MRI in Muscle Wasting Disorder

Assessment of Disease Progression in Muscle using Quantitative Magnetic Resonance Imaging in a Natural History Study of Dysferlinopathy

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INTRODUCTION

- Dyferlinopathy is a rare hereditary condition that affects the body's conducting system and muscles. This disorder is caused by mutations in the dysferlin gene which leads to a decrease in the dysferlin protein that is required for normal muscle functioning. As a result, a group of rare muscle wasting disorders is manifested.
- Patients typically present with the condition in early adulthood and symptoms associated with this disorder are highly variable (for reasons which are not yet understood), ranging from no symptoms to severe functional disability. The condition's heterogeneity is illustrated in the magnetic resonance (MR) scans below.
- As the disease progresses over time, healthy muscles are gradually replaced by fats (1)

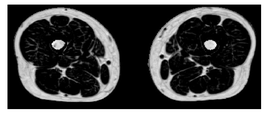


Figure1.1 MR scan of a mildly affected thigh

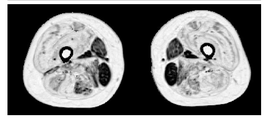


Figure1.2 MR scan of a severely affected thigh

Figure1.3 MR scan of a mildly affected calf

Figure1.4 MR scan of a severely affected calf

The brighter/ whiter the scan, the higher the fat infiltration

AIMS

- Understanding the natural history of dysferlinopathy is essential as the neuromuscular field moves towards clinical trial readiness. This project aims to:

1) Evaluate a whole thigh-and-leg-muscle Region of Interest (ROI) approach to monitor disease progression
2) Assess the disease progression in 27 subjects from baseline to year 1
3) Determine the correlation between years symptomatic and disease progression
4) Determine the difference between males and females in terms of disease progression

SUBJECTS

- 27 subjects
- 3 worldwide locations: Tokyo, Sydney, Marseille
- Gender: Males- 11, Females- 15 , N/A- 1
- Age: 34.31 ± 10.33
- Years Symptomatic: 14.15 ± 7.33

METHODS

- MR scans were performed on 1.5T or 3T systems of different vendors: Siemens- Philips- GE
- MR images were obtained at the level of the right and left thighs and calf encompassing 12 thigh muscles and 7 leg muscles
- Figure 1.5 and 1.6 shows the conventional way of drawing ROIs around every muscle in the thighs and calf respectively to determine a fat fraction value for each muscle
- In this project, a whole thigh-and-leg muscle ROI approach was used to determine the fat fraction value as shown in Figure 1.7 (thigh) and 1.8 (calf) with exclusion of the thigh bone, calf bone and shin bone
- For whole thigh-and-leg analysis an overall fat-fraction value for each limb was calculated, taking into account cross-sectional area of each slice using the equation below :

$$\bar{x} = \frac{\bar{x}_1 A_1 + \bar{x}_2 A_2 + \bar{x}_3 A_3 + \ldots \bar{x}_{20} A_{20}}{A_1 + A_2 + A_3 \ldots A_{20}}$$

$\bar{x}$= mean
A= area
1-20= slice number

- These values were then used to perform statistical analysis with the clinical data retrieved from the subjects

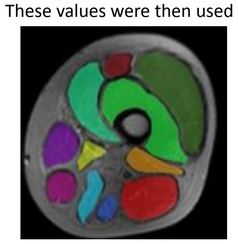


Figure 1.5 Left thigh

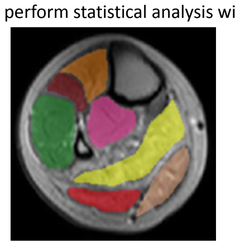


Figure 1.6 Left calf

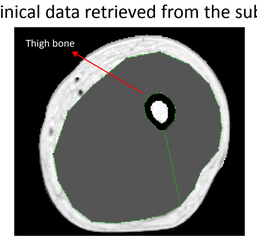


Figure 1.7 Left thigh

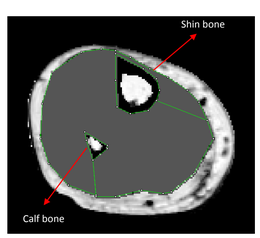


Figure 1.8 Left calf

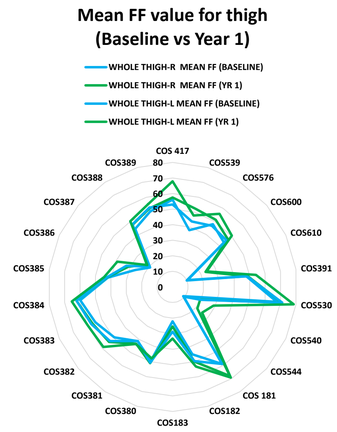
RESULTS

	Mean FF value	Standard Deviation
Right thigh (Baseline)	40.82	16.73
Right thigh (Year 1)	45.82	15.29
Difference	4.537	3.971
Left thigh (Baseline)	43.03	16.40
Left thigh (Year 1)	48.82	15.44
Difference	5.788	4.677

Table 1.1 shows the mean FF value and standard deviation for right and left thigh. A significant progression is shown as P value obtained was 0.00.

