Diagnosis and Treatment of Limb-Girdle and Distal Dystrophies

Case Presentation

A 22-year-old man of Asian and northern European ancestry presents for an evaluation of his muscle weakness. In high school he was very athletic and was awarded a college scholarship for his abilities in the high jump. Unfortunately, shortly after his sophomore year he began to experience difficulty maintaining the height of his high jump. He recalls in retrospect that his calf raises in the gym had become more challenging at about the same time. By midway through his junior year he had developed mild difficulty running, which eventually required that he quit track and field. Despite a slow, progressive decline in leg strength over the subsequent year he delayed seeking medical attention until he developed difficulty performing arm curls in the gym. By then he noted that he was losing muscle bulk in his calves and biceps brachii. He was evaluated by a family practice physician and underwent initial laboratory screening that included a complete blood count, a comprehensive metabolic panel, and tests of blood levels of thyroid-stimulating hormone, vitamin B₁₂, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and creatine kinase (CK). Results were remarkable for a markedly elevated CK (5,432 U/L; normal CK levels < 300 U/L but varies by sex and ethnicity). ECG and echocardiogram were normal. A muscle biopsy was obtained at the local community hospital and reportedly demonstrated endomysial inflammatory infiltrates. He was initially diagnosed with polymyositis and was started on oral prednisone 60 mg/d. After 6 months without benefit and further subtle progressive decline in strength, he was referred to a regional referral center and evaluated by a general neurologist. Repeat CK level was 15,234 U/L. Nerve conduction test was normal, whereas an EMG demonstrated the presence of myopathic potentials with early recruitment in most muscles tested, most prominently in the calves and biceps femoris. He was subsequently referred to a tertiary care facility for specialty evaluation.

His past medical and surgical history are otherwise insignificant.

The only medication he is currently taking is prednisone 60 mg/d.

He has no known drug allergies.

Social history is notable for occasional alcohol use but no more than 2 to 3 beers per week. He denies prior tobacco or illicit drug use.

He is a graduate student studying sports physiology and has maintained a 4.0 grade point average since starting high school. His childhood development history is otherwise unremarkable, both physically and cognitively.
Family history is without any suggestion of neuromuscular disease and is otherwise noncontributory. Of some interest is his northern European and Asian ancestry.

In addition to that reported in the history of present illness, a complete review of 14 systems is otherwise unremarkable.

On physical examination, he is a well-developed and well-nourished male in no distress.

Temperature is 36.7º, blood pressure is 123/66, pulse is 62, and respiratory rate is 14.

No bruits are noted over his carotids, and heart sounds are normal.

He is alert and oriented to person, place, and date. Both short-term and delayed memory are intact. Speech is fluent with intact naming, repetition, and comprehension. Insight and thought content are appropriate for age and education.

Pupils are equally reactive to light and accommodation. Visual fields are full to confrontation, and extraocular muscles are intact. Facial sensation and strength are normal. Hearing is intact bilaterally to finger rub. Palate, tongue, and uvula are midline. Sternocleidomastoid and trapezius strength are normal.

On motor examination, there is atrophy of bilateral gastrocnemius and biceps femoris muscles. There is no scapular winging. No myotonia or fasciculations are noted.

Motor strength testing reveals the following: neck flexors 5; limb muscles (right/left): deltoid 5-/5-, biceps 4/4+, triceps 5/5, brachioradialis 4+/4, wrist flexors 5/5, wrist extensors 5/5, interossei 5/5, iliopsoas 4/4, gluteus medius 5-/5-, quadriceps 5-/5-, hamstrings 4+/4+, tibialis anterior 5/5, gastrocnemius 4+/4, extensor hallucis longus 5/5.

Sensation is preserved normal to pinprick, touch, vibration and joint sense.

Deep tendon reflexes are 2+ in the upper extremities and at the knees. Ankle jerks are 1+ bilaterally. Plantar responses are flexor.

Station is normal. Casual gait also is normal, but the patient is unable to walk on his toes on the left. He has mild difficulty rising from the floor.

Additional diagnostic studies include an MRI of the lower extremities that demonstrates fibrous and fatty degeneration of the gastrocnemius and soleus muscles.

The patient is counseled about a possible diagnosis of muscular dystrophy and the suspicion of a dysferlinopathy on the basis of his history and pattern of weakness. Genetic testing is performed and confirms a mutation in the dysferlin gene (DYS). You tell the patient that he has limb-girdle muscular dystrophy type 2B (LGMD2B). Prognosis is discussed. He is counseled with regard to this being an autosomal recessive disorder so he would not likely pass it on to his children unless his wife also carries the same gene mutation. He is referred for physical and occupational
therapy. You discuss ongoing research studies in muscular dystrophy with him, and he expresses a wish to be added to a registry should he qualify for any future clinical trials. A total of 80 minutes was spent with this patient during the office visit. Greater than 50% of this time was spent with education, counseling, and coordination of care.

