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Workshop report

184th ENMC international workshop: Pain and fatigue in neuromuscular disorders 20–22 May 2011, Naarden, The Netherlands

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1. Introduction

This European Neuromuscular Centre (ENMC) care workshop was attended by 19 professionals working in the field of neuromuscular disorders (pediatric and adult), pain or fatigue from 8 different countries (USA, Great Britain, Germany, France, Italy, Sweden, Denmark and the Netherlands), and 3 patient representatives coming from the Netherlands. This ENMC organized workshop aimed to achieve consensus on the definition of pain and fatigue in NMD, to define a core set of measurement instruments for pain and fatigue in NMD, and to discuss possible interventions. Prior to the workshop, all participants received a questionnaire on the assessment instruments and interventions that they regularly used to, respectively, assess and treat pain and fatigue. Two experts on (chronic) pain and fatigue in general (Henriët van Middendorp and Hans Knoop) were invited to present an overview of definitions, mechanisms, and measurement instruments for pain and fatigue. Next to that, several participants presented data on the prevalence of pain and fatigue in the various NMD populations. Through group discussions with all participants, consensus was reached on the definition and core set of measurement instruments (to be used)/for use in future research and clinical practice in NMD.

2. Background

Pain and fatigue are common symptoms in neuromuscular disorders (NMD) with a prevalence of 30–90%, present in all types of NMD, both in adults and children [1–6]. Pain and fatigue have a strong impact on many activities of daily life, including mobility, work, school, leisure, and sleep [4,7]. The differences in reported prevalence could be due to different definitions of pain and fatigue, and various types of measurements. In order to develop effective treatment approaches, both definitions and methods to measure pain and fatigue should be agreed on.

3. Questionnaires

Questionnaires were sent to all participants prior to the workshop to get an overview of the questionnaires on pain and fatigue that are currently used in research and practice in NMD [8]. In addition, the various interventions used to treat pain and fatigue were investigated. To assess pain in adults, nearly all participants used the SF-36 (items related to pain), a Likert scale, visual analog scale (=VAS), numeric rating scale (=NRS), and the McGill Pain Questionnaire. For neuropathic pain, more specific scales were mentioned, such as the Douleur Neuropathic 4 (=DN4), Neuropathic Pain Symptom Inventory (=NPSI), or ID-pain. In children, all used the VAS or the Faces Pain Scale (of which there are many different versions), few used body images to indicate the site of pain or the PedsQol (pain items), and one used the San Salvadour scale for severely handicapped children or the Douleur Enfant Gustav Roussy Scale for children between 2 and 6 years of age.

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For fatigue in adults, most of the participants used the Fatigue Severity Scale (=FSS), Borg CR-10 scale, NRS for fatigue, and some used the Modified Fatigue Impact Scale or the Checklist Individual Strength (=CIS). Specific for Myotonic Dystrophy type 1 (DM1), the following sleepiness scales were reported: Daytime Sleepiness Scale (DSS), Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), and Unnalinna Narcolepsy Scale (UNS). For children, the (modified) Borg scales were reported and the six minute walking test for ambulant children.

As possible interventions for pain, all participants mentioned guidance and advice for daily activities with special attention for overuse, physical therapy, and possible drugs such as pregabalin, citalopram, duloxetine, amitriptyline, creatine monohydrate, and paminodrate.

For fatigue, possible interventions that were reported included polysomnography to evaluate nocturnal hypoventilation and treatment, guidance and advice for daily activities with special attention for overuse, physical therapy, and cognitive behavioral therapy. Only for DM1 drugs to treat sleepiness were mentioned such as modafinil, citalopram, and Ritalin.

The level of evidence for the efficacy of the interventions is low; available evidence is restricted to drug treatment for neuropathic pain and sleepiness and fatigue in DM (see Cochrane reviews).

4. Participants' research on pain and fatigue in NMD

Baziel van Engelen reported on several studies in NMD populations, consisting of cross-sectional data of adult DM 1 ($n = 322$), DM type 2 ($n = 29$), OculoPharyngeal Muscular Dystrophy (OPMD) ($n = 35$), Chronic Progressive External Ophthalmoplegia (CPEO) ($n = 28$), FacioScapuloHumeral Dystrophy (FSHD) ($n = 139$), and Charcot Marie Tooth (CMT) ($n = 137$), as well as longitudinal data of adult DM1 ($n = 79$), FSHD ($n = 65$), and CMT ($n = 73$). To assess pain and fatigue in these studies, the McGill pain questionnaire and VAS were used for pain, and the CIS and SF-36 for fatigue. The reported fatigue was between 54% (OPMD) and 68% (CPEO), with significant impact on daily functioning. The pain scores were between 47% (DM1) and 96% (CPEO), with a different distribution pattern for each specific type of NMD. Pain scores were independent of age, impairments, physical activity level, or muscle force. The longitudinal study in FSHD ($n = 60$) and DM1 ($N = 75$) resulted in an FSH health status model and a DM1 health status model. Pain and fatigue were main determinants of health status in both diseases [7]. These models enable to rationally develop treatment strategies in FSHD and DM1 and form the starting point of the study presented by Nicoline Voet: the protocol of the FACTS-2-FSHD trial. In this recently finished study, aerobic exercise training is compared to cognitive behavior therapy (data currently in analysis). Pain and fatigue are measured by CIS, VAS for pain, 6 min walking test, and SF36.

Birgit Steffensen reported on a study of self-reported pain and fatigue in patients with FSHD and their healthy relatives or caregivers. The FSS and VAS were used to assess fatigue; pain was measured on a 1–7 scale as adapted from the FSS, by VAS, and by localization on a body image. Pain and fatigue scores were significantly higher in patients than in healthy persons, there was no statistical difference between patients who were still able to walk and those who were not, and there was a tendency towards higher pain and fatigue scores in patients with less muscle strength.

Marie Kierkegaard reported the results of a cross-sectional study on 70 persons with DM1. The ICF checklist was used for self-rating of perceived pain. Fatigue and excessive daytime sleepiness was evaluated with the FSS and ESS, as well as with the ICF checklist. Fatigue, daytime sleepiness and pain were rated as a problem in 76%, 80% and 51%, respectively. The impact of the cut-off level for fatigue and excessive sleepiness when using the FSS and ESS was stressed. For example, with a score equal or above 4 in FSS 52% are classified as experiencing fatigue compared to 17% when a cut-off score equal or above 5 is used.

Cornelia Kornblum discussed her study of 22 patients with DM1, 22 with DM2, and 22 controls. The FSS, DSS, ESS, PSQI, and UNS were used to assess fatigue and sleepiness as part of a more extensive psychological test set. DM1 showed more sleepiness and fatigue in all measurements compared to the other groups; only the mean KFSS-, DSS-, and PSQI-scores were above the cut-off for pathological performing. The DM2-patients showed more fatigue and a lower sleep quality (mean KFSS- and PSQI-scores were above the cut-off for pathological performing); no differences were found in daytime sleepiness. DM1 and DM2 patients were both more fatigued than healthy controls, and DM1 more than DM2.

Luca Padua showed the results of a study in 392 patients with peripheral nerve diseases, in which the Neuropathic Pain Symptom Inventory (NPSI), VAS, ID-pain, and DN4 were assessed. In 60% of the patients, the VAS-pain was 3 or higher, and approximately 30% had a VAS of 5 or higher. On ID-pain and DN4, 50–60% had symptoms of neuropathic pain. The NPSI showed no statistical difference between the different symptoms of neuropathic pain, in which paraesthesias had the highest score. In another study on 65 patients with FSHD, the SF-36, VAS-pain, and ID-pain were assessed. According to the ID-pain, 7% of the patients had very probable neuropathic pain, 20% probable neuropathic pain, 24% possible neuropathic pain, 33% no pain, and 16% joint pain exclusively.

