Review Article

# A review on the investigation of peripheral neuropathy at Mater Dei Hospital

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## Introduction

The term peripheral neuropathy encompasses a wide range of disorders. The underlying causes of peripheral neuropathy are diverse. It is very difficult to ascertain the incidence of peripheral neuropathy with any degree of certainty, but it is a manifestation of several common multisystem disorders, whose incidence is on the rise, such as diabetes and Human Immunodeficiency (HIV) virus infection. Worldwide, the population prevalence is about 2,400 per 100,000 (2.4%), rising with age to 8,000 per 100,000 (8%).[1] Peripheral neuropathy can significantly impact an individual's quality of life especially if undiagnosed and untreated.

Investigation of peripheral neuropathy is expensive and time consuming, and is best performed in a stepwise approach. Even in the best of circumstances, an aetiological diagnosis is not always achieved. At present, the existing guidelines deal with the treatment of peripheral neuropathy but there are none on how patients with peripheral neuropathy should be investigated.

## Aims of the audit

The aims were to assess how patients in Mater Dei Hospital were investigated for peripheral neuropathy and whether a definite diagnosis was ultimately reached.

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## Methodology

### *Patient Population and Data Collection*

Approval was obtained from the data protection officer at Mater Dei Hospital. 536 EMG results from the year 2011 were randomly selected from the database of the Neuroscience department. These were reviewed and the patients with a neurophysiological diagnosis of peripheral neuropathy were identified. The investigations performed within a year, before or after, the EMG date for these patients were studied. Demographics, source of referral, indication for EMG and diagnostic data were collected for each patient, using PACS, Isoft Clinical Management, Electronic Case Summary, and patient's records. All the data was inputted in a tabulated format using Excel and then analysed.

In this audit, Complete blood count (CBC), Renal profile, Calcium, Liver profile, Fasting blood glucose (FBG) or haemoglobin A1c (Hba1c), Thyroid function tests, vitamin B12, urinalysis for microscopy and Chest X-ray were considered to be first line investigations. Second line investigations include HIV serology, vasculitic screen, serum protein electrophoresis (SPE) and tumour markers, and ultrasound of the abdomen. Serum Angiotensin Converting Enzyme (ACE) levels, paraneoplastic panel, anti ganglioside antibodies, Cerebrospinal fluid (CSF) analysis, nerve biopsy and genetic testing were considered to be specialised tests [Table 1][2].

## Results

118 patients with a neurophysiological diagnosis of a peripheral neuropathy were identified from the first 536 EMG results of the year 2011. From the total of 118 patients with peripheral neuropathy, 116 were selected for further review.

44 patients (37.3%) were female and the remaining 62.7% were male (*n*= 74). The mean age was 59.3 years with a range of 4-86 years.

When looking at the remaining 418 EMG results: 34% (n=182) were reported as normal, 40.7% were reported as mononeuropathy (*n*=218), 0.6% plexopathy (*n*=3), radiculopathy in 0.4% (*n*=2), anterior horn cell disease in 0.4% (*n*=2) and myopathy in 0.4% (*n*=2).

***Table 1**: Summary of investigations for peripheral neuropathy*

| | | |
|---|---|---|
| History And Examination | First tier | CBC, renal profile, liver profile, calcium, FBG/Hba1c, ESR, TFTs, B12 levels, urinalysis, CXR |
| | Second tier | Vasculitic screen, HIV serology, SPE, tumour markers, US abdomen |
| | Third tier | ACE levels, paraneoplastic panel, anti-ganglioside antibodies, CSF analysis, nerve biopsy and genetic testing |

The commonest indication for the 536 EMG tests was mononeuropathy (53.9%, *n*= 290) followed by peripheral neuropathy in 24.4% (*n*=131). The commonest mononeuropathy diagnosed was carpal tunnel syndrome (41%). In a number of cases more than one indication was selected for the EMG. Peripheral neuropathy was most commonly combined with carpal tunnel syndrome (3.7%).