Questions

1. A 20-year-old woman presents with a 6-month history of weakness in her legs. She has difficulty climbing stairs and rising from chairs. On clinical examination, she has mild hip-girdle weakness (MRC grade 4+/5), her hamstrings are 4/5, and ankle plantar flexors are 3/5. Her knee extensors and ankle dorsiflexors are normal, as are her arms. There is no scapular winging or muscle hypertrophy, although she has atrophy of the medial gastrocnemius muscles bilaterally and is unable to stand on her tip toes. Sensation is intact. Muscle stretch reflexes are 2/4 and symmetric throughout except at the ankles, where these reflexes are absent. Her serum CK level is 12,000 U/L. Which of the following would be the most appropriate next step?

A. Perform an EMG/nerve conduction study (NCS)
B. Obtain a dried blood spot analysis for alpha-glucosidase activity, as it would be important not to miss a possible treatable condition (e.g., late-onset Pompe disease)
C. Order a Western blot for dysferlin analysis on peripheral monocytes or sequencing of the DIS gene for mutations
D. Perform a gastrocnemius muscle biopsy, as this muscle is the most severely affected
E. Treat the patient empirically with prednisone 1.0 to 1.5 mg/kg daily for presumed polymyositis

The correct answer is C. The age of onset and pattern of weakness is classic for Miyoshi myopathy/dysferlinopathy and is supported by the markedly elevated serum CK level. The clinical impression can be confirmed noninvasively by performing Western blot analysis on peripheral monocytes or direct mutation analysis of the DYS gene that encodes for dysferlin. The clinical phenotype and markedly elevated CK levels do not suggest Pompe disease. EMG/NCS are useful in localization, although with a CK of 12,000 U/L it has to be a myopathy. EMG can at times help narrow the diagnosis of the type of myopathy (e.g., if there were myotonic discharges); however, in this case the EMG is not likely to assist in the diagnosis. One could consider a muscle biopsy to confirm the diagnosis of a dystrophy or exclude another cause. If the results are dystrophic, one could do immunostaining or immunoblot of muscle tissue for dysferlin.

2. A 24-year-old man presents with a 4-year history of progressive weakness in his proximal arms and legs. He is of Spanish descent but has no family history of any neuromuscular problems. On examination, he has scapular winging. No muscle atrophy or hypertrophy is appreciated. Manual muscle testing reveals weakness in the proximal legs more than in the proximal arms. Sensation and muscle stretch reflexes are normal. His serum CK is 5,300 U/L. A biceps brachii muscle biopsy reveals variability in muscle fiber size, mild increase in endomysial
connective tissue, scattered necrotic and regenerating fibers, lobulated muscle fibers on NADH-TR stain, and rare, small foci of endomysial inflammatory cells composed of many eosinophils. Which of the following would be the most appropriate next step?

A. Perform genetic testing for CPN3 (calpain-3) mutation
B. Order a Western blot for dysferlin analysis on peripheral monocytes or sequencing of the DYS gene
C. Perform genetic testing for facioscapulohumeral muscular dystrophy (FSHD) given the prominent scapular winging and inflammation on biopsy
D. Order genetic testing for all available limb-girdle muscular dystrophies (limb-girdle muscular dystrophy [LGMD] panel), as it is impossible to guess which type of LGMD he is most likely to have
E. Begin treating the patient with prednisone 1.0 to 1.5 mg/kg daily for presumed eosinophilic polymyositis

The correct answer is A. The clinical phenotype is typical of LGMD2A that is caused by a mutation in CPN3 that encodes for calpain-3. LGMD2A is the most common form of LGMD in patients from Spain and southern European backgrounds. There are several reports of patients having been erroneously diagnosed with eosinophilic myositis who actually had calpainopathy. The limb-girdle pattern of weakness, high CK level, and inflammation on biopsy can be seen in dysferlinopathies, but scapular winging is not typical. Rarely, patients with FSHD can have a limb-girdle pattern of weakness and inflammation on biopsy mimicking myositis, although CK is not usually as elevated, making calpainopathy most likely.

3. Myofibrillar myopathy has been associated with mutations in the genes that encode for which of the following proteins?

A. Desmin
B. Myotilin
C. BAG-3
D. Z-band alternatively spliced PDZ motif-containing protein
E. All of the above

The correct answer is E. Mutations in the genes that encode for filamin-C, myotilin, ZASP, BAG-3, desmin, alpha B crystallin, and titin have been associated with myofibrillar myopathy.

4. A 26-year-old woman is referred for evaluation of slowly progressive weakness she has been experiencing for 3 years. On examination, she has mild atrophy of humeral muscles and MRC grade 4+/5 in her elbow flexion, elbow extension, and foot dorsiflexion. She also has moderate contractures at her elbows, knees, and ankles and rigidity of her spine. Family history is notable for sudden cardiac death in her father, who exhibited similar clinical features as she does now. The most appropriate diagnostic test would be which of the following?

A. Muscle biopsy
B. Genetic testing for mutations in the gene that encodes for emerin
C. Genetic testing for mutations in the gene that encodes for lamin A/C
D. Genetic testing for mutations in the gene that encodes for dystrophin
E. Genetic testing for myotonic dystrophy

The correct answer is C. The pattern of muscle weakness, early contractures, autosomal dominant inheritance, and cardiac disease are characteristic of autosomal dominant Emery–Dreifuss muscular dystrophy or LGMD1B, both of which are caused by mutations in the gene that encodes for lamin A/C.

**Diagnosis Coding**

This is a case presentation and not a medical record, but it is clear from the text that the final diagnosis in the chart is LGMD2B. ICD-9-CM² distinguishes congenital hereditary muscular dystrophy from hereditary progressive muscular dystrophy. ICD-10-CM³ has one code for all muscular dystrophy (MD). Individual types of MD may be listed as inclusion terms, but the absence of an inclusion term does not mean that these codes cannot be used for a specific diagnosis. As in the case of multiple sclerosis, which has only one code, ICD-9-CM² and ICD-10-CM³ will not produce population data on LGMD and other specific MD types. These data are currently available only from registries. Adding manifestation codes can sometimes indicate severity, but there is no specific or severity-indicating code for this patient’s degree of weakness.

For this case the diagnosis coding is as follows:

**ICD-9-CM²**

359.1 Hereditary progressive muscular dystrophy
Muscular dystrophy:
NOS
Distal
Duchenne
Erb’s
Fascioscapulohumeral
Gower’s
Landouzy-Dejerine
Limb-girdle
Ocular
Oculopharyngeal

**ICD-10-CM³**
G71.0 Muscular dystrophy
   Autosomal recessive, childhood type, muscular dystrophy
   Benign [Becker] muscular dystrophy
   Benign scapuloperoneal muscular dystrophy with early contractures
   [Emery-Dreifuss]
   Congenital muscular dystrophy NOS
   Congenital muscular dystrophy with specific morphological abnormalities
   of the muscle fiber
   Distal muscular dystrophy
   Fascioscapulaohumeral muscular dystrophy
   Limb-girdle muscular dystrophy
   Ocular muscular dystrophy
   Oculopharyngeal muscular dystrophy
   Scapuloperoneal muscular dystrophy
   Severe [Duchenne] muscular dystrophy


This vignette describes both the initial visit with the neurologist and what could be interpreted as a “follow-up” or established patient visit. These occur in the ambulatory setting and thus are covered by the codes for New Patients (9920X), Consults (9924X), and Established Patient (9921X) where X is a value from 1 to 5. The higher the level of service, the more work is required and the greater the reimbursement will be. It is not clear from the vignette if the initial visit was as Consult or New Patient type of visit. With a consult the patient must meet the “3Rs”: referred from a provider, an opinion rendered, and a response written to the referring provider asking for the second provider’s opinion. In addition this patient must not have been seen in the provider’s practice within the last 3 years. All other initial visits are considered as New Patient. Some insurance carriers (Medicare is the largest) do not pay for consultations. The requirements for level of service are identical for Consultations and New Patients, with the big exception in terms of work involved being the requirement with a Consultation for a letter to the provider requesting a consult. From a professional standpoint it would make sense that the provider let the entire care team know his or her opinion with a New Patient visit, but this is not mandatory for proper CPT coding.

The history provided in this case meets most, but not all, requirements for a comprehensive history. What the case lacks are the details in the review of systems (ROS). To meet a comprehensive history, you must meet the minimum requirement for “comprehensive” for all elements of the current history, past medical/surgical, social and family history, and ROS. The minimal requirement for a comprehensive ROS is listing 10 of the 14 systems, with at least one positive or negative element in each system. The history itself mentions the neurologic system, counting as one system. There is no mention within the history of any other systems, positive or
negative, and without positive or negative comments for other systems, in this vignette only one system (the neurologic system) counts toward the ROS contribution to E&M. Therefore, an “unremarkable” ROS, as reported in this vignette, not only fails to meet the comprehensive ROS (at least 10 systems) but also fails to indicate a detailed ROS (2–9 elements). In this context the neurologic system is a system, and this one system would render the level of service or ROS as “expanded problem focused.” This one omission in reporting would vastly limit the overall level of service in a new patient visit to a 99202 or 99242, regardless of the extent of the examination or medical decision making (MDM) that will take place during this visit. For the purpose of this discussion, it is assumed the authors made needed changes to their ROS so that it would qualify as comprehensive. In this vignette, the physician has performed a comprehensive single-system neurologic examination, which includes all bulleted neurologic elements, three vital sign elements, statement of general appearance, fundoscopic exam, and one of three cardiovascular exam elements. MDM is the third, and arguably most complex, element needed to determine the level of service. MDM comprises three parts: the number of diagnostic or management treatment options, the amount of data review, and the level of risk. This case presents extensive data review: blood work, muscle biopsy, EMG data, and cardiac studies sum to four or more “tests” and thus meet the “high complexity” level; the MRI was performed after the initial visit and would not count in the data review of this visit. In this case the estimate of the other two of these elements is profoundly complex. There are very few physicians who know what a dysferlinopathy is, much less can offer a differential diagnosis of any muscle disorder past “Duchene muscular dystrophy and polymiositis.” In fact most general neurologists will need to refer to a text to establish a differential diagnosis. In this case one can argue the differential diagnosis is extensive, or having four or more diagnostic possibilities. On the one hand this is a trivial concept, because there are 24 distinct genotypes for the LGMD phenotype. And of course the heavy lifting really is not done in the clinic with regard to determining the specific genotype—this is done by way of genetic testing or panel testing. But one could argue that putting work into the differential diagnosis may help determine whether to order testing for one gene, a small panel of genes, or the broad genetic panel. In this case it would be prudent to choose high-complexity (four or more) diagnostic options but “bullet-proof” that choice with a statement in the assessment that indicates specifically the complex issues with genotype–phenotype and the need to determine without doubt the correct diagnosis for purposes of anticipatory MDM and genetic counseling, and that outlines at least four different potential diagnoses. Otherwise an auditor could conclude from the ICD-10 code, which has collapsed an entire fellowship into one code, that this is straightforward MDM because one genetic test was ordered. Finally the determination of risk is likewise complicated. At one level the risk of LGMD meets the criterion for one definition of high risk, that being “chronic illness or injuries which pose a threat to life or bodily function.” On the other hand, at this point in the patient’s life, the disability is stable and would fall into a low-risk state. In this situation it may be best to “vote” to assess this as a low-risk disease state, to be conservative, but there could certainly be viable arguments to the contrary. The ultimate level of MDM is the “lower of the higher two
determinants” — in this case the data review (comprehensive) and number of potential diagnoses (comprehensive) are the higher two elements, therefore positioning the MDM at a high (which is the highest) level. For initial visits all three elements are required to justify a code. Therefore this case (when the ROS is remedied) includes a comprehensive history, comprehensive physical examination, and a high level of MDM, and would justify a 99205 or 99245 E&M code. Again, if the ROS remains as is, the code choices are 99202 or 99242.

The patient has a genetic test and returns for a visit. Established patients require documentation and analysis of only two of three elements: history, exam, and MDM. However, in this situation it is reasonable to consider using the time spent with the patient and not the three-element approach. (Time can be used for initial visits as well, but in most circumstances the provider must do the work of history, exam, and the process of MDM anyway.) It is unlikely the provider will need to do much more than a cursory history or repeat the exam. And there is certainly not much new to justify a robust or high level of MDM. What needs to happen at that visit is for the provider to offer the patient education, counseling, and coordination of care — all of which take time. CPT allows providers to be paid for time alone, if the time spent with education, counseling, and coordination of care exceed 50% of the total visit time. In this situation one can envision 90% of the time spent on this activity. If more than half the visit is spent on these activities, one can choose a 99213 for a 15-minute visit, a 99214 for a 25-minute visit, or a 99215 for a 40-minute visit. Unless one chooses extended-care codes, one cannot be paid more (until the activities exceed 74 minutes, which would be unlikely). One must document in the note the total visit duration, with the percentage of time spent being greater than 50% of the time on education, counseling, and coordination of care.

Although every neurologist’s practice will vary, with patients whose circumstances are similar to this patient’s, most of one’s established patient codes should be submitted in accordance with the counseling and coordination of care (time-based) method. However, when these patients follow such visits with a visit to physical medicine and rehabilitation (PM&R), the PM&R physician will likely bill using the bullet method, because neurology and PM&R provide different types of patient care. Every neurologist must decide what the patient’s needs are for a given visit and then decide on the most important goals to accomplish.

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