	Mean FF value	Standard Deviation
Right calf (Baseline)	36.50	15.10
Right calf (Year 1)	42.23	16.63
Difference	5.73	8.29
Left calf (Baseline)	39.07	14.64
Left calf (Year 1)	43.80	16.07
Difference	4.73	8.56

Table 1.2 shows the mean FF value and standard deviation for right and left calf. A significant progression is shown as P value obtained was ≤ 0.02



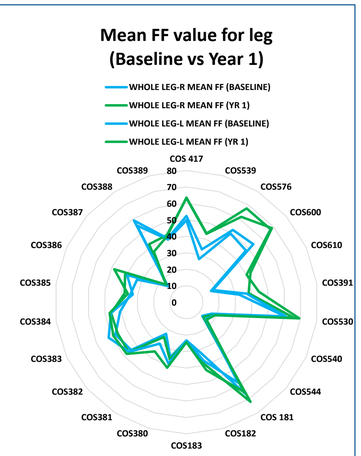


Figure 1.8 shows two spider plots illustrating progression of disease in thighs and leg from baseline to Year 1 in 27 subjects

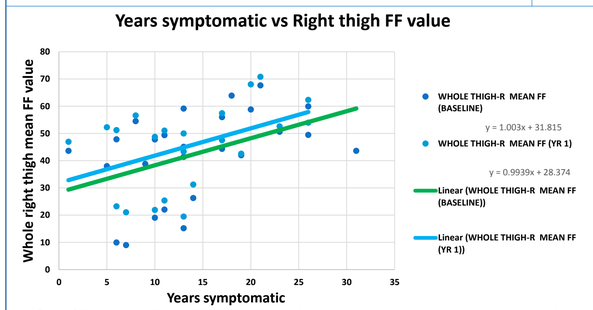


Figure 1.9 shows a scatter plot illustrating the relationship between years symptomatic and fat fraction value. Left thigh and the calf showed similar pattern.

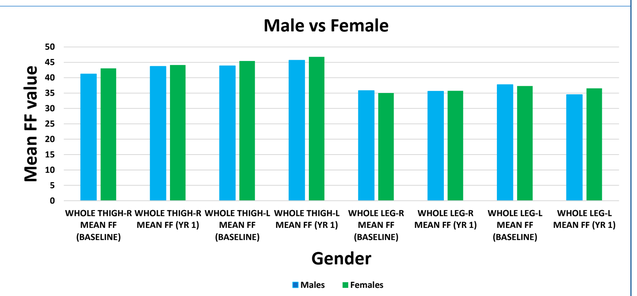


Figure 1.10 shows a bar chart illustrating the difference in mean FF value between females and males

DISCUSSION& CONCLUSION

- A whole thigh-and-leg muscle analysis seems like a viable option to monitor disease progression as results obtained reaffirm outcomes from previous studies that used individual muscle analysis (1). However, extensive research is needed to consolidate the fact that a whole thigh-and-leg muscle analysis can be used as an absolute predictor of future disease progression.
- Dysferlinopathy natural history involves replacement of muscle tissue with fats. Fat infiltration generally increases over time however heterogeneity in different limbs and degree of fat infiltration exists.
- Thigh muscles seem to be affected earlier in the disease process with higher severity of infiltration
- There is a positive correlation between years symptomatic and rate of disease progression
- There is no significant difference between females and males in terms of disease progression

SIGNIFICANCE

By measuring disease progression, accurate details regarding full clinical spectrum of different forms of dysferlinopathy can be collected. This will then aid in assessing efficacy of potential therapies as there is no cure for this disorder yet.

REFERENCES

1) Smith FE, Straub V, Bushby K, Rufibach L, Blamire A. Quantitative imaging and spectroscopy to assess clinical outcome in a natural history study of dysferlinopathy. Neuromuscular Disorders. 2015;25:S22-S3.

GLOSSARY

MR- Magnetic Resonance
MRI- Magnetic Resonance Imaging
ROIs- Region of interests

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