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Polyneuropathy Of Unknown Etiology In An Adult Female With Anatomic Variants

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Background:

One of the earliest descriptions of neuralgia dates back to John Fothergill in 1773.[1] However, the concept of nerve pain can be traced to physicians like Rhazes (d. 925), Haly Abbas (d. 982), Avicenna (d. 1037), and Jorjani (d. 1137) who discussed multiple aspects of neuropathic pain including its classification, etiology, differentiating characteristics, qualities, and pharmacologic and nonpharmacologic treatments.[2] Currently, neuropathy is a general term describing many signs and symptoms caused by dysfunction of the nervous system.[3] Peripheral neuropathies are largely associated with pins and needles sensation, but can also include a range of symptoms from paresthesias to severe chronic dysesthesia. The burning pain of severe polyneuropathy can become so intense that it significantly impacts quality of life. In order to effectively treat neuropathy, it is essential to determine the underlying mechanism.[3]

According to Levine (2018), neuropathy can be caused by diabetes mellitus, impaired glucose tolerance, primary systemic amyloidosis, familial amyloidosis, Fabry disease, Lupus, vitamin B12 deficiency, celiac disease, Sjögren's syndrome, sarcoidosis, paraproteinemia, HIV, or paraneoplastic syndrome. In addition, neuropathy can also be produced by various immune-mediated responses, inherited diseases, alcohol abuse, chemotherapy, medications, and trauma.[4] Recently, SARS CoV-2 (COVID-19)

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has been reported to produce possible neuropathic pain in up to 2.3% of patients hospitalized with COVID-19, but this prevalence is probably underestimated because chronic neuropathic pain may develop months after injury to the nervous system.[5] Prevalence of neuropathy ranges from 0.8 to 17.9%, with an estimated male-to-female ratio of 1:2; about 8% of adults over 65 report some degree of neuropathy.[7,8]

Current treatment options for neuropathies include: tricyclic antidepressants (i.e., amitriptyline), serotonin norepinephrine reuptake inhibitors (i.e., duloxetine), anticonvulsants (i.e., carbamazepine), antispasticity agents (i.e., baclofen), weak opioid agents (i.e., tramadol), topical agents (i.e., lidocaine, capsaicin), and antiarrhythmics (i.e., mexiletine). Opioids are becoming controversial in treatment of neuropathy due to increasing concerns of public abuse, as well as adverse effects on gastrointestinal function.[4] Surgical treatments include spinal cord stimulator, nerve decompression, and sympathetic blocks. Rehabilitation modalities include desensitization, cardiovascular exercise, and biofeedback. In most cases, the goals in treating chronic neuropathy are 50% reduction of pain and resultant increase in function.

IVIg has had positive results in treating neuropathic pain caused by idiopathic small fiber neuropathy and current studies are looking at blocking angiotensin II (type 2) receptors and the use of erythropoietin.[4] Treatment choice should be based on side effect profile, patient choice, medication interaction, pathophysiology, and pharmacogenomics.

Case Presentation:

In 2019, a 55-year-old Caucasian, right-handed female presented to an outpatient clinic with neuropathic signs and symptoms (ache, burning, stabbing, tingling, numbness, throbbing, sharp, shooting) occurring anteriorly on upper chest, bilateral palms, left groin, bilateral lower extremities. Pain occurred posteriorly over the entire back, radiating through bilateral upper extremities and ending on distal fingertips, while also affecting posterior bilateral lower extremities and bilateral plantar surfaces. Overall, the patient rated the pain 7 out of 10 on the Wong-Baker pain scale.

The patient's symptoms began gradually after a fall in 2006 resulting in left shoulder injury. Years later, the patient developed chest and back nerve pain radiating to the neck and jaw, with pain getting worse in 2014, and by 2015 it was constant and intense. MRI revealed left shoulder tendonitis and cervical spine degenerative disc disease (DDD). Electromyography (EMG) studies revealed moderate bilateral carpal tunnel syndrome (CTS) without evidence of cervical radiculopathy. Patient refused gabapentin and chose physical therapy and Cervical Epidural Spinal Injection (CESI) which temporarily relieved her cervical pain.

A year after her initial presentation, the patient developed neck and low back pain with MRI showing worsening of cervical spine DDD with moderate central canal stenosis, and C5-C6 moderate left and mild right foraminal stenosis. Lumbar spine MRI revealed DDD with anterolisthesis of L4-L5-S1 and mild disc collapse. MRI also showed mild levoscoliosis of the upper thoracic spine. Repeat EMG showed bilateral CTS with normal lower extremities. The patient was diagnosed with bilateral CTS, cervical and lumbar spondylosis, chronic neck and low back pain with lower extremity radiculopathy. She was prescribed gabapentin 100 mg twice daily.

