Lecture 1: PPS – from a clinical to genetic syndrome

Prof. Kristian Borg, Karolinska Institue (Sweden)

Borg began the presentation with definitions and evolution of Post-Polio Syndrome from an acute and then what is often mistaken as a "stable" condition.

Muscle Changes

Borg presented images from histochemical muscle stains demonstrating the size of the fascicles, and the consistency, or reliance on muscle fibre type. He then presented some findings of a muscle group in the legs (did not have a label, didn't catch a name if he did say it) where there was also evidence of patches of type IIb fibres, with some pockets of type I fibres. This is interesting with fatigue and the properties, or capacity of a muscle to maintain force generation. Clinically this is noted when manual muscle testing is performed, in that someone has capacity to produce force, but not for long. This capacity is often described as there being so few muscle fibres for the continued contraction, and was a contribution of type IIa, rather than type IIb fibres. Borg's images show that a "Polio muscle" can have high force potential, sometimes made up of fast twitch properties. Equally, previous research has shown "Polio muscles" (even other research from Borg) are made up of almost exclusively slow twitch muscle fibres, and would have limited capacity to generate force, or perform a rapid contraction, hence sometimes clinical observation of delayed muscle contraction with manual muscle testing.

Motor Units and overuse

Borg presented Tibialis Anterior (main muscle that lifts toes up at the ankle) for muscle contractions with respective number of motor units being used from initial to final contraction, and with repeated effort. The most striking aspect of these images that were presented on the same slide was very little to no difference between all three types of contractions/temporal considerations. This highlighted the limited capacity motor units have in resting with volitional control contractions, and also the fatigue that could develop not only related at the synapse but also intramuscular fatigue from sustained repeated efforts. Again, this is interesting to consider on the muscle fibre type and how this would relate to fatigue.

Borg then discussed the number of muscle fibres within the fascicle area of each motor unit for Tibialis Anterior. The size was much larger than to be expected. The ratio of motor unit size to fibre number was also nonlinear and not reflective of the properties of "normal" motor unit:muscle fibre expectations for this muscle. It wasn't clear for me whether this was something Borg had looked at, or he was sighting other colleagues' work that had been completed previously (i.e. Grimby).

Inflammation

Borg provided more histochemical figures demonstrating intramuscular inflammation and interfascicular inflammation. Later he showed the difference in appearance between non-PPS and PPS muscle images to highlight the degree this was an issue.

Pathophysiology of Denervation- Reinnervation

- Overstress of remaining motor units
- Overuse of remaining motor units
- Age
- Amyotrophic lateral sclerosis
- Persistent polio virus infection
- Immunological factors

The above bullet points is taken directly Borg's slide. It was interesting the terminology on this slide with the first two points. A Rehabilitation Specialist from the US asked Borg to elaborate on the difference and significance of each of the first two points when he described "overuse" and "overstress" of motor units. I am not sure whether Borg heard the question, or interpreted what was being asked with his response. I interpret the difference (so potentially completely wrong) as the latter representing neurological factors on innervating all available motor units more often than it should be expected which has the potential to create fatigue and issues with innervation/re-innervation rates at an acute, subacute and chronic response to this work being performed. These sources of fatigue may come from the central factors (e.g. the cortex, descending drive, or perception of effort) or peripheral factors (e.g. the limited latency between contractions, response time between contractions and action potentials, or the number of motor units recruited as a percentage of total motor units). The overuse of motor units may be on the capacity to (continually) maintain the large size/network of a motor neuron to enable ongoing innervation, far greater than what would be expected for the properties of the motor unit (chronic impact) and without the adequate number of motor units to enable an ordered response to workload demands of volitional muscle contraction (the "size" principle).

Borg stated there was a need for a systematic review between how Amyotrophic Lateral Sclerosis (ALS) presents and PPS presents and any connection between PPS and ALS. To his knowledge this had not been done, and was worthy of further investigation. It is an interesting comment as ALS looks similar to PPS. The rate of progressive degeneration is the obvious difference but it is interesting to see histochemical images of fascicles affected by ALS and their similarity in appearance to PPS. I wonder if Borg is looking for more evidence related to any genetic or viral factors with how people may be more predisposed for development of PPS / ALS. This is an area I am still reading about (and by no means feel I have my head around the pathology possibilities, particularly in ALS), but what I have read thus far was ALS presented with different inflammatory patterns to PPS.

Borg stated the element that continues to come to the fore with his investigations is on the importance of immunological factors to explain PPS and how it can be managed.

Inflammation

Borg identified previous research he had undertaken on patients with PPS and the levels of cytokine markers in the body. He presented figures of key markers compared to controls and also Multiple Sclerosis (MS) patients. PPS was significantly higher than controls. MS and PPS had very different results to controls

(different in presentation). There were varying results between each group in what Borg presented, although clearly inflammatory markers were significantly higher than controls.

Borg highlighted the inflammatory markers can be found peripherally (i.e. within the muscle) and in the Central Nervous System (CNS), which also highlighted the rationale for treating with IvIg as the effects from PPS were broad.

Borg also discussed the pathophysiology of one of the markers that was very high (TNF-α) which at levels can lead to break down of a key protein in the muscle (hence alluding to TNF-α potentially being the start of the denervation process) and unable to enable muscle contraction.

IvIg

Borg broke down results from his IvIg investigations quite simply- there were responders, non-responders and negative responders. Borg stated it was easy to explain why there were non-responders: they didn't have PPS. The negative responders were harder to explain and required more investigation.

I would have really liked to hear Frans Nollet's opinion regarding Borg's presentation as he went on to describe the results from IvIg with Polio Survivors showing either the intervention resulted in changes in function/pain and lowered inflammatory markers or that authors found high inflammatory markers (highlighting the benefits of IvIg). Nollet's study is one (to my knowledge anyway) that did not find the same significance as other authors. It would have been ideal to have heard more from each of them on the explanation as to why there are such differences and the relative importance of IvIg. The results from Borg of the responders are amazing, and there is something related to inflammation. There are a number of factors involved, and inflammation is a difficult area to demonstrate causation which will make it difficult to find the exact factors, or potentially, I imagine, also the dosage for an intervention.

FORCE Study

Borg discussed his ongoing research with the FORCE study which is a multicentre, double-blinded Randomised Control Trial (RCT) and the primary investigator is Marinos Dalakos. This is sponsored by Grifols (Spanish Pharmaceuticals company).

IvIg Results thus far

Borg demonstrated the prediction rates thus far for IvIg (compared to controls) for a range of conditions. He did not highlight all the different diseases presented, however the rates were above 90% for PPS. This was far different from the rates of other diseases/conditions, highlighting MS which had prediction rates of 20-40% for treatment with IvIg.

Conclusion

- Borg believes the neurophysiology only explains the pathophysiology of PPS and the potential for reduction (or prevention) of PPS could come from IvIg.
- Immunology may explain some of the symptoms of PPS and the background for denervation.

- There may be a genetic background for susceptibility of PPS and thus the inflammation (no time to expand this).