With regards to the peripheral neuropathy cohort, the main source of referral was the department of Neuroscience (61%, *n*=72). The other two major sources of referral were the department of Medicine with 16.1% (*n*= 19) and the Orthopaedics department with 13.6% (*n*= 16). 47.4% of EMGs booked from the department of medicine were from the diabetes clinic. Of note 6 patients, that were included in this audit, were referred from the paediatrics department (5.1%). The remaining 5 were booked from the Geriatrics department, Gozo general hospital, pain clinic and the Department of Surgery.

***Peripheral Neuropathy Cases***

When looking at the indications for those 116 cases with an eventual neurophysiological diagnosis of peripheral neuropathy, in 64.4% the main indication was in fact peripheral neuropathy. In 16.1% the indication was mononeuropathy, 13.57% had a combined indication, and the remaining 5.83% were requested for suspected cervical myelopathy, trauma, myotonic dystrophy, myopathy and critical illness neuropathy.

***Investigations***

Co-morbidities that are associated with peripheral neuropathy were reviewed for all the 116 patients. At the time of request of EMG, the commonest documented co-morbidity detected was diabetes in 40.7% of cases followed by malignancy in 9.3% and drugs in 5.9%. Other relevant known co-morbidities at time of request included advanced chronic kidney disease (3.4%), hepatic cirrhosis (2.5%), nutritional e.g. vitamin B12 deficiency (2.4%), infectious diseases e.g. HIV (1.2%), endocrine (1.2%) and vasculitis (1.2%). In 44.1% no relevant co-morbidities were identified. The neurology department was involved in 58.1% of peripheral neuropathy cases (*n*=68). In the majority of cases this occurred prior to the EMG test.

All the investigations performed on the 116 patients 1 year before and 1 year after the EMG's were searched. When looking at the first line tests that form part of the peripheral neuropathy work-up: a complete blood count was found in 94.8% of cases, renal profile in 93.1% of cases, serum calcium in 67.2%, FBG/Hba1c in 78.4%, LFTs in 88.8%, ESR in 62.1%, TFTs in 83.6% and vitamin b12 levels in 60.3%. Urinalysis was available in 38.8% of patients and a chest x-ray was taken in 54.3% of patients. A proportion of these investigations were performed after the EMG was done as seen in figures 1 and 2.

With respect to the second line investigations anti-nuclear antibody levels were taken in 41% of patients with 58.3% being taken prior the EMG. Anti-nuclear cytoplasmic antibody levels were taken in 23% of patients only. 63% of these were available up to 1 year prior to EMG. Serum protein electrophoresis and tumour markers were taken in 46% and 44.4% of patients respectively. 53.3% of SPE results and 44.4% of tumour marker results were taken before the EMG. An ultrasound abdomen was requested in 22.2% of patients with 57.6% being done prior the EMG.

In terms of specialised tests, anti-ganglioside antibodies were taken in 18.5% of patients, ACE levels in 7% and the paraneoplastic panel in 18.8%. CSF analysis was performed in 16 patients (13.7%) and a nerve biopsy was taken in 6 patients (5.15%). Genetic studies were done for a total of four patients.

