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Balance impairments and neuromuscular changes in breast cancer patients with chemotherapy-induced peripheral neuropathy ☆

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HIGHLIGHTS

- Breast cancer patients with symptoms of chemotherapy-induced peripheral neuropathy (CIPN) suffer from balance impairments and neuromuscular dysfunction.
- Balance impairment is associated with a higher antagonistic co-contraction of lower-leg muscles.
- CIPN is related to a prolonged H-reflex latency and an impaired capability to inhibit spinal excitability (H-reflex).

ABSTRACT

Objective: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of cancer treatment. Resulting sensory and motor dysfunctions often lead to functional impairments like gait or balance disorders. As the underlying neuromuscular mechanisms are not fully understood, we compared balance performance of CIPN patients with healthy controls (CON) to specify differences responsible for postural instability.

Methods: 20 breast cancer patients with CIPN (PAT) and 16 matched CONs were monitored regarding centre of pressure displacement (COP) and electromyographic activity of M. soleus, gastrocnemius, tibialis anterior, rectus femoris and biceps femoris. We calculated antagonistic co-contraction indices (CCI) and elicited soleus H-reflexes to evaluate changes in the elicitability and sensitivity of spinal reflex circuitry.

Results: PAT's COP displacement was greater than CON's ($p = .013$) and correlated significantly with the level of CCIs and self-reported CIPN symptoms. PAT revealed prolonged H-wave latency ($p = .021$), decreased H-reflex elicitability ($p = .001$), and increased H-reflex sensitivity from bi- to monopedal stance ($p = .004$).

Conclusions: We summarise that CIPN causes balance impairments and leads to changes in elicitability and sensitivity of spinal reflex circuitry associated with postural instability. We assume that increased simultaneous antagonistic muscle activation may be used as a safety strategy for joint stiffness to compensate for neuromuscular degradation.

Significance: Sensorimotor training has the potential to influence neuromuscular mechanisms in order to improve balance performance. Therefore, this training modality should be evaluated as a possible treatment strategy for CIPN.

☆ Place where the work was done: Tumour Biology Centre Freiburg, Germany.

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1. Introduction

As screening measures and treatment options improve, the number of cancer survivors increases (Siegel et al., 2012). Many must deal with long-term physical health effects (Rowland and Bellizzi, 2014), including functional impairments due to chemotherapy-induced peripheral neuropathy (CIPN) (Stubblefield et al., 2009). CIPN occurs with an estimated incidence of 30–70% depending on factors such as substance class or cumulative dose (Mantyh, 2006). Taxanes (i.e. paclitaxel), mainly used in breast cancer treatment, cause CIPN in 57–83% of patients (Stubblefield et al., 2009). About 12% of US women will develop breast cancer during their lifetime (Siegel et al., 2015). Most women with late stage breast cancer and nearly a third with early-stage undergo taxane-based chemotherapy (Siegel et al., 2012).

CIPN symptoms occur with paraesthesia like numbness and/or pain in a stocking-and-glove distribution (Argyriou et al., 2012). It is well known that neuropathy correlates with a loss of proprioception that causes postural and functional impairments (Resnick et al., 2000; Simoneau et al., 1995; van Schie, 2008). In CIPN patients, these impairments are often described as gait or balance disorders (Grisold et al., 2012; Visovsky and Daly, 2004; Wampler et al., 2007), most probably linked to a higher risk of falling (Tofthagen et al., 2012; Stubblefield et al., 2009), accompanied by significant limitations in daily life activities (Quasthoff and Hartung, 2002; Stubblefield et al., 2009; Windebank and Grisold, 2008). However, the consequences for patients' daily life are often underestimated (Grisold et al., 2012) and little is known about the specific impairments of postural instability in CIPN (Wampler et al., 2007) or compensation strategies for functional deficits. In view of the lack of evidence-based treatment methods to manage functional impairments (Hershman et al., 2014), investigations need to address the underlying mechanisms of CIPN-induced postural instability.