The patient continued to have persistent neck and back pain after starting gabapentin. Physical exam revealed cervical pain with limited ROM in all axes, as well as lumbar pain with all lumbar spine movements. Muscle strength was normal for all muscle groups with no spasticity, and normal reflexes with intact sensation and proprioception. A second CESI injection and lumbar epidural spinal injection (LESI, L5-S1) provided no relief. Gabapentin was increased to 300 mg three times daily.

In 2017, after no improvement, rheumatology was consulted and laboratory results showed a mild abnormal positive anti-nuclear Ab (1:160) with speckled pattern, and moderate positive histone antibodies. The patient was diagnosed with drug-induced lupus, advised to stop taking gabapentin, and was started on pregabalin. Differential diagnoses including fibromyalgia and thoracic outlet syndrome (TOS) were considered. A third EMG showed bilateral wrist median mononeuropathies and bilateral Martin-Gruber Anastomoses (Figure 1). Adson's maneuver was positive, however TOS was not confirmed on ultrasound.

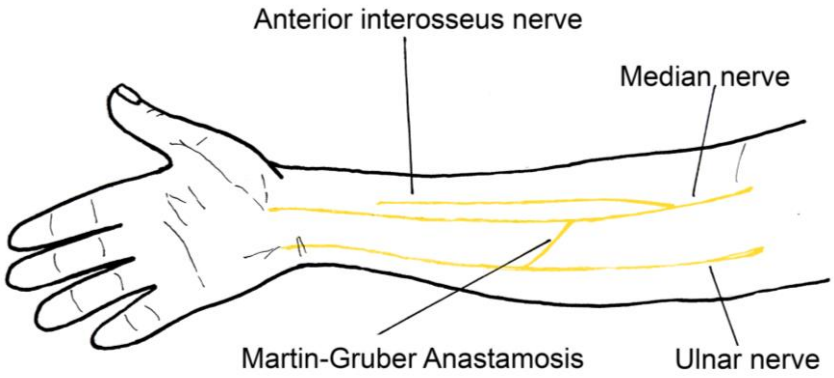

Figure 1. Showing Martin-Gruber Anastomoses. Drawn by E. Dominiak. (Note: Radiological images are accurate for diagnostic purposes, but are not clear for illustrative purposes. Therefore, drawings are used for all figures.)

The patient's pain became severe. She developed tremors and lost the ability to flex her digits. A neurologist diagnosed fibromyalgia and began therapy for TOS. Repeat laboratories confirmed positive anti-nuclear and anti-histone antibodies. MRI of the left shoulder revealed probable superior labral tear. MR neurogram of the brachial plexus was negative. Based on physical exam, a vascular surgeon diagnosed LUE vasculogenic TOS without evidence of neurogenic TOS or other brachial plexopathy. The patient was tapered off pregabalin due to no drug response.

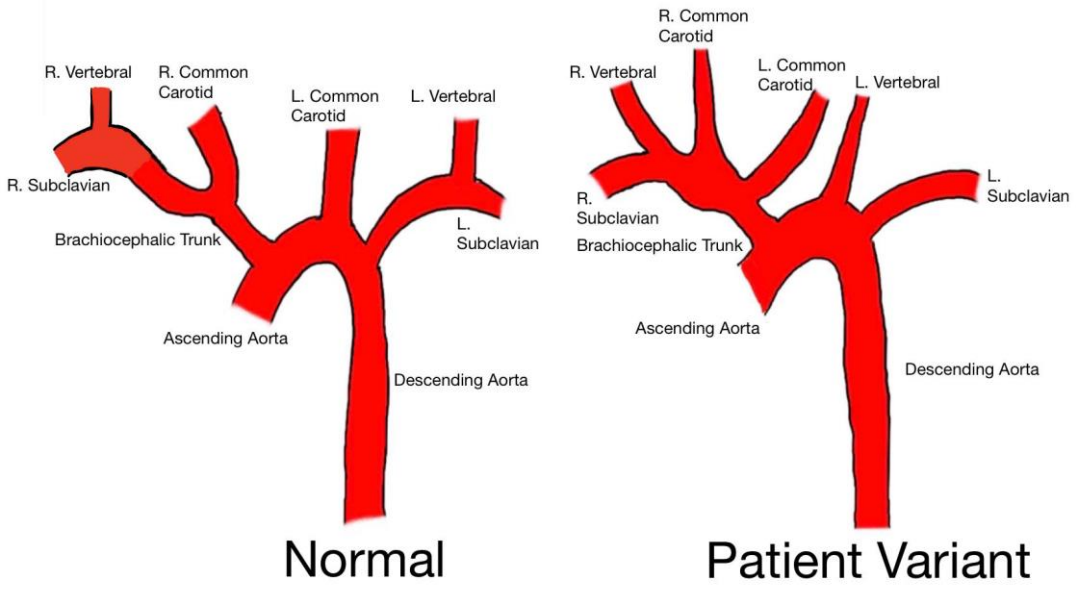

Figure 2. Common origin of the brachiocephalic and left common carotid arteries, as well as independent origin of the left vertebral artery directly off of the aortic arch compared to normal anatomy. Drawn by D. Tookey.

In 2018, dynamic CT angiogram revealed a second anatomic variant: Direct Vertebral Artery 2 variant of Bovine's arch (Figure 2, above). Elbow ultrasound revealed a third anatomic variant, bilateral anconeus epitrochlearis (Figure 3), without evidence of bilateral ulnar compression. Thoracic spine MRI showed a minimal annular bulge and tiny paracentral disc herniation at T5-T6, a tiny posterior central disc protrusion at T6-T7, a small left paracentral disc extrusion at T7-T8, and a small right paracentral disc extrusion at T9-T10. Lumbar spine (L-spine) MRI revealed a new disc herniation at L3/L4. Cervical spine (C-spine) MRI revealed mild straightening of the cervical lordosis. Repeat physical exam again revealed 5/5 strength in all muscle groups, and normal reflexes bilaterally.

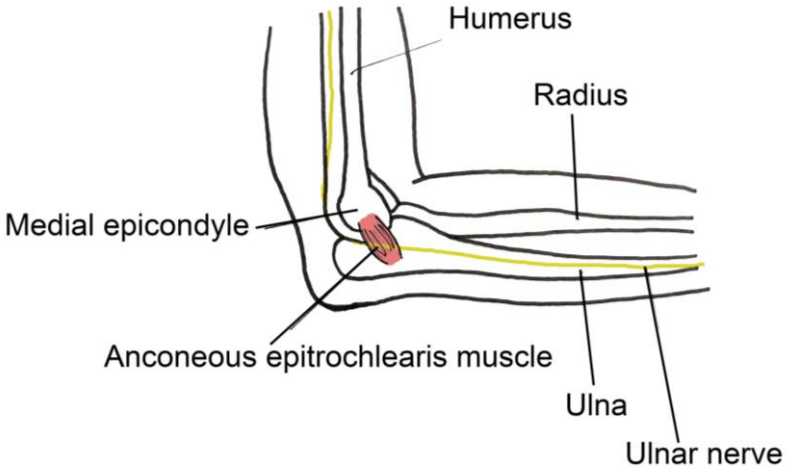

Figure 3. Showing anconeus epitrochlearis muscle (left upper extremity). Drawn by E. Dominiak

Repeat EMG showed markedly increased medial antebrachial cutaneous sensory amplitude compared to the prior study and was now within normal limits. Median motor amplitude was also increased. There was no evidence of cervical motor radiculopathy or lower trunk plexopathy, however there was evidence of a median mononeuropathy manifested as forearm focal conduction block accompanied by temporal dispersion and neurogenic changes on needle examination.

Due to chronic, multisystemic symptoms, additional labs were done to rule out autoimmune or multifactorial causes. Celiac panel was negative, creatinine was mildly decreased at 0.7 mg/dL, vitamin B1 was mildly elevated at 203, sedimentation rate (ESR) was mildly elevated at 29, C-reactive protein (CRP) was mildly decreased at 0.7, ANA titer showed speckled 1:320, and histone Ab was weak positive at 1.1.

In 2019, EMG/NCV studies revealed severe right and moderate left CTS, with borderline sensory neuropathy and decreased median motor nerve velocity of 43 m/s of the left forearm consistent with the 2015 study. Neurology concluded that this reduced velocity may be due to pronator teres syndrome caused by the presence of the anconeus epitrochlearis. C-spine MRI showed a shallow disc osteophyte complex and facet arthropathy at C5-C6 causing moderate chronic cord compression and central spinal stenosis with moderate bi-foraminal stenosis. L-spine MRI showed shallow disc osteophyte complex and facet arthropathy throughout mid/lower L-spine causing mild multilevel left/central stenosis with moderate right foraminal stenosis with new finding L-spine dextroscoliosis. Sacral MRI demonstrated a small left sacral insufficiency fracture as well as left sacroiliac joint nonspecific periarticular bone marrow edema.

In 2020, the patient presented to outpatient Physical Medicine and Rehabilitation private

practice with neuropathic pain and a complicated past medical history, including: left-sided meniscal tear, labrum tear and shoulder fracture, C-spine diastrophic dysplasia, small fiber neuropathy, large fiber polyneuropathy, L5-S1 herniated nucleus pulposus, left lower extremity allodynia, drug-induced lupus, peptic ulcer disease, thyroid nodule, and clinical TOS. EMG/NCS showing mild bilateral CTS (right worse than left), with significant improvement compared to a 2017 study, no evidence of large fiber neuropathy, brachial or lumbosacral plexopathy, entrapment neuropathy, or myopathy. Chronic L5-S1 radiculopathy was unchanged from previous EMGs and skin biopsy showed significantly reduced epidermal nerve fiber density, consistent with small fiber neuropathy. Medications included: Tramadol, bone and nerve supplements, turmeric, and medical THC for pain control. Family history was limited due to adoption, however the biological mother had breast cancer at age 79. Surgical history included bilateral carpal tunnel release, three C7-T1 CESI, and L5-S1 LESI. Social history included that the patient was married with 3 children (ages 26-31, all healthy), was a current smoker of 15 pack years, and had no alcohol or other illicit drug use. Despite over 4 years of physical therapy, all activities of daily living (ADLs) were limited. Positive review of systems included headaches, dizziness, lightheadedness, vision issues, neck problems, back pain, shortness of breath, chest pain, problems with urination, osteoporosis, joint pain, numbness/tingling, sleep issues, anxiety. Last menstrual cycle was in 2014 with a recent normal mammogram and pelvic exam. Vast early spine degenerative change as listed in table 1 could be considered a variant of expected pathophysiology.

Table 1:

C3-C4	Mild facet hypertrophy
	Small posterior disc bulge herniation
	Mild indentation on the ventral thecal sac Mild spinal canal stenosis
C4-C5	Mild disc height decrease
	Annular bulge
	Small osteophytes formation
	Left facet hypertrophy
	Mild spinal canal stenosis
C5-C6	Moderate disc height decrease
	Annular bulge
	Small osteophyte formation
	Facet hypertrophy
	Mild ligamentum flavum hypertrophy
	Mild-moderate spinal canal stenosis
C6-C7	Mild annular bulge
	Minimal levoscoliosis
T2-T6	Minimal annular bulge
T6-T7	Small broad-based left paracentral disk protrusion
T7-T9	Small posterior central disc protrusion
L1-L4	Multilevel grade I retrolisthesis
	DDD
L4-L5	Broad-based posterior disc bulge
	Indentation of anterior thecal wall
	Moderate spinal canal stenosis
	Moderate bilateral neural foraminal stenosis
L5-S1	Posterior disc bulge

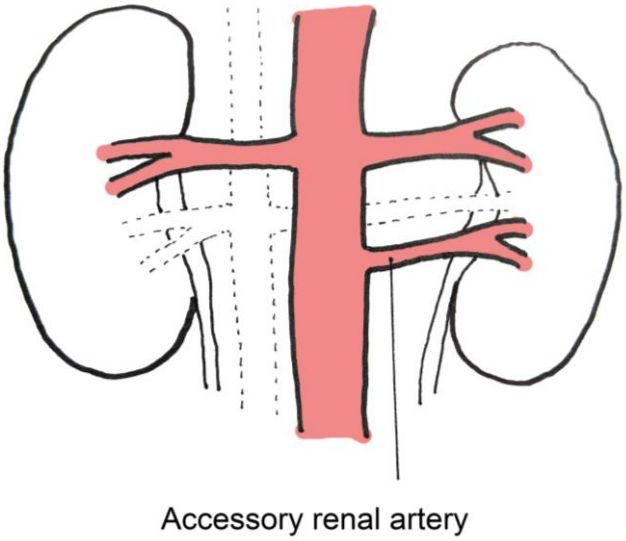

Figure 4: Example of a retroaortic left renal vein and accessory left renal artery. Drawn by E. Dominiak

Abdomen and pelvic CT revealed a fourth anatomic variant, a retroaortic left renal vein and two left renal arteries (Figure 4).

Abnormal laboratory findings were HbA1c 5.9, absolute eosinophils 0 cells/uL, thiamine levels 311, mean corpuscular volume 99, mean corpuscular hemoglobin 32.5, vitamin B12 levels >1500 pg/mL, coproporphyrin III 92.0 mcg/g creatinine, and histone Ab levels remained weakly positive at 1.2, interpretation stated that "it does not appear that the patient has an immune complex-mediated process to explain her symptoms." All results were weak and not indicative of a specific diagnosis. Pharmacogenomic[9] findings are listed in table 2.

Table 2: Patient Pharmacogenomics. Notice Methylenetetrahydrofolate reductase (MTHFR) deficiency

Gene:	Result:	Gene Location:[10]
AGTR1	Decreased Responder	3q24
ANKK1	Decreased Responder	11q23.2
ATM	Increased Responder	11q22.3
CDA	Poor Responder	1p36.12
CNR1	Decreased Metabolizer	6q15
CYP2C19	Rapid Metabolizer	10q23.33
CYP3A5	Poor Metabolizer	7q22.1
ERCC1	Decreased Responder	19q13.32
GSTP1	Decreased Responder	11q13.2
HFE	Decreased Responder	6p22.2
KIF6	Increased Responder	6p21.2
LDLR	Decreased Responder	19p13.2
MTHFR	MTHFR DEFICIENCY	1p36.22
NAT2	Poor Metabolizer	8p22
SCN2A	Decreased Responder	2q24.3
SLCO1B1	Decreased Function	12q12.1
VKORC1	Low Sensitivity	16q11.2

Due to the presence of multiple anatomic variants, early spine DDD, multiple complaints and weak laboratory results, genetic sequence analysis was conducted. Sequence analysis[11] revealed 3 variants of unknown significance (Table 3):

Table 3. Patients genetic sequence analysis. Note patient does not exhibit clinical manifestations of above.

MUTATION	CLINICAL PRESENTATION
SPG11 (c.5315G>A, p.Arg1772His)	1. Autosomal recessive spastic paraplegia 11
	2. Juvenile amyotrophic lateral sclerosis 5
	3. Charcot Marie Tooth Disease 2X
WNK1 (c.2234G>A, p.Ser746Asn)	1. Autosomal dominant pseudohypoaldosteronism type 2C
	2. Autosomal recessive hereditary autonomic sensory neuropathy type 2A
AIFM (c.1047 C>T, silent)	1. X-linked Charcot Marie Tooth Disease Type 4
	2. Cowchock syndrome
	3. X-linked spondylometaphyseal dysplasia with hypomyelinating leukodystrophy
	4. X-linked deafness

To date, no direct cause has been identified that can explain her symptoms, anatomic variants, early spine DDD, and genetic findings.

Discussion:

This case presents a 56-year-old female suffering from severe, chronic neuropathy, early-onset DDD, clinical thoracic outlet syndrome without structural evidence, and multiple anatomic and genetic variants. Early-onset of pathology in conjunction with bilateral Martin-Gruber anastomoses, direct vertebral artery 2 variant of bovine arch, bilateral anconeus epitrochlearis, left retroaortic renal vein, and double left renal arteries may suggest a novel syndrome. Also considered was a de novo syndrome. At this time, we do not have a definitive cohesive diagnosis. The ruling out of expected diseases such as: diabetes, Sjörgen's, hypo/hyperthyroidism, Charcot-Marie-Tooth disease, multiple sclerosis, vitamin B12 deficiency, and other disorders may further suggest a novel or de novo syndrome. Of interest, the patient has a number of gene variants accounting for poor, decreased, or increased response to medications. Genetic sequencing identified 3 gene mutations without clinical manifestations, which may subclinically account for the patient's symptoms.

We believe that the above variants are genetically linked. It is noteworthy that pharmacogenomics showed involvement of multiple genes on chromosomes 1, 6, and 11. Human genes for muscle development, specifically MYOD1 is on chromosome 11 and both myogenin and PAX7 are located on chromosome 1.[12] Peripheral myelin gene ADGRG6 is located on chromosome 6.[13] Aortic arch development gene SOX13 is located on chromosome 1.[14] Potential abnormalities on chromosomes 1, 6, and 11 could account for the clinical presentations. Further genetic testing of the patient and offspring could be extremely helpful.

While there is evidence supporting a novel syndrome, there are limitations as well. The patient is adopted, therefore a full family genetic workup cannot be done. Some studies failed to show definitive results. Finally, only one patient is presented. This case, however, provides clinicians a baseline for similar patients, and accumulation of future data may reveal a specific cause for this patient's symptoms.

The absence of a definitive diagnosis does not exclude the treatment of symptoms to decrease

pain and improve quality of life. We postulate that potential treatments could include spinal cord stimulator, intrathecal pain pump, and calcitonin gene related peptide (CGRP) antagonists. However, the patient is reluctant to try new treatment due to past experiences.

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