***Figure 1**: Results of first tier of investigations 1 year before/after EMG*

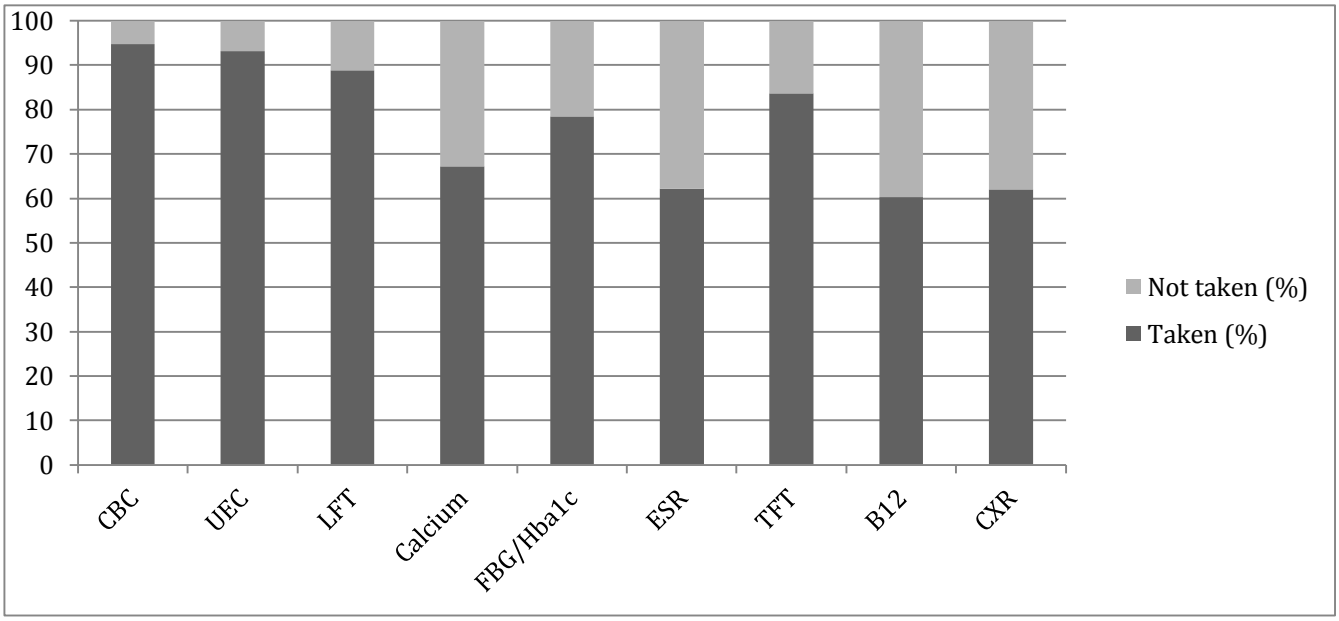



***Figure 2**: First line investigations done prior or after EMG*

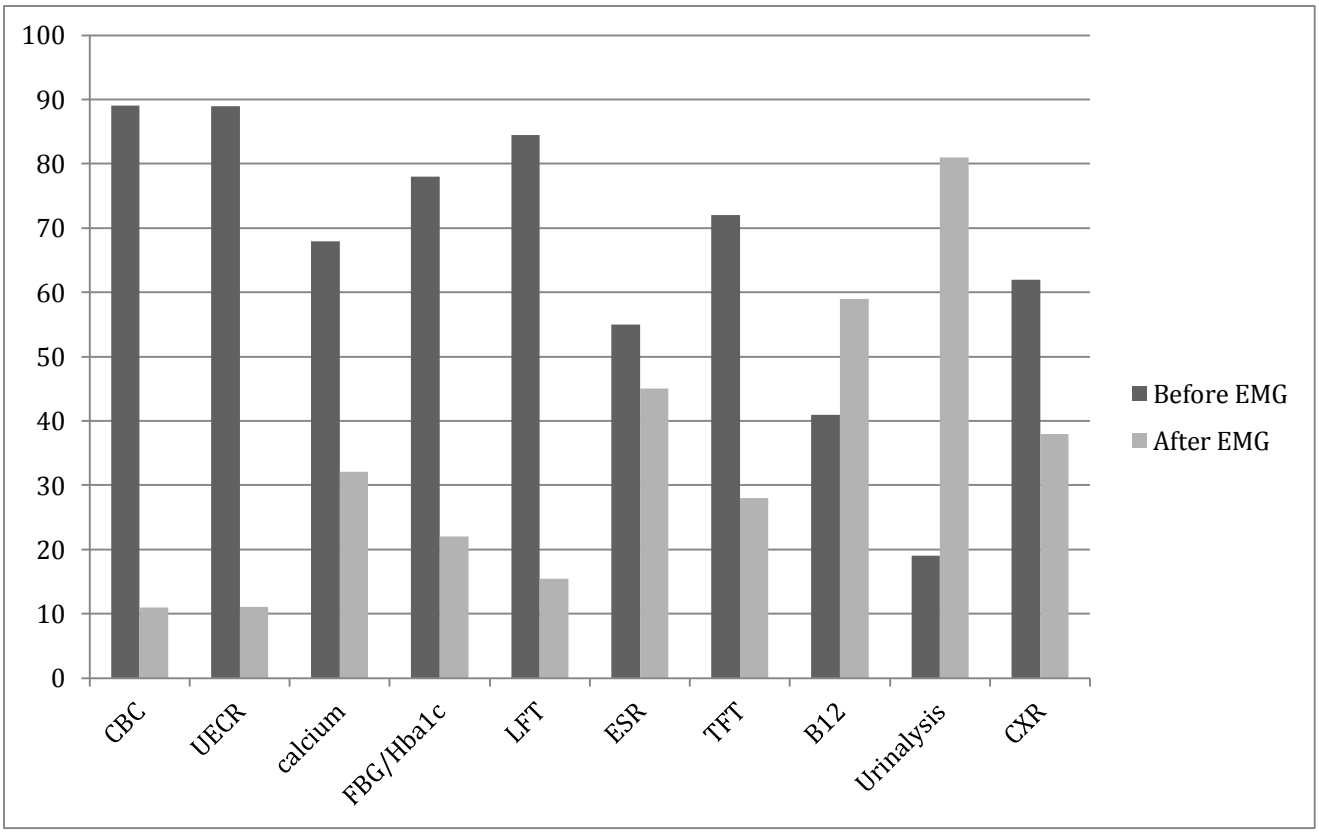
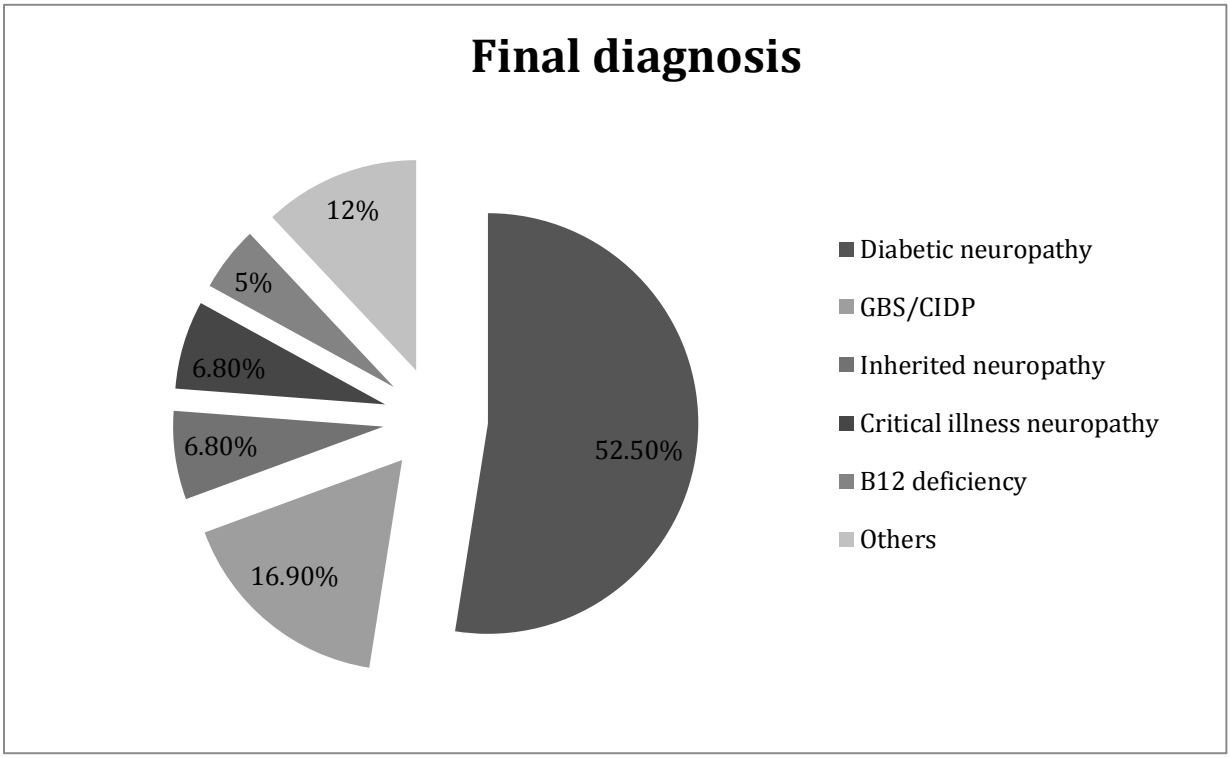


