsy specimens. Pathology reports were classified as either providing definitive pathology or not providing definitive pathology. Definitive pathology included reports with diagnoses of microvasculitis, inflammatory or autoimmune neuropathy, no evidence of inflammation with chronic neuropathic changes definitively present, biopsy consistent with chronic inflammatory demyelinating polyneuropathy, and amyloid neuropathy. No definitive pathology included reports with diagnoses of possible neuropathy, possible neuropathic process, neuropathic change, neuropathic process not otherwise specified, possible non-diagnostic without neuropathic changes, possible autoimmune or inflammatory process, and no unequivocal neuropathic changes.

Alteration of treatment by the referring service was determined by reviewing post-biopsy documentation and identifying language referring to the pathology result and treatment(s) offered to the patient based on the pathology result. Changes in treatment plans based on pathology reports included offering steroid therapy, intravenous immunoglobulin therapy, plasma exchange therapy, or continuing current therapy if started empirically.

Prior to any chart abstraction the project received approval from the home institution's Institutional Review Board for protection of human subjects (IRB 502-16-EX).

Statistics

We predefined a level of significance, alpha, of 0.05 prior to beginning the chart review. We used a Fisher exact test to compare levels of significance between referring service and definitive pathology as well as between referring service and alteration in treatment based on pathology result. Data analysis was carried out using SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

A total of 76 nerve biopsies were identified between January 1, 2012 and July 1, 2016. The age range of patients was 19 to 84 years old with a mean of 58 years and standard deviation of 16 years. There were 29 (38%) males and 47 (62%) females. There were 69 (91%) sural nerve biopsies, 4 (5%) superficial radial nerve biopsies and 3 (4%) peroneal nerve biopsies.
Table 1 shows the referring service versus definitive pathology results. Neurology services referred 71 (93%) of the nerve biopsies while rheumatology and internal medicine referred 4 (5%) and 1 (2%) of the nerve biopsies, respectively. For neurology referrals, 41 of 71 referrals (58%) returned definitive pathology on biopsy versus 3 of 4 referrals (75%) for rheumatology and the single referral from internal medicine returned definitive pathology. The p-value between referring service and obtaining a definitive pathology result is 0.7857 and thus did not reach statistical significance.

<table>
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<tr>
<th>Referring Service</th>
<th>Definite pathology</th>
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<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
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<tr>
<td>Neurology</td>
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<td>30</td>
<td>71</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>3</td>
<td>1</td>
<td>4</td>
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<tr>
<td>Internal Medicine</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>45</td>
<td>31</td>
<td>76</td>
</tr>
</tbody>
</table>

Table 2 shows the referring service versus alteration in treatment plan based on the pathology result. Neurology altered treatment in 56 of 71 referrals (79%) based on pathology results. Rheumatology altered treatment in 3 of 4 referrals (75%) and internal medicine made no alterations in treatment of their single referral. The p-value between referring service and alteration in treatment based on pathology result is 0.2504 and thus did not reach statistical significance.

<table>
<thead>
<tr>
<th>Referring Service</th>
<th>Alteration in treatment</th>
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<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Total</td>
</tr>
<tr>
<td>Neurology</td>
<td>56</td>
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<td>59</td>
<td>17</td>
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**Discussion**

Our single institution evaluation of nerve biopsy requesting services and their respective clinical and pathological outcomes did not demonstrate significant difference in the outcomes between services. However, the data still sheds light on nerve biopsy referring services and the potential yield of biopsy results based on the referring service. To the best of our knowledge this evaluation is the first reported study to look for a potential association between the requesting service and pathological diagnosis. There have been limited mentions of referring services for nerve biopsy in the literature prior to this study.

Ruth et al. [5] discuss their results of 67 patients who underwent sural nerve biopsy through the department of neurology. They found only 34% of their biopsies to have specific histologic findings, 32.8% of biopsies to have diagnostic consequences and 26.9% of biopsies to have therapeutic consequences.

Claussen et al. [11] discussed their results of 115 simultaneous nerve and muscle biopsies for suspected vasculitis. They state 101 (88%) of biopsies were at the request of "primary physicians" and the remaining 14 (12%) of the biopsies originated from their neurology clinic. They do not specify the specialty of the "primary physicians" who requested the majority of the biopsies in their study. Their study found a 39.1% diagnostic sensitivity for vasculitis in the nerve biopsies and a lower rate of 16.5% diagnostic sensitivity of muscle biopsies for vasculitis.
Gabriel et al. [12] states all patients in their prospective sural nerve biopsies of 50 consecutive patients were evaluated by a neurophysiologist prior to nerve biopsy to help classify the nerve issue as multiple mononeuropathy, axonal neuropathy or demyelinating neuropathy. They make no mention of who originated the biopsy request. They found 60% of biopsies altered treatment, 32% did not alter treatment, and 8% disagreed with the original diagnosis.

