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A Case of Mistaken Identity: Limb Girdle Muscular Dystrophy as Multiple Sclerosis

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Abstract

In this case, we present a case of a 53 year old patient with multiple comorbidities who presented for left sided weakness and tingling. Patient was seen by multiple neurologists and was treated for multiple sclerosis due to abnormal MR brain lesions. After being established with a 5th neurologist, patient was eventually worked up and found to have Limb Girdle Muscular Dystrophy type 2a (Calpainopathy).

Keywords: limb girdle muscular dystrophy (LGMD); Proximal girdle weakness; Calpainopathy; Weakness; Multiple sclerosis (MS)

Introduction

In clinical practice, physicians try to obtain a single unifying diagnosis for a collection of symptoms. However, as patients often have multiple comorbidities, patients may have symptoms caused by several concomitant diseases. In this case, we discuss a case of a patient with long standing progressive weakness and sensory abnormalities currently being treated for MS who was found to have a limb girdle muscular dystrophy.

Limb Girdle Muscular Dystrophy (LGMD 2a) is an autosomal recessive disease typically characterized by progressive and symmetric weakness of proximal limb-girdle muscles. This is the most common form of limb-muscle dystrophy and is approximately 30% of cases. The disease is heterogenous and displays a great deal of phenotypic variability and can have onset younger than age 12 or as late as after age 30. There are three autosomal recessive phenotypes based on the distribution of muscle weakness as well as age of onset including Pelvifemoral limb-girdle muscular dystrophy (Leyden-Mobius LGMD), Scapulohumoral LGMD (Erb LGMD), HyperCKemia. The autosomal dominant form of calpainopathy is variable and has a heterogeneous clinical phenotype however is typically milder than the recessive form. Patients with the autosomal dominant form can range from very mild symptoms to wheelchair dependence after age 60 [1-4]. Typically, the most common symptom in 80-99% of people is generalized muscle weakness, typically proximal muscle weakness, while 30-79% of people will have ankle flexion contractures, calf muscle hypertrophy, congenital finger flexion contractures, and difficulty walking [4]. Disease typically is isolated to muscle and without intellectual delay or heart involvement.

Multiple Sclerosis is a progressive, chronic inflammatory demyelinating disease involving the central nervous system, affecting women at a higher rate than men. MS is more common in the US population than limb girdle muscular dystrophy, with a prevalence of approximately 149 per 100,000 individuals in the US compared to limb girdle muscular dystrophy which may occur at rates estimated to be between 1-7 in 100,000 persons [2,3]. The true prevalence of LGMD is difficult to determine due to the heterogeneity of the disease. Given the relative rarity of LGM compared to MS, it is quite possible that the progressive nature of LGMD in combination with typically white matter changes from diabetes, hypertension, and migraine headaches may lengthen time to diagnosis, lead to misdiagnosis, or inappropriate treatment plans. As this case outlines, providers need to be aware of alternative etiologies including LGMD in order to correctly diagnosis and appropriately treat patients.

Patient Case

Patient is a 53-year-old African American female with a history of hypertension, neck pain with cervical foraminal stenosis, hyperlipidemia, obesity, and headaches who originally presented to neurology clinic for hospital follow up of acute weakness of the left side and tingling. Patient was initially diagnosed in the

hospital with a conversion disorder after stroke workup; however, the patient continued to complain of progressive weakness that also began to include the right side and began having tingling of left arm and fingers. Patient was sent for MR which demonstrated bilateral subcortical white matter lesions as well as white matter lesions in the pericallosal region. Patient was sent for LP and usual studies were within normal limits and no oligoclonal bands were seen in CSF. At follow up, patient was started on copaxone for presumed oligoclonal band negative MS. During these follow up visits, patient continued to report progressive weakness with superimposed intermittent episodes of severe weakness, eventually requiring assistance with ADLs and becoming wheelchair dependent. Over the course of approximately 5 years, the patient continued to functionally decline with progressive weakness while complaining of sensory changes in the left arm and occasionally down the legs. She was established with another neurologist who noted she did not meet McDonald's criteria for MS and that her cerebral lesions had not progressed in relation to her symptoms. She was kept on copaxone at this time although it was believed her chances of MS were relatively low, however patient was seen by another outside neurologist before presenting to be re-established with the same neurology group.

Patient was established finally with a fifth neurologist after symptoms continued to progress despite continuing on Copaxone. Patient stating that her trunk had become so weak that she could not even sit without supporting herself against a wall. On physical exam, the patient was noted to be wheelchair bound. Patient with weakness in all limbs and weakness was noted to be greater proximally rather than distally. Weakness was noted particularly in spinal trunk muscles, proximal hand muscles and thighs. Proximal weakness noted to be 3/5, and distal strength noted to be 4/5 bilaterally and symmetrically. Truncal weakness also noted. Patient with normal reflexes without upper motor neuron signs. Patient did have vibration sensation mildly impaired distally in bilateral toes however pinprick and vibration were otherwise normal. Patient had some difficulty with coordinated movement testing due to proximal weakness; however, no ataxia was noted [5,6].