Bernard Wuyam showed the preliminary results of an ongoing study on the assessment of neuromuscular

dysfunction by means of magnetic nerve stimulation in muscular dystrophies and CMT, and the effect of exercise.

Ulla Werlauff showed results of studies on the perception of pain and fatigue in persons with spinal muscular atrophy (SMA) (52 persons: 7.8–72.6 years) and congenital myopathies (95 persons: 5.5–75.2 years). The PedsQoL (generic, specific), SF-36, Egen classification 2 scale, FSS, and Modified Fatigue Impact Scale were used to measure pain and fatigue. In congenital myopathies, pain was a problem in all muscles (overload?) whereas in SMA-type 2 it was not, or related to an event like surgery. In this study, fatigue was a problem in congenital myopathies but not in SMA. From her results, Ulla Werlauf concluded that PedsQoL, SF-36 and Modified fatigue impact scale were not very sensitive or conclusive. The recommended scale would be the FSS.

Imelda de Groot showed results of former studies in adults with SMA and ALS and an ongoing study in DMD. In an open questionnaire study in 99 adult SMA-patients, divided into two groups (SMA type1–2 and type 3), neck pain was most prevalent in both groups (38% in SMA1-2, and 34% in SMA3); fatigue was reported in 64% in SMA3, in contrast to 34% in SMA1-2. In a study in 74 persons with ALS, no correlations were found between functional abilities (measured with ALS-FRS), and pain or fatigue (measured with SF-36). In the ongoing study in boys with DMD ($N = 30$) and training, the preliminary results show that boys with DMD have similar adaptations to physical exercise (heart rate and EMG-adaptations) as healthy age-matched controls ($N = 99$) and comparable subjective fatigue (measured by OMNI scale), but that some boys can perceive/experience fatigue in rest.

Yaacov Anziska showed preliminary results of two studies: one study in children with NMD (7 with myopathy/limb girdle muscular dystrophy, 9 with DMD, 3 with CMT, and 2 with myasthenia gravis; age range 5–19 years). The Epworth Sleepiness Scale, the Vignos, and Brooke ratings scales, the Children's Depression Inventory, and the PedsQoL 3.0 Neuromuscular Module for Patients and Parents were used. Except for the myopathy/DMD-group, there was no correlation between PedsQL-scores of the patients and those of their parents. There was evidence of mild abnormal mood disorders and mild-moderate sleepiness. A study of 31 adults (5 patients with DM1-2, 14 LGMD, 5 CMT, 5 motor neuron diseases, 2 myasthenia gravis) in which the SF-36 was used gave similar results.

Carole Bérard showed results of a study in 22 boys with DMD with pain and osteopenia (7 ambulant, and 15 non-ambulant). In 21 of the 22 boys, a moderate to severe pain was measured with NRS, most of the boys (21) experienced pain during physiotherapy; 11 also spontaneously, 9 during the night and 5 (non-ambulant) during transfers. There was no correlation between the NRS-pain score and osteopenia.

Anna-Karin Kroksmark shared some practical experiences on pain and fatigue in children with DMD from studies performed at her centre. In these studies, PedsQoL, Multidimensional Fatigue Scale, Sleep quality index, and questions about pain and tiredness were used. Pain has an increasing interest in the network in Sweden and a national survey is now being performed. Adapted Faces scales were shown.

Caron Coleman showed her work on establishing how to measure pain in children: one size does not fit all! Due to the different developmental stages the following measurements were recommended for clinical utility: 0–5 years and cognitive or learning difficulties-observation and parent/caretaker report; 5–7 years-faces and questions to child and parents regarding location, frequency, quality (if possible) and impact on function; 8+ years-combination of faces/NRS and questions as above; 13+ years Brief Pain Inventory/faces/NRS.

Heinz Jungbluth gave an overview of different childhood NMD in which exertial myalgia with or without rhabdomyolysis is a common primary or secondary feature. One of the open questions that need to be addressed in future research is whether the different mechanisms underlying these features in distinct disorders will require different treatment approaches.

Marion Main shared some thoughts on pain and fatigue in children with NMD. Pain can be caused by secondary complications of the disorder, such as contractures, cramps, muscle soreness etc. A warning was given that the physiotherapist can be a cause of pain due to treatments like stretching. She pointed at the lack of knowledge on the topic of fatigue with regard to the role of weakness in the development of fatigue and the important role of exercise in the management of pain and fatigue.

Finally, Jo Auld gave advices on the psychometric properties that outcome measures on pain and fatigue should encompass.

5. Conclusions

Pain as well as fatigue are currently measured by various methods and several NMDs have been studied so far. It can be concluded that pain and fatigue are highly prevalent and important problems, both in adults and children. It is important to differentiate pain and fatigue from sleepiness, depression, de-conditioning, and side effects of drugs. Specific types of pain and fatigue, related to the underlying NMD and/or stage of the NMD can be distinguished. These should be differentiated from aspecific pain and fatigue, which are not primary related to NMD.

Fatigue can have physiological features, such as loss of voluntary force or endurance during exercise/activity (both of peripheral and central origin). This type of fatigue is activity-related. This aspect of fatigue is also applicable for cognitive fatigue, defined as a reduction in cognitive performance over time.

6. Proposed definitions

As presented by the experts on pain and fatigue, both pain and fatigue are multidimensional concepts and include the following aspects:

- Characteristics: acute or chronic ("long lasting"), intensity, frequency, location, quality.
- Cause(s).
- Consequences or impact on: body function(s), activities of daily life, and participation.
- Cognitive-behavioral factors (predisposing and/or perpetuating).

The proposed definition of pain in NMD is from the International Association of Study on Pain (IASP): pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

Fatigue can have many definitions. The proposed one is: experienced/subjective fatigue is lack of energy or the existence of weakness or exhaustion – mentally, physically or both.

7. Proposed measurement core-sets

Several instruments to measure pain and fatigue in NMD were discussed with experts in the research field [8]. Two types of measurement core-sets are proposed: one to use in daily practice and one for research purposes.

For pain the following core-sets are proposed:

Core-set (daily practice):

- Numeric Rating Scales (faces for children)/FLACC in young children.
- Modified Brief Pain Inventory.
- Hospital Anxiety and Depression Scale (HADS).
- Pay attention to organic/biomechanical causes/ neuropathic pain (if the latter is suspected: use ID-pain or DN4).

Research (extended screening):

- Pain Disability Index (PDI) or Brief Pain Inventory (BPI).
- SF-36.
- HADS and/or Beck's Depression Index (BDI).
- Cognitive-behavioral factors.
- In case of neuropathic pain, use ID-pain or NPSI.

For fatigue:

Core set (daily practice):

- NRS.
- Checklist Individual Strength (CIS) (norms, multiple dimensions), or if CIS is not available fatigue severity scale (FSS) (impact of fatigue).
- Look for organic/biomechanical causes/forced vital capacity.

Extended/research:

- Physical activity (e.g. actography, activlim).
- Disability scale (e.g. SIP, SF-36).
- Psychological distress (e.g. Hospital Anxiety and Depression Scale).
- Sleep disturbances.
- Social support scale.
- Fatigue-related cognitions.
- Pain.

8. Future plans

This workshop only covers discussions and proposals for definitions of pain and fatigue in NMD and the core set of measurements for daily practice and research. The management of pain and fatigue is still a point to discuss in the future. It was decided to collaborate on the use of the core-sets and share data with each other in order to get more insight in the possible contributing factors of pain and fatigue in NMD. Based on these results, possible management approaches can be discussed in a next workshop on Management of pain and fatigue in NMD.

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