Fatigue

Normal mechanisms and the experience for people with neuromuscular diseases

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Normal mechanisms of fatigue:

- Metabolic
- Neural

Neuromuscular diseases:

- Muscular fatigue
- Experienced fatigue
- Impact
- Causes
- Interventions
Definitions of Fatigue

A reduced capacity for force development

(Bigland-Ritche et al 1986)

An exercise induced reduction in the maximum force capacity of a muscle

(Gandevia 2001)

Fatigue is sensed when we have exercised to the point we feel the task requires greater effort than it should

(MacIntosh and Rassier 2002)

Overwhelming sense of tiredness, lack of energy and feeling of exhaustion

(Krupp amd Pollina 1996)
Neurotransmitter released diffuses across the synaptic cleft and attaches to ACh receptors on the sarcolemma.

1. Action potential generated is propagated along the sarcolemma and down the T tubules.

2. Action potential triggers Ca\(^{2+}\) release from terminal cisternae of SR.

3. Calcium ions bind to troponin; troponin changes shape, removing the blocking action of tropomyosin; actin active sites exposed.

4. Contraction; myosin cross bridges alternately attach to actin and detach, pulling the actin filaments toward the center of the sarcomere; release of energy by ATP hydrolysis powers the cycling process.

5. Removal of Ca\(^{2+}\) by active transport into the SR after the action potential ends.

6. Tropomyosin blockage restored blocking actin active site; contraction ends and muscle fiber relaxes.

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• Reduced Ca2+ release or increased uptake
• Impaired NM transmission; attenuated membrane AP
• Altered voltage sensors
• Impaired SR Ca2+ channel opening

(Westerblad 2002)
Peripheral Fatigue

- ATP $\rightarrow$ ADP + Pi
- ↑ concentration of $\text{H}_2\text{PO}_4^-$
- Relationship seen between H+, $\text{H}_2\text{PO}_4^-$ and force generation

(Miller 1995)
Peripheral Fatigue

High frequency fatigue
- After an acute bout of exercise
- ↓ response to high frequency stimulation
- Due to effect of metabolites
- Rapid recovery with recovery of metabolites

Low frequency fatigue
- After prolonged exercise
- ↓ response to LF stimulation (HFF OK)
- ↑ period of recovery
- Long lasting decrease in SR Ca^{2+}
- Impaired excitation contraction coupling
Central Fatigue

- Defined as impaired firing rate or reduced motor unit recruitment during fatiguing exercise
- Twitch interpolation
- ↓MU firing rates and slowing contractions
- Can be caused by: nociceptive input, reduced voluntary usage

(Kuruganti et al 2009)
Fatigue in NMDs

Prevalence in adults:

FSHD: 61% report severe fatigue (n=139)
MD: 74% report severe fatigue (n=322)
CMT: 64% report severe fatigue (n=137)

(Kalkman et al 2005)

GBS/CIDP: 80% report severe fatigue (n=113)

(Merkies et al 1999)
Severe fatigue??

Is it increased muscle fatigability?

(Lindeman et al 1999)
Severe fatigue?

Is it increased muscle fatigability?

- “Experienced” fatigue: an overwhelming sense of tiredness and feeling of exhaustion, not the same as weakness (Kalman et al 2005)

- What is the experience?
Energy depletion

“It’s like packing up, it’s like my body’s letting me down and it’s telling me to stop now or you’re not gonna carry on.” (Sheila)

“It’s like everything’s heavy isn’t it.” (Anita)

Overwhelming onset

“It’s like an overwhelming tidal wave that I can almost feel approaching and it’s absolutely overwhelming and I just have to sit down and I’m asleep.” (Jill)
Different types of fatigue

“There’s tiredness and then there’s the fatigue tiredness and we see them as two different things. We can be tired and it is just normal tiredness if we’ve done too much and then we describe fatigue tiredness” (Sarah)

Not refreshed by rest

“The thing is you still go to bed and you have a damn good night’s sleep and you still wake up tired. So you’re starting at a minus before you’ve even started.” (Kathy)

(Ramdharry et al 2010)
Abnormal experience

“... I would describe it as more than knackered... more than everybody else” (Wendy)

“...that’s when I really noticed how different it was comparing myself to other people my age doing similar things to what I was doing” (Sheila)
Physiological investigation of the causes

(Schillings et al 2007)

- FSHD, MD, CMT: 2 min sustained contraction of biceps brachii
- Superimposed stimulation
- Experienced fatigue measure
- Calculated peripheral fatigue, central fatigue and central activation
- Less peripheral muscle fatigue then controls
- Minimal central fatigue
- Overall failure of central activation at the start of the contraction
- Relationship between central activation failure and experienced fatigue
Proposed model of fatigue

(Kalkman et al 2007)

