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Concordance of Phantom and Residual Limb Pain Phenotypes in Double Amputees: Evidence for the Contribution of Distinct and Common Individual Factors

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Abstract: Most, but not all, limb amputees develop phantom limb pain (PLP) or residual limb pain (RLP), and large interindividual differences in pain intensity and course are apparent. The present cross-sectional study of 122 double amputees investigated the possible role of genetic factors in PLP and RLP, assuming that strong individual predisposition results in high intraindividual concordance in pain phenotype. Intraindividual concordance was observed in 116 (95%) patients for development of PLP and in 110 patients (90%) for development of RLP. For both pain types, high intraindividual concordance was also observed for remission and current intensity. Moderate association for lifetime history and current intensity of PLP and RLP was observed both within and between limbs. The high intraindividual concordance in pain phenotypes suggests strong individual predisposition for PLP and RLP development. However, the finding of only moderate association between PLP and RLP suggests that susceptibility to these pain phenomena involves distinct, as well as common, risk factors. Genome-wide studies in large samples of single amputees may facilitate the dissection of these phenotypes and their underlying mechanisms.

***Perspective:** The observation of high intraindividual concordance for PLP and RLP in 122 double amputees suggests that individual factors contribute to post-amputation pain. The relatively low intraindividual association between PLP and RLP suggests that these factors are at least partially specific for each pain type.*

***Key words:** Phantom limb pain, residual limb pain, concordance, heritability of pain, multiple amputations.*

Neuropathic pain is related to lesions, disease, toxins, or medications that disrupt the structure/function of the somatosensory nervous system.[48] This type of pain affects up to 18% of the population, is difficult to treat, and causes long-term suffering, depression, and disruption of function.[47] Surgical or

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traumatic limb amputation is associated with 2 major types of neuropathic pain[5,25]: pain referred to the missing limb (phantom limb pain [PLP]), and residual limb pain (RLP) (pain in the remaining portion of the limb).[16,46] PLP occurs in about 75% of limb amputees, whereas about 60% have RLP.[19] Both types do not necessarily co-occur, although they are correlated.[19] Sensory-discriminative characteristics, such as pain intensity, frequency, and duration, remain stable for many years after amputation, with a low rate of spontaneous remission but high interindividual variability.[21,46]

Much of the variability observed in these pain phenotypes may be driven by the individual genetic background.[4,34] Twin and family studies[36] of other chronic pain conditions have revealed heritabilities of 20 to 70%. Corresponding heritability estimates for postamputation pain are unavailable because, for obvious reasons, the required twin samples do not exist. However, animal models of neuropathic pain have yielded heritability estimates similar to those seen in human chronic pain conditions.[13,35,52] For example, a study in rats based on autotomy behavior after paw denervation as a model of neuropathic pain[43] compared autotomy levels expressed after sequential denervation of 2 limbs spaced weeks apart. The investigators reported that autotomy levels after the first denervation were highly predictive of the levels of the same behavior after the second denervation. The investigators proposed that this finding may indicate a strong individual predisposition for certain levels of autotomy behavior.

In humans, 2 studies have reported a high concordance in pain phenotype between injured body sites after surgery[9] or amputation,[29] and their results have been interpreted as "tentative evidence of heritability."[12] Bruce et al[9] compared postsurgical chronic pain in 1080 patients who underwent coronary bypass surgery that necessitated grafting the saphenous vein in the leg. Those who developed chronic postsurgical pain in the chest also tended to develop chronic pain in the leg. In a sample of 11 bilateral upper limb amputees, Lacoux et al[29] reported concordance for the presence of PLP and nonpainful phantom sensation in all patients, and 10 of the 11 patients were concordant for RLP. However, the small sample size clearly limits the generalizability of this study.

The aims of the present study were to 1) investigate the hypothesis that PLP and RLP are each determined by a strong individual predisposition that results in high concordance in pain phenotype between limbs; and 2) determine the association between PLP and RLP, both between and within limbs, to examine whether common or distinct risk factors are implicated in their development. This was investigated in a sample of 122 double amputees. A precise phenotype characterization of PLP and RLP was performed for each limb.

To investigate the individual predisposition for each type of pain, we tested between-limb concordance of the lifetime history and the current intensity of both PLP and RLP. For the relationship between PLP and RLP, we tested the association between PLP and RLP both between and within limbs in terms of lifetime history and current intensity.

Methods

Sample

Between August 2009 and November 2013, a total of 31,887 questionnaires were sent to cooperating organizations in Germany for distribution to individuals with a major amputation of 1 or more limbs (in the context of the PHANTOMMIND [Phantom Phenomena: A Window to the Mind and the Brain] project).[3] In total, 3,862 questionnaires were returned together with a signed/dated informed consent document (response rate, 12%). Returned but incomplete questionnaires were completed via telephone interviews. A total of 361 questionnaires were excluded because of missing information. Of the remaining 3,501 questionnaires, 122 were completed by individuals who had undergone a double amputation. The study was approved by the ethics review board of the Medical Faculty Mannheim, University of Heidelberg and was conducted in accordance with the Declaration of Helsinki.[1]

Questionnaire

The questionnaire was based on the Phantom and Stump Phenomena Interview,[51] with the addition of items concerning demographic variables, other physical diseases, and general pain experiences. For all questions about the amputation procedure and subsequent pain experiences, the patients were asked to provide separate responses for each limb. For the purposes of the present analyses, the following items were evaluated:

1. The patients were asked to indicate the site of the amputation, the length of the residual limb, the reason for the amputation, when it was performed (year and month), and whether they had experienced pain in the affected limb before the amputation.
2. Patients were asked whether they had experienced PLP or RLP in the following 2 time frames: "ever" (ie, since the loss of the limb) and "within the last 3 months." PLP and RLP were categorized using both i) 2 categories (no lifetime history of pain vs lifetime history of pain) and ii) 3 categories (no lifetime history, symptom free for at least the last 3 months [remission], or lifetime history of pain with symptoms within the last 3 months [current]).
3. Patients asked to rate the average intensity of PLP and RLP experienced during the 4 weeks preceding the survey on a scale of 0 (no pain) to 10 (intolerable pain). These intensity ratings were used to quantify the current intensity of PLP and RLP.

Statistics

The data analysis was performed with the SPSS software package (version 20, IBM Corp, Armonk, NY). Concordance in PLP and RLP between different amputation sites, and intraindividual association between PLP and RLP both within and between limbs, were assessed using the χ^2 test for categorical variables and correlational analysis for continuous variables. The analyses were carried out separately in 3 groups (leg-leg,