Diagnostic delay in patients with FKRP-associated muscular dystrophy

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2020-2021 Wellstone Medical Student Research Fellow

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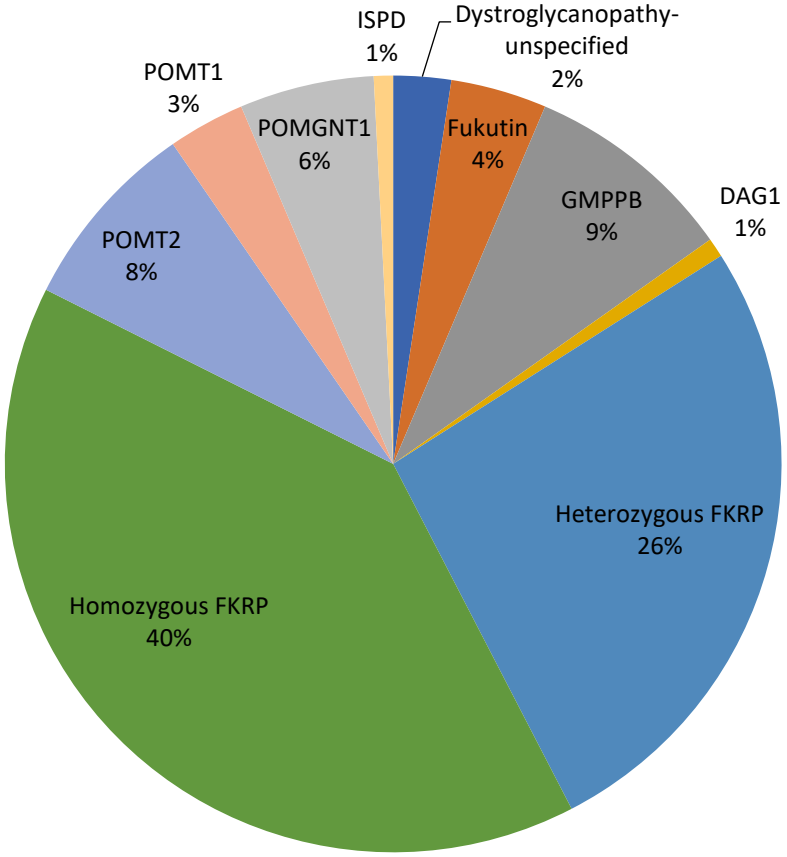
Overview

- Delayed diagnosis is common in neuromuscular disease
- Treatments are emerging for many types of muscular dystrophy. Treatments will be most effective if started early in the disease process, therefore it's important to be aware of course patients take from earliest symptoms to diagnosis and what elements make that process faster and slower

Wellstone Natural History Study

- Project includes all dystroglycanopathies
- For this analysis, focused on patients with most commonly affected gene *FKRP*



Methods

- Included Wellstone participants with documented *FKRP* mutations.
- Excluded participants whose diagnosis followed that of an affected family member
- Time from symptom onset to a diagnosis of muscular dystrophy (not specific subtype) was determined

68 patients included in study

- Initial signs/symptoms were grouped:
  - **Chronic motor dysfunction**
    - Weakness
    - Falls
    - Difficulty climbing stairs
    - Delayed motor milestones
    - Abnormal gait
    - Slower than peers
  - **Elevated liver function tests (AST/ALT)**
  - **Acute/intermittent symptoms**
    - Acute weakness associated with infection or illness
    - Myalgias (muscle cramps or pain)
    - Myoglobinuria (dark, Coca-Cola colored urine)

Table 1. Demographics

	Total	Male	Female
Total	68	36	32
c.826C>A Homozygotes	39	18	21
All Other Genotypes	29	18	11
Median Age at Enrollment [Range]	31 [1-72]	16 [1-72]	35.5 [3-60]

Most patients first presented with chronic motor dysfunction

- Age at onset and age at diagnosis differed by symptom group

First Presenting Sign/Symptom	# of patients	Median Age at Onset in years; (IQR)
Chronic motor dysfunction	40	6 (2-9)
Weakness	13	8 (2-24)
Falls	3	8 (5-8)
Difficulty climbing stairs	4	3.5 (3-6)
Delayed motor milestones	3	1 (0.8-1)
Abnormal gait	6	2 (1.3-4.3)
Slower than peers	11	8 (7.5-11)
Elevated liver function tests (AST/ALT)	7	14 (5.5-20.5)
Acute/intermittent symptoms	21	9 (5-13)
Acute weakness associated with infection or illness	5	2 (1-3)
Myalgias (muscle cramps/pain)	7	8 (6-10.5)
Myoglobinuria (dark Coca-Cola colored urine)	9	13 (10-16)
Total	68	8 (2-12)