***Figure 3**: Final diagnoses of peripheral neuropathy cases*




Medical notes of all 116 patients were reviewed in search for a documented diagnosis. Each patient fit in 1 of 3 possibilities: no data (no documentation at all was found relevant to the final diagnosis), no diagnosis (patient was investigated but a final diagnosis was not achieved) and diagnosis present (aetiological diagnosis documented in the medical report). Results showed 11 cases with no data, 46 with no diagnosis and 59 patients with a diagnosis. Diagnoses were diabetic neuropathy (*n*=31), Guillaine-Barre syndrome/ Chronic Inflammatory Demyelinating Polyneuropathy (*n*=10), hereditary neuropathies (n=4), critical illness neuropathy (*n*= 4), B12 deficiency (*n*=3), monoclonal gammopathy associated neuropathy *(n*=3), vasculitic neuropathy (*n*=2) and drug-induced neuropathy (*n*=2) [Figure 3].

**Discussion**

A definite diagnosis of the aetiology of peripheral neuropathy is not always possible. The most common generalized polyneuropathy is diabetic sensorimotor polyneuropathy together with alcohol related neuropathy.[3] Thus, history taking is still paramount in the work up of this condition as it can give important clues as to what the cause may be e.g. concomitant diabetes, alcohol abuse and family history of neuropathy.

Neuropathic pain can cause distress and significantly affect the patient's quality of life. Apart from symptomatic treatment, one should aim to direct the treatment to the underlying cause. This reinforces the need to obtain a diagnosis whenever it is possible. In the challenging cases where the cause is not apparent from the history it is best to adopt a methodological approach. Different tiers of investigations ensure that the diagnostic process is efficient, rational and cost effective.

In this audit, 22% (N=118) of all the EMG's reviewed were confirmed to be peripheral neuropathy. Of note 9 patients in total were referred from the diabetes clinic. As expected, the majority (61.4%) were referred from the Neuroscience department. Four paediatric cases were identified from the cohort. This would explain the low mean age observed (59.3 years). Peripheral neuropathy was the indication for the test in 78% of cases. This implies that in the remaining 22% of cases the diagnosis was incidental.

Diabetes mellitus was the commonest co-morbidity documented in the cohort. Despite this, a FBG and/ or an Hba1c were not taken in 21.4% of patients. An Hba1c is still indicated in known diabetics because it can help assess diabetic control. Diabetic neuropathy is the commonest cause of neuropathy in Western countries with up to a third of the direct costs of diabetes attributed to neuropathy-related morbidity.[4] It may be present in up to 66% of type 1 and 59% of type 2 diabetics making it one of the commonest complications of diabetes.[3] The EMG can be normal in a diabetic patient with peripheral neuropathy symptoms due to small fibre neuropathy. In this audit 26.7% of the patients were confirmed to have diabetic peripheral neuropathy.

Baseline investigations such as a complete blood count or renal profile grouped in this study as the first tier were not taken in all the patients during the 2 year time limit preset for this audit. In this audit 39.7% of our cohort remained without an aetiological diagnosis. In the subset of patients that remained without a diagnosis (*n*=46) only 8 patients (16.3%) had completed the first tier of investigations over the 2 year period. In the remaining 38 patients several investigations were missing: urinalysis missing in 71% (*n*=27), ESR missing in 45% (*n*=17), vitamin B12 levels missing in 40% (*n*=15), calcium levels missing in 37% (n= 14), FBG/HBa1c levels missing in 26% (*n*=10) and 21% did not have a chest x-ray taken (*n*=8). A complete blood count was the only investigation available for all these patients. Irrespective of whether these tests would have been abnormal or not they are still needed for the investigation of peripheral neuropathy. The fact these core investigations were missing could reflect the lack of a systemic approach adopted when investigating patients with peripheral neuropathy.

It is estimated that about 20% of patients seen at peripheral neuropathy clinics are idiopathic despite intensive evaluation.[5-6] Chronic idiopathic axonal polyneuropathy is an entity met in the literature relevant to this condition. It is a diagnosis of exclusion, with uncertain prevalence. The cause is not known and is probably heterogeneous, but a possible association with impaired glucose tolerance or metabolic syndrome has been suggested. One study found a closer association with hypertriglyceridaemia (a feature of the metabolic syndrome) rather than with impaired glucose tolerance.[7-8] This raises the issue whether we should include a lipid profile and an oral glucose tolerance test as part of the second tier of investigations. It is possible that an inherited neuropathy was missed in those 46 patients that remained without a diagnosis. However these are rare and have an estimated prevalence of one in every 2500 individuals.[9]

The audit was limited by the fact that we could not access results of investigations done within the private sector and this could have biased our data. Other clinical data such as co-morbidities was not necessarily documented in the sources of information that we used. Thus we could have underestimated the prevalence of co morbidities in our cohort.

Specialised tests were performed in a significantly lower proportion of the patients. This was expected as these tests are not indicated in all cases with peripheral neuropathy. It was interesting to note that genetic testing was performed in 4 patients. One was inconclusive whilst the other diagnoses were Facioscapulohumeral dystrophy, Charcot-Marie Tooth disease and Myotonic dystrophy.

**Conclusion**

This audit has shown that there are a significant proportion of cases of peripheral neuropathy that remain without an aetiological diagnosis. Using a stepwise approach which involves a good history and examination followed by the recommended investigations can help make this process more efficient and facilitate the path towards achieving a final diagnosis. Ultimately not all patients will have a diagnosis despite being properly investigated. On the other hand, not all patients will require all the investigations available and this could be for numerous reasons such as the diagnosis can be clear from the history or the patient may refuse specialised tests.

In a significant proportion of patients in this audit the cause of peripheral neuropathy was identifiable from the history, examination and the first tier of investigations e.g. B12 deficiency. In these situations where the cause and management is clear specialist referral is not necessary. Of note, 20 out of the total 31 diabetic neuropathies were still being diagnosed by or referred to neurologists. On the other hand, it is wise to keep an open mind when investigating peripheral neuropathy even in known diabetic patients.

This audit highlights the significance that a thorough history, examination and baseline investigations can have in achieving a diagnosis for peripheral neuropathy. Such baseline investigations are readily available even to general practitioners in the community. This will help avoid unnecessary specialist referrals. Red flags that warrant referral to a neurologist are an uncertain cause, severe symptoms, rapid progression as well as the presence of weakness or motor symptoms.[1]

A re-audit, using a standard proforma based on the investigations mentioned, will be done in a prospective fashion so as to see whether its implementation can lead to an improvement in the diagnostic yield of peripheral neuropathies.

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