Reports in the literature indicate that enhanced postural skills (e.g. small sway paths in challenging postural tasks, quick balance recovery after perturbation) are accompanied by neuromuscular adaptations (Bruhn et al., 2004; Taube et al., 2007; Zech et al., 2010) and emphasise that changes on spinal and supraspinal levels are associated with alterations in postural control mechanisms (Gruber et al., 2007; Schubert et al., 2008; Taube et al., 2007; Yaggie and Campbell, 2006). Studies analysing spinal reflex circuitries via H-reflex measurements have shown that good balance skills correlate with diminished excitability of spinal reflexes (Taube et al., 2007). The inhibition of spinal excitability, such as for example from a simple to a difficult postural task or after a balance training intervention, apparently reduces involuntary postural oscillations and is thus assumed to lead to distinctly enhanced balance performance (Taube et al., 2008). This inhibitory mechanism allows the execution of controlled muscle activation programs on supraspinal levels (Taube et al., 2008), while facilitated spinal excitability is associated with exaggerated postural oscillations and thus stronger postural sway in a balance task (Taube et al., 2008).

In cancer patients suffering from CIPN, proprioceptive feedback and central nervous system (CNS) function at the spinal level are strongly affected (Mantyh, 2006). In particular, large myelinated afferent fibres such as Ia fibres are injured by neurotoxic agents, i.e. taxanes (Mantyh, 2006). Furthermore, injuries to peripheral nerves interfere with proprioceptive cues, known to be essential for a quiet stance (Fitzpatrick and McCloskey, 1994; Peterka and Benolken, 1995). Taxanes among other chemotherapeutic agents are well known to cause selective injuries to the peripheral nervous system, inflammation in the dorsal root ganglion and peripheral nerves, destabilisation of microtubules essential for axonal transport and neurochemical reorganisation in areas of the spinal cord involved in processing somatosensory information (Mantyh, 2006). These cellular and molecular neurotoxic mechanisms are associated with significant impairments in nerve function related to a reduced or even absent reliability of afferent feedback transmitted via sensory axons (Mantyh, 2006; Stubblefield et al., 2009). It can be emphasised that changes in Ia afferent transmission at the spinal level identifiable in H-reflex sensitivity may be responsible for gait and balance disorders (Wampler et al., 2007) and may cause overall changes in sensorimotor performance in these patient groups (Streckmann et al., 2014).

Regarding sensorimotor interaction, there is evidence that an enhanced balance performance is accompanied by less simultaneous contraction of antagonistic muscles, while reduced balance skills are associated with increased co-contractions (Hu and Woollacott, 1994; Nagai et al., 2011). Reduced co-contraction is a key factor when accurate balance regulation is required during demanding postural tasks and consequently is associated with less postural sway (Nagai et al., 2012). In contrast, when upright equilibrium is threatened based on poor balance skills, supraspinal control mechanisms are believed to be responsible for higher co-contraction targeting joint stiffness as a safety strategy for keeping equilibrium (Bruhn et al., 2004; Hortobágyi et al., 2009; Nagai et al., 2011). Thus we speculate that greater postural sway in CIPN patients (Wampler et al., 2007) is accompanied by higher co-contraction.

Taken together, these neuromuscular adaptations (i.e. changes in H-reflex sensitivity and co-contraction of antagonistic muscles) are known to affect balance control substantially (Bruhn et al., 2004; Heitkamp et al., 2001; Sayenko et al., 2012; Zech et al., 2010). We also know that neuropathy-induced loss of somatosensory information and/or processing leads to postural instability (Bonnet et al., 2009). However, the neuromuscular mechanisms underlying functional impairment especially in CIPN have been inadequately investigated. This study's aim was therefore to compare the balance performance of CIPN patients and healthy controls and to detect differences in the underlying neuromuscular mechanisms responsible for CIPN-induced balance impairments.

2. Materials and methods

2.1. Experimental design

We applied a repeated-measures matched-subject study design. Thus, we compared a group of breast cancer patients suffering from CIPN (PAT) with one of healthy controls (CON) to assess differences in their balance performance and associated neuromuscular mechanisms. We assessed the centre of pressure (COP) displacement, electromyographic (EMG) activity and spinal excitability in bi- and monopedal stance. Bipedal stance was used as a reference for normalisation.

2.2. Subjects

36 females (mean age 48, range 39–55 years) at the Tumour Biology Centre Freiburg participated in this study – 20 non-bed rest breast cancer patients after taxane-based chemotherapy reporting neuropathy symptoms due to chemotherapy, and 16 healthy controls matched by sex, age, height and weight (Table 1). All participants gave written informed consent to the study, which was approved by the Ethics Committee of the University of Freiburg and conducted according to the Declaration of Helsinki.

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