Patient was sent for imaging which showed unchanged white matter lesions without interval radiographic progression for approximately 5 years (as seen in Figure 1). Given low concern for MS, other etiologies were explored and patient was sent for EMG. EMG was consistent with a generalized myopathy with minimal denervating features (Figure 2). Patient was next sent for a muscle biopsy of left deltoid which demonstrated myopathy with lobulated muscle fibers most consistent with Limb Girdle Muscular Dystrophy, suspected to be LGMD2a (Figure 3). Patient was sent for genetic counseling and was established in a neighboring muscular dystrophy clinic.

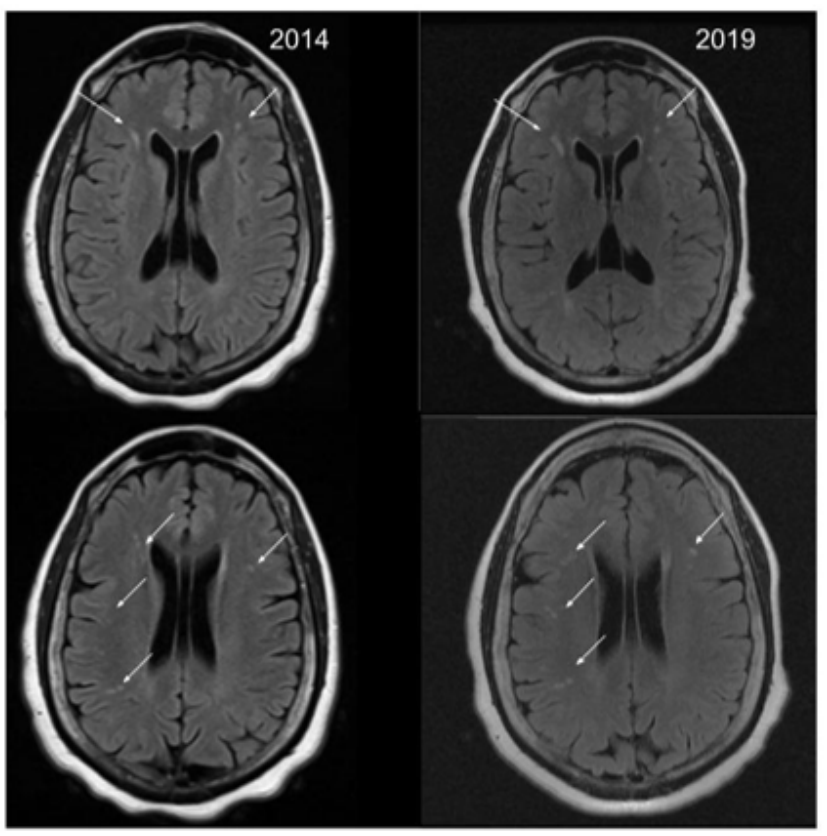

Figure 2: Nerve Conduction Study and Electromyoeogram Results: Nerve conduction study and Electromyoeogram Results consistent with generalized myopathy with denervating features.

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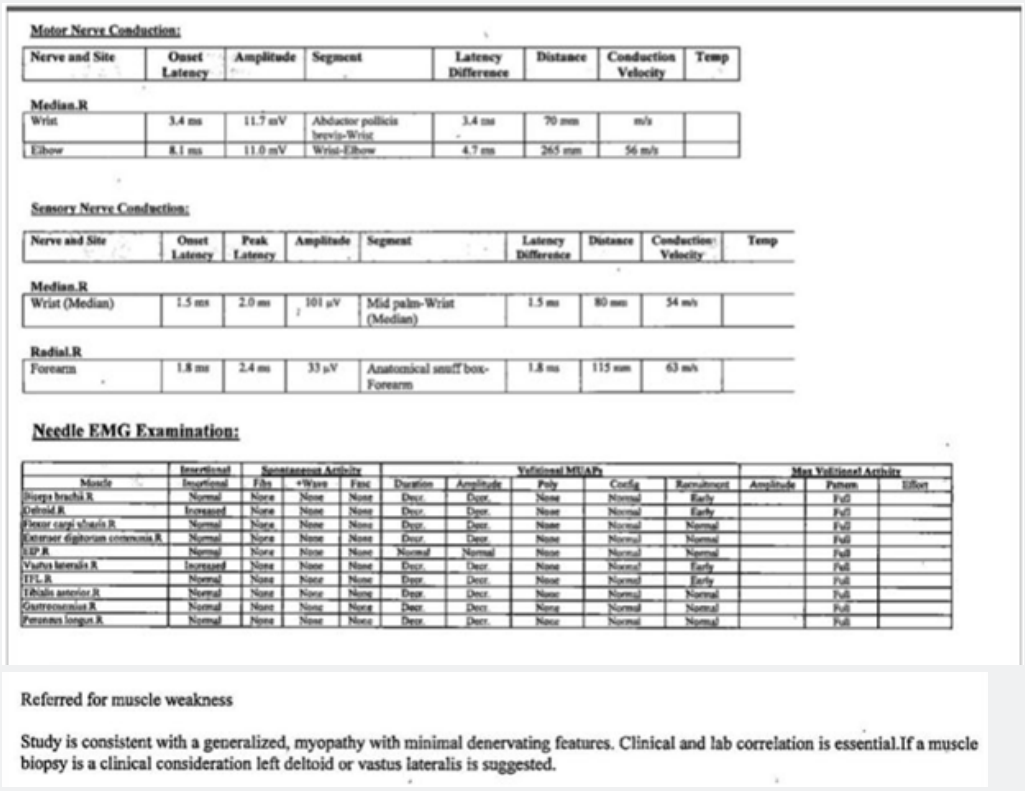


Motor Nerve Conduction:

Nerve and Site	Onset Latency	Amplitude	Segment	Latency Difference	Distance	Conduction Velocity	Temp
Median.R							
Wrist	3.4 ms	11.7 mV	Abductor pollicis brevis-Wrist	3.4 ms	70 mm	m/s	
Elbow	8.1 ms	11.0 mV	Wrist-Elbow	4.7 ms	265 mm	56 m/s	

Sensory Nerve Conduction:

Nerve and Site	Onset Latency	Peak Latency	Amplitude	Segment	Latency Difference	Distance	Conduction Velocity	Temp
Median.R								
Wrist (Median)	1.5 ms	2.0 ms	101 µV	Mid palm-Wrist (Median)	1.5 ms	80 mm	54 m/s	
Radial.R								
Forearm	1.8 ms	2.4 ms	33 µV	Anatomical snuff box-Forearm	1.8 ms	115 mm	63 m/s	

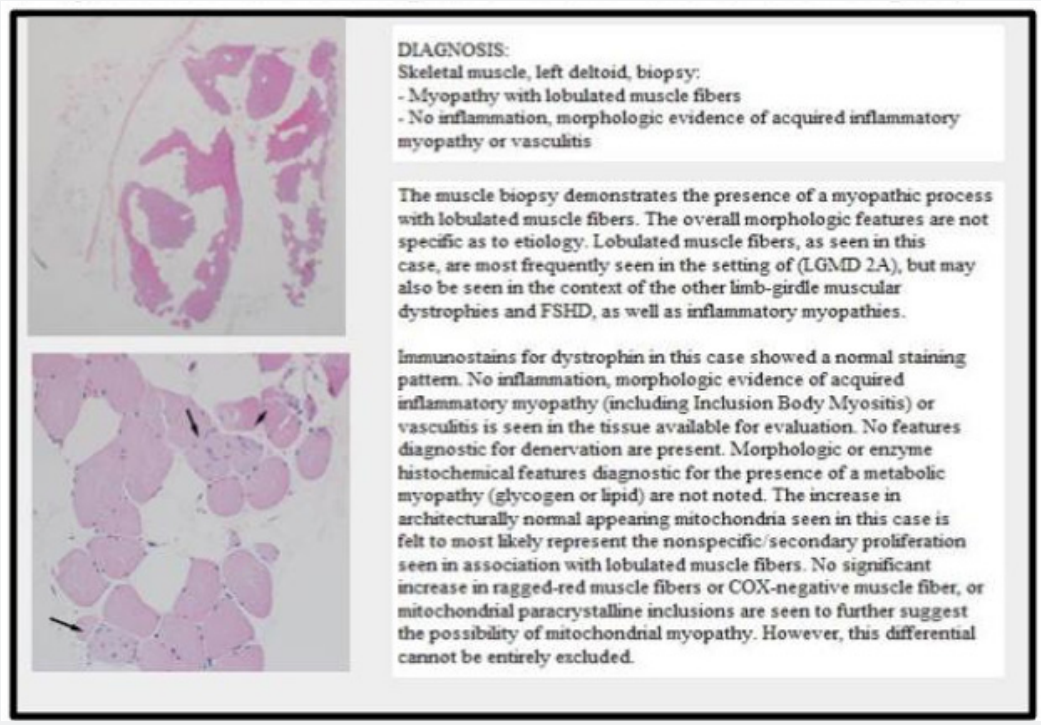
Needle EMG Examination:

