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The influence of experimental pain intensity in the local and referred pain area on somatosensory perception in the area of referred pain

Eva Kosek\textsuperscript{a,c} and Per Hansson\textsuperscript{a,b,c}

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The aim of this study was to investigate the influence of experimental pain intensity in the local and referred pain area on somatosensory perception thresholds in the area of referred pain. Pain was induced by intramuscular electrical stimulation of the left infraspinatus muscle in 12 healthy individuals. The stimulation corresponded to the local pain threshold ("mild local pain"), the referred pain threshold ("mild referred pain"), and a pain intensity corresponding to 2 on a 10-point category scale in the referred pain area ("moderate referred pain"). Quantitative sensory testing was performed to assess perception thresholds in the referred pain area and the homologous contralateral area before and during stimulation. Perception thresholds to light touch (LTTs), pressure pain (PPTs), and to innocuous as well as noxious warmth and cold were assessed. During stimulation the LTTs increased in the referred pain area compared to baseline, uninfluenced by pain intensity. Perception thresholds to innocuous cold and warmth increased bilaterally during the stimulation, without relation to pain intensity. Heat pain thresholds were not affected. Compared to baseline, PPTs increased bilaterally during stimulation corresponding to 'mild local pain' and 'mild referred pain', respectively, and a further increase was seen during 'moderate referred pain'. The decreased sensitivity to innocuous cold, warmth, and pