

Use of NaF and FDG PET/CT Scan for the Assessment of Charcot Joint in Charcot-Marie-Tooth Disease: All That Glitters is Gold?

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Abstract

Increasingly Charcot neuroarthropathy (CN) is being recognized in patients with Charcot-Marie-Tooth (CMT) disease. In this report, we describe a case of CN in a CMT patient, adding to the very scarce literature describing this association. We additionally report his unique evaluation with fluorodeoxyglucose (FDG) and sodium fluoride (NaF) positron emission tomography/computed tomography (PET/CT) scanning, the study of which is limited in CN despite its promising role. A 54-year-old known case of CMT, presented with left foot pain, and swelling for 4 months. Weakness and sensory deficits as a result of CMT were evident in both lower and upper limbs. His x-ray was suggestive of CN. Both FDG and NaF PET/CT scanning demonstrated increased tracer uptake in the first tarsometatarsal joint (TMTJ), in keeping with CN. Recognition of the association of CMT with CN is of vital importance as early diagnosis relies on high clinical suspicion. Characterizing risk factors of CN in CMT patients is still under study. Moreover, there is lack of data evaluating the role of PET/CT in CN and specifically in the context of CMT.

Keywords: Arthropathy, Charcot, CMT, Hereditary, Neuropathy

Introduction

Charcot-Marie-Tooth (CMT), or hereditary motor sensory neuropathy, is a group of primary hereditary neuropathies that is genetically and phenotypically heterogeneous. Patients with CMT often present clinically with distal sensory loss and weakness that often starts in the lower limb. CMT has been associated with multiple musculoskeletal complications, including pes cavus, valgus deformity of the ankle, scoliosis, clawing of the toes, and, increasingly, Charcot neuroarthropathy (CN)¹.

CN, also known as Charcot or neuropathic joint, is a progressive destructive condition of a joint and the

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Edited by: G. Lyritis Accepted 10 January 2024 surrounding bone in which loss of sensation is a prerequisite. The exact pathophysiology is still unclear, but it is a general consensus that the etiology is multifactorial. It includes factors such as repetitive micro-trauma and autonomic dysfunction leading to increased blood flow and bone resorption². Presentation is typically with swelling of a joint associated with warmth and redness. This swelling may or may not be painful. Early diagnosis of CN is difficult, and it is often misdiagnosed as a myriad of conditions including septic arthritis and osteomyelitis. One of the suggested ways to reduce morbidity due to delayed management is the high index of suspicion of at-risk populations³. This highlights the importance of recognizing the association between CMT and CN. In this paper, we report a case of CN in a genetically proven CMT patient. We also share the results of his evaluation with positron emission tomography/computed tomography (PET/ CT) scanning using both fluorodeoxyglucose (FDG) and sodium fluoride (NaF) as tracers.

Case presentation

A 54-year-old known case of CMT presented with a fourmonth history of left foot pain and swelling. He reported



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no history of trauma, and no surgical interventions were performed prior to this presentation.

On weight bearing, he had a tendency for severe valgus in both feet, which is more marked on the left side. Moreover, the patient had swelling of the medial left foot, warmth as well as mild tenderness over the first metatarsophalangeal joint. Upper limb motor power was reduced at his elbow extensors and finger flexors, which were recorded as 4/5. Intrinsic muscle weakness of the hand with wasting was evident. Muscle power weakness was more profound in the lower limb. Power in his hips was intact; however, his knees had a power of 4/5. His ankle motor power was the most severely affected, with a power of 2/5 in both plantar flexors and dorsiflexors. The patient had apparent intrinsic foot wasting with clawing. A sensory exam revealed stocking hypoesthesia with impaired joint position sense and vibration. His left lower limb was more severely affected than the right. Deep tendon reflexes were absent bilaterally.

His foot x-rays showed bone erosions in the left first metatarsal bone and adjacent cuneiform bone as well as surrounding soft tissue swelling. The first tarsometatarsal joint (TMTJ) space was also reduced. There was no scintigraphic evidence of osteomyelitis or septic arthritis on Technetium 99m hexamethylpropyleneamine oxime (Tc-99m HMPAO) labelled white blood cell scan. FDG PET/CT demonstrated increased metabolism at the left calcaneotalar region as well as the base of the left first metatarsal bone and adjacent cuneiform bone. Increased osteoblastic activity at the left TMTJ was evident on NaF PET/CT. Right, concave lumbar scoliosis was seen on scout view. Low-dose CT showed reduced joint space of the first tarsometatarsal joint and multiple subchondral cysts (Figure 1).

The clinical presentation, along with imaging findings, was consistent with a diagnosis of left first tarsometatarsal joint Charcot process. Hence, a total contact ankle foot orthosis was prescribed.

Our patient was diagnosed with CMT about three years ago. His symptoms started as frequent falls and weakness noticed first in the lower limbs. At that time, his weakness was predominantly in the ankle muscles. The peripheral neuropathy was also more severe in the left lower limb. Nerve conduction studies showed generalized severe demyelinating sensory-motor polyneuropathy with uniformly low velocities. Genetic studies revealed duplicates within the PMP22 gene suggestive of CMT A1. There was no family history of CMT.

Discussion

Herein, we present a case of concomitant CMT and CN. Although reported in the literature, this association remains underrecognized in clinical practice. To the best of our knowledge, this case represents the fifth reported in the literature in a genetically proven CMT patient and the only case that has undergone evaluation with PET/CT¹. Most commonly, CN is seen in association with diabetes mellitus. Other associated conditions include syphilis and spinal cord





injury^{2,3}. The consequences of delayed diagnosis of this arthropathy become evident when the outcomes of patients with CN related to diabetic neuropathy are assessed. Delays in diagnosis lead to the progression of the foot deformity, conferring an increased risk for ulceration, infection, amputation, and mortality⁴. Hence, awareness of the possibility of this diagnosis in association with CMT is vital.

CN in diabetes usually occurs after ten years of diagnosis of diabetes mellitus⁵. The time to onset of CN likely represents the time it takes for peripheral neuropathy to develop and progress. In our case, CN occurred only after three years of the onset of symptoms of CMT. It is essential to look at this aspect of CN to gain more understanding of this rare entity. It is reasonable to assume patients with CMT will be at risk of CN when the peripheral neuropathy has become severe enough. CMT is a progressive neuropathy, and the average progression rate per year has been studied in children with CMT. It was found that CMT subtypes progress at different average rates in a two-year period. The most common subtype, CMTA1, progressed at an average of 14% change from baseline during the studied duration. In contrast, progression is agespecific for some subtypes, such as CMT1B⁶. It only takes a few years for the peripheral neuropathy in some cases of CMT to lead to significant sensory loss, hence the relatively early presentation soon after diagnosis in our patient. The rapidity of progression of CMT is likely more significant than years since diagnosis. This is supported by previous reports of CN occurring in CMT with more severe sensory deficits¹. Our patient developed CMT during the fifth decade, unlike most previously reported cases, which had childhood onset CMT¹.

Repetitive microtrauma may precipitate the development of CN. This trauma may be extrinsic or intrinsic. We hypothesize that intrinsic trauma is more critical in patients with CMT because of the pre-existing abnormal biomechanics secondary to the foot and ankle deformities. Whether certain deformities in CMT predispose to CN development is yet to be elucidated. Our patient had a more severe valgus deformity in the affected limb. He also had right lumbar concave scoliosis. The sensory neuropathy and, as a result, the foot deformity was more severe on the affected side.

It is suggested in the literature that triple arthrodesis is a possible risk factor for the development of CN since it reduces hindfoot mobility and increases stress on the ankle joint; the present case may give new insights^{1,7}. One previous report shares several similarities with this case, including the presence of valgus deformity and lumbar scoliosis⁷. This patient, however, unlike our case, underwent triple arthrodesis. It is still plausible that triple arthrodesis plays a role, but since multiple patients, including our case, developed CN without undergoing the procedure and many CMT cases who undergo the procedure do not develop CN, other factors are involved.

Predication of the development of CN in CMT may aid in decisions around treatment. If we recognize that specific foot and/or ankle deformities predispose to this condition, early surgical intervention may benefit some patients, while

avoidance of certain interventions, such as triple arthrodesis, may have a role. The presence of scoliosis in those with CMT who develop CN may be a contributing factor since it alters lower limb biomechanics and can theoretically increase repetitive microtrauma. The presence of associated scoliosis was omitted in all but one previously published case^{1.7}.

Understanding the challenges that arise when considering a diagnosis of CN is important. Although difficult, high clinical suspicion and vigilance will often lead to early diagnosis and commencement of treatment. X-rays and MRI are often the modalities used in the assessment of suspected CN. Plain x-rays are important in the diagnosis of CN. Since early CN may not demonstrate any changes on plain films, the use of MRI for its superior sensitivity is crucial. It is worth mentioning that MRI is superior to x-rays in the early stages of CN but merely serves to confirm findings found on x-ray in later stages⁵. Hence, it is suggested that MRI imaging should be reserved for select cases, e.g., concerns regarding infection⁵.

The radionuclide NaF is known for its affinity to bone and has been evaluated and proven as the superior imaging modality for several benign and malignant disorders of joints and bones, including skeletal metastasis. Additionally, nuclear imaging offers quantitative data regarding tracer uptake, which may have clinical applications in monitoring disease progression and surgical intervention planning^{4,8}. The study of NaF PET/CT scanning in the context of CN is limited. A very recent case series, which included three diabetic patients with CN who underwent evaluation with NaF PET/CT, showed that all three patients had increased tracer uptake, suggesting bone remodelling. Our paper provides new information regarding NaF PET/CT in CN as all patients were assessed nine months or later after reconstruction surgery for CN. Herein, we demonstrate that NaF PET/CT can be positive as early as four months after the onset of symptoms, even without any surgical intervention⁴.

FDG PET/CT is helpful in inflammatory conditions since tracer uptake signifies increased metabolic activity. In a report of CN patients who underwent FDG PET scanning, all participants had increased tracer uptake. Applying the quantifiable information provided by this scan in patients with CN is a prospective indication⁹. In addition to the first TMTJ, the calcaneo-talar region demonstrated increased uptake on FDG PET/CT but not the NaF scan. This can be explained in two ways. As the valgus deformity was more severe on the left, this ankle is at risk for degenerative changes, which shows up as non-specific inflammation. The other plausible hypothesis is that it represents an early subclinical Charcot process.

Our radiologists could not rule out osteomyelitis or septic arthritis based on NaF or FDG PET/CT scan alone. The WBC labelled nuclear study was conclusive for this purpose.

Several questions still need to be answered regarding this association. First, whether CN is limited to specific subtypes of CMT, all previous reports were of patients with CMT A1, the most common subtype¹. Secondly, whether diabetes increases the risk of CN in CMT is an essential factor to be examined in future studies as more cases are recognized since CMT in itself may be associated with diabetes, and diabetes is associated with CN¹⁰. In those with established CN, the quantifiable information obtained from PET/CT may aid in decisions regarding the duration of off-loading or surgical interventions timing or type, and evidence is needed to study this possibility.

Conclusion

The association between CMT and CN is not well known and is often underrecognized and misdiagnosed. Recognition is central to commencing correct management and delaying the progression of further joint deformity. Additionally, as PET/ CT provides information regarding metabolic activity and bone remodelling, the usefulness of this imaging modality in CN is promising.

Authors' Contributions

Ameerah Alsaqobi contributed to data collection, data interpretation, manuscript preparation, and literature search. Biju Gopinath contributed to the overall planning and coordination, data collection, and data interpretation. All authors read and approved the final version of the manuscript.

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