Of our 76 total nerve biopsies, neurology referred 71 of the patients (93.4%) and rheumatology 4 of the patients (5.3%), which is similar to Gabriel et al. [12] and Ruth et al. [5]. Both Gabriel et al. [12] and Ruth et al. [5] looked exclusively at neurology referrals for nerve biopsy. Claussen et al. (2000), however, were specifically looking at nerve biopsies solely for vasculitis compared with our nerve biopsies for all pathologies.

In our study, neurology had a lower definitive pathologic diagnosis than rheumatology (57.7% vs 75%) but the importance of this is not clear due to the few rheumatology requests for nerve biopsy (4 total). Internal medicine only requested one nerve biopsy which did have a definitive pathologic diagnosis but no treatment impact. We carried out a post-hoc analysis of neurology versus all other requesting services grouped together (rheumatology and internal medicine) for definitive pathologic diagnosis and found the p-value to be 0.899.

The failure to find statistical significance between requesting service and pathologic diagnosis can occur due to one of two issues: either no difference exists or Type II error. As is noted in the literature [5,11,12] most referrals for nerve biopsy occur after extensive workup by a neurologist. We found this to be the case with our biopsy requests as well. This makes logical sense as neurologist have the training needed to effectively work up and diagnose nervous disorders. Additionally, we serve as the neurosurgery service at a tertiary academic center and most patients have had extensive work-up when they are referred to our service for nerve biopsy.

Anecdotally our neurosurgery service has been sent referrals for nerve biopsies from primary care services including general practitioners, family medicine and internal medicine for which we recommended the patients undergo further evaluation by neurology prior to nerve biopsy as we believed the workup at the time of initial nerve biopsy request may have been incomplete. Some of these cases progressed to biopsy and are included in this series while others were diagnosed by neurology prior to the need for a nerve biopsy. We acknowledge in retrospect this suggested referral to neurology prior to nerve biopsy can influence the results of our current study but adamantly believe the best interest of the patient was served in such cases to provide each patient with an efficiently obtained, reliable diagnosis.

In regard to a clinically useful pathologic nerve biopsy which led to changes in treatment, rheumatology referred biopsies altered treatment in 75% of biopsies while neurology altered treatment in 78.9% of biopsies, even though neurology referred biopsies only had a definitive pathologic diagnosis in 57.7% of biopsies vs 75% of rheumatology referred biopsies. Based on chart documentation we believe there is an identifiable explanation for the discrepancy between neurology requests with definitive pathologic diagnosis and neurology requests altering treatment. In most of the instances where treatment was altered based on non-definitive pathologic result the treating neurology team referenced a preponderance of other clinical evidence supporting a treatment decision strategy without pathology excluding the principal diagnosis on the differential list. In such cases the neurology team stated the non-diagnostic pathologic result could be used as data to help exclude other diseases from the differential and allow the treating team to be more confident in a recommended treatment strategy.

Our study does have several limitations. Although we are the first to specifically try to address the influence referring service has on nerve biopsies, we are not the first or largest to look at predictive factors of nerve biopsies. As noted earlier, our inability to achieve statistical significance in either of our two primary endpoints can be due to either no difference existing or type II error. Additionally, we also noted our neurosurgery service serves a tertiary referral center and were able to redirect some potential nerve biopsies to our neurology department for further non-
invasive evaluation prior to obtaining a nerve biopsy. We recognize all providers who seek a nerve biopsy may not always have the benefit of an academic neurology service to refer to for additional specialized evaluation prior to biopsy which could limit the generalizability of our study.

We also note that of 76 patients only 5 (6.6%) were referred by specialties other than neurology. This gives a skewed distribution of referrals which limits the power of our study but is in-line with referral patterns noted in the literature [5,11,12]. Although our biopsies were analyzed by the same quaternary pathology lab there were at least three distinct pathologists who rendered reports over the 54 months of the study timeframe and five separate neurosurgeons who performed the biopsies. Variations in surgical techniques and pathologic interpretations could affect the results of the biopsy. Additionally, there were a multitude of neurologists who sent the referrals, but two neurologists requested greater than 60% of all nerve biopsies. The heterogeneity of these groups could also affect the results of our study.

We were not able to identify a statistically significant difference between referring services for a nerve biopsy and the finding of definitive pathologic results or the use of pathologic results to alter treatment. Important to note, however, is the majority of referrals were from neurologists which is similar to previous reports in the literature. Given the unique training of neurologists we feel a neurology evaluation should be sought prior to nerve biopsies in an attempt to maximize the utility of biopsies in altering treatment. Given the limited power of our current study, we recommend further examination of referring service and pre-operative workup as methods to increase diagnostic yield of nerve biopsies.

Acknowledgement

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References