	Insertional	Spontaneous Activity			Voluntional MUAPs					Max Voluntional Activity		
Muscle	Insertional	Fibs	+Wave	Fasc	Duration	Amplitude	Poly	Config	Recruitment	Amplitude	Pattern	Effort
Biceps brachii R	Normal	None	None	None	Decr.	Decr.	None	Normal	Early		Full	
Deltoid R	Increased	None	None	None	Decr.	Decr.	None	Normal	Early		Full	
Flexor carpi ulnaris R	Normal	None	None	None	Decr.	Decr.	None	Normal	Normal		Full	
Extensor digitorum communis R	Normal	None	None	None	Decr.	Decr.	None	Normal	Normal		Full	
IDP R	Normal	None	None	None	Normal	Normal	None	Normal	Normal		Full	
Vastus lateralis R	Increased	None	None	None	Decr.	Decr.	None	Normal	Early		Full	
TFL R	Normal	None	None	None	Decr.	Decr.	None	Normal	Early		Full	
Tibialis anterior R	Normal	None	None	None	Decr.	Decr.	None	Normal	Normal		Full	
Gastrocnemius R	Normal	None	None	None	Decr.	Decr.	None	Normal	Normal		Full	
Peroneus longus R	Normal	None	None	None	Decr.	Decr.	None	Normal	Normal		Full	

Referred for muscle weakness

Study is consistent with a generalized, myopathy with minimal denervating features. Clinical and lab correlation is essential.If a muscle biopsy is a clinical consideration left deltoid or vastus lateralis is suggested.

Figure 2: Nerve Conduction Study and Electromyoeogram Results: Nerve conduction study and Electromyoeogram Results consistent with generalized myopathy with denervating features.



DIAGNOSIS:
Skeletal muscle, left deltoid, biopsy:
- Myopathy with lobulated muscle fibers
- No inflammation, morphologic evidence of acquired inflammatory myopathy or vasculitis

The muscle biopsy demonstrates the presence of a myopathic process with lobulated muscle fibers. The overall morphologic features are not specific as to etiology. Lobulated muscle fibers, as seen in this case, are most frequently seen in the setting of (LGMD 2A), but may also be seen in the context of the other limb-girdle muscular dystrophies and FSHD, as well as inflammatory myopathies.

Immunostains for dystrophin in this case showed a normal staining pattern. No inflammation, morphologic evidence of acquired inflammatory myopathy (including Inclusion Body Myositis) or vasculitis is seen in the tissue available for evaluation. No features diagnostic for denervation are present. Morphologic or enzyme histochemical features diagnostic for the presence of a metabolic myopathy (glycogen or lipid) are not noted. The increase in architecturally normal appearing mitochondria seen in this case is felt to most likely represent the nonspecific/secondary proliferation seen in association with lobulated muscle fibers. No significant increase in ragged-red muscle fibers or COX-negative muscle fiber, or mitochondrial paracrystalline inclusions are seen to further suggest the possibility of mitochondrial myopathy. However, this differential cannot be entirely excluded.

Figure 3: Muscle Biopsy of left Deltoid with Report
Skeletal muscle Biopsy of left Deltoid: H&E stained section showing partial fatty replacement (top images) and muscle fibers with internalized nuclei (lower image with arrows). Pathology Report as above.

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Discussion

In this example, patient's progressive symptoms were presumed to be due to MS given clinical progression of weakness and sensory changes in the setting of white matter changes on MRI of the brain. Despite an initial large differential diagnosis at presentation, the patient was treated for several years with MS medications despite progressive symptoms and decline in function. Diagnosis was eventually revisited and a correct diagnosis of muscular dystrophy was obtained relying primarily on evidence from muscle biopsy and nerve conduction studies in addition to clinical exam. The case was complicated by symptoms which were not consistent with LGMD, including sensory changes and paresthesias from cervical foraminal stenosis as well as cerebral white matter lesions likely related to chronic hypertension and hyperlipidemia. These other findings from comorbidities unfortunately lead to a delay in diagnosis.

It is also worth mentioning that while often elevated creatinine is typically seen in LGMD2a, it is not always seen [1], and in advanced disease with chronic and long-term muscle wasting, creatinine may also be normal. In this patient, creatinine was normal (0.6-1.0) which may have been due to the long-standing nature of the disease.

This case illustrates how common issues such as nonspecific white matter lesions from hypertension and hyperlipidemia and spinal stenosis can give misleading clinical picture and lead to a delay in diagnosis. Occam's razor is a philosophical principle which originally states Entities should not be multiplied without necessity and is commonly used in relation to the idea that the simplest solution or a single unifying diagnosis for a collection of symptoms is the most correct. However, in clinical practice, Hickam's dictum may be more appropriate. Hickam's dictum states patients can have as many diseases as they damn well please which may be more applicable as many patients often have multiple comorbidities which may interfere or influence the diagnostic process.

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