- FHSD, MD, CMT measures of fatigue and other impairments
- Correlation analysis and computer modelling techniques
Triggers of fatigue

**Activity: too much or too little**

“If you have days out, then the next day you’re shattered.” (Anita)

“Inactivity, makes me feel more tired and fatigued than actually exercise” (Joe)

**Stress**

“...but my mind would still tick over about work and I suppose it’s all those things isn’t it? ... your mind’s active but physically you can’t do it...but that makes you tired ... but it is something else, you know, the worries, the stress.” (Ron)
Coping with limitations

“it was only really when I hit my 30's where everything started to slow down ...the CMT progressing ...not being able to go skiing or going on beach holidays it's very mentally fatiguing just dealing with it.” (Mark)

Work and family roles

“I work part-time but some weeks I work full-time, so at the end of that week I'm shattered and I can't do very much at the weekend. In fact some weekends I can sleep all weekend which is very frustrating for my wife.” (Mark)
Prolonged concentration

“I get tired when I’m having to concentrate on the co-ordination as well” (Amanda)

“a physio who comes and gets me to walk looking ahead rather than down, ...well that’s about five different things I’m having to mentally think about doing ... and I’m absolutely exhausted after that” (Jill)
Impact on function

(Ramdharry et al 2009)

- 18 people with CMT, 14 matched, healthy controls
- Treadmill walking until level 17 of Borg RPE scale
- Same task performed by controls: speed and time
- Correlation with clinical measures
Fatigue severity (FSS) v Walk time:
$$R = -0.68, P = 0.002$$

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<thead>
<tr>
<th></th>
<th>Pw CMT N=18</th>
<th>Controls N=14</th>
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<tbody>
<tr>
<td>Walk time (min)</td>
<td>48.3 ±40.5</td>
<td>44.0 ±40.8</td>
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<tr>
<td>Borg scale (final)</td>
<td>17</td>
<td>8</td>
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Impact on function

(Kalkman et al 2007)
Impact of fatigue

Physical function
“Over a substantial period of time I suppose I could walk a fair distance but really no more than about 100 yards before I have to stop” (Janet)

Psychological effects
“I get very short-tempered...” (Alan)
“...it impairs your judgement”
“It distracts you.” (various participants)
Impact of fatigue

**Work and family roles**

“I’d have periods of real fatigue and then I’d have to ring in with something else … so I’d ring in with upset stomach ….and then gradually I cut from 36 hours to 30 …. Really I suppose you could say they medically retired me because of the fatigue” (Sue)

“It really hurts when you hear other parents and other kids … not only will they go and have a game of football they might have spent the morning doing the housework, … then come home, do the tea, do the washing and sort out … and there's no way you could even think about that” (Joe)

(Ramdharry et al 2010)
Reduced socialisation

“I’d have friends round on a Friday evening and come nine, ten o’clock they’d all be up having a drink and having, you know, having a good time and I’d have to go to bed because I just couldn’t do it.” (Sheila)

Personal safety

“... I’m dripping with fatigue, I’m doing 95 in the fast lane to get home to bed!”

“...perhaps put myself at risk, because driving home when you’re tired ...‘I’ve gotta get home’.” (various participants)
Management of fatigue

• Medication
  – Small, inconclusive studies of Modafinil in CMT

• Exercise
  – Reduction in fatigue measures seen in small studies of people with CMT, GBS

• Fatigue management
  – No studies at present
  – NHNN: NMD patients referred to OT for fatigue Mx. Current MSc study underway

• What people say works for them
Management of fatigue

Positive attitude
“We tend to turn that as a joke rather than letting it bother us... ...we turn it into a positive not a negative.” (Anita)

Taking rests
“I try and make sure I get plenty of sleep when I know I’ve got something on... pity you can’t store sleep and bank it! (Sue)

“I regularly pull over on the way home and have a, have a little doze in the car, that works very well, just 10 minutes eyes shut and then you feel a bit more refreshed.” (Brian)
Management of fatigue

Exercise

“I can go down to the gym and that stimulates me” (Ron)

“when it takes all your energy to actually get through the day, the thought of exercise is depressing” (Brian)

Adaptations to ADL

“I haven’t been to Tescos for years and years and years, another energy management thing, online shopping was available”

“a wheelchair, it’s something to sit in comfortably whilst some one else does the work... it’s an energy management thing” (Kathy)
Management of fatigue

Organisation, planning, pacing

“You have to plan ahead in order to be able to cope with where you’re going to go and what you’re going to do”

“It’s an energy management process ... you have to conserve, you have to make a choice between what’s absolutely essential” (Kathy)
Clinical message and future research focus

Understanding the mechanism so we can understand what is a “normal” and “abnormal” experience

Understand the impact on activity and function that may be independent of disease severity

Tailor our treatment approaches to what we think are the main issues: peripheral or experienced fatigue
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