IQR= interquartile range (25th percentile to 75th percentile)

Most patients first presented with chronic motor dysfunction

- Age at onset and age at diagnosis differed by symptom group
- Delayed motor milestones and acute weakness associated with infection or illness presented earliest and were diagnosed at the youngest ages

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Most patients first presented with chronic motor dysfunction

- Age at onset and age at diagnosis differed by symptom group
- Delayed motor milestones and acute weakness associated with infection or illness presented earliest and were diagnosed at the youngest ages
- Elevated liver function tests (AST/ALT) and myoglobinuria (dark, Coca-Cola colored urine) presented the latest and were diagnosed at the oldest ages

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University of Iowa Carver College of Medicine
University of Iowa Health Care
NIH/NINDS/Wellstone MDSRC Muscular Dystrophy Specialized Research Center

Years-long delays from first symptom to diagnosis

- Median time from sign/symptom onset to diagnosis was 6.5 years and differed by symptom group

First Presenting Sign/Symptom	# of patients	Diagnostic Delay in years; (IQR)
Chronic motor dysfunction	40	7.5 (1.9-14.4)
Weakness	13	10 (1-15.5)
Falls	3	2 (1.5-6.5)
Difficulty climbing stairs	4	4.5 (0.8-9.5)
Delayed motor milestones	3	1.5 (1.3-2.8)
Abnormal gait	6	9.5 (3.3-15)
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Years-long delays from first symptom to diagnosis

- Median time from sign/symptom onset to diagnosis was 6.5 years and differed by symptom group
- Shortest diagnostic delays seen in delayed motor milestones and acute weakness associated with infection or illness

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Years-long delays from first symptom to diagnosis

- Median time from sign/symptom onset to diagnosis was 6.5 years and differed by symptom group
- Shortest diagnostic delays seen in delayed motor milestones and acute weakness associated with infection or illness
- Longest delays seen in myoglobinuria (dark, Coca-Cola colored urine) and weakness

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Symptoms prompting a diagnosis

- Many patients did not receive a MD diagnosis until they developed a different type of symptom than they first presented with
- The sign/symptom category that most commonly resulted in a diagnosis was chronic motor dysfunction (45 patients), diagnosed at median age of 19 years.
- Of those without clear weakness as first symptom (55 patients), 36.4% were not diagnosed with MD until weakness became apparent.

Diagnostic delay is decreasing over time

- Median time from first sign/symptom to MD diagnosis has decreased by decade between 1970-1979 and 2000-2009

Table 4: Delay in diagnosis by decade of first sign/symptom

Decade Signs/Symptoms Presented	# of patients	Diagnostic Delay in years (IQR)	Median Age at Initial Symptom (IQR)
1970-79	12	18.75 (10.5-27.0)	7.0 (2.0-11.0)
1980-89	12	13.0 (1.5-23.0)	8.5 (3.0-13.5)
1990-99	15	12.0 (8.0-18.0)	9.0 (5.0-24.0)
2000-09	29	4.0 (1.0-6.0)	8.0 (2.0-12.0)

IQR= interquartile range (25th percentile to 75th percentile)

Discussion

- Results suggest that part of delay relates to when patient first seeks medical evaluation, as has been seen in other forms of muscular dystrophy.
  - Exercise-induced myoglobinuria led to the longest diagnostic delay. Many subjects reported thinking it was ‘normal’ or ‘a sign of a good workout’ to have dark urine after exercise.
  - Elevated liver function tests, delayed milestones, and acute weakness associated with infection or illness were associated with relatively short delay in diagnosis.
- Ease of diagnosis with advancements in technology and physician awareness of LGMD may be decreasing the delay in diagnosis over time.

THANK YOU FOR JOINING US!

2021 Iowa Wellstone Dystroglycanopathy Patient and Family Conference

July 16-17
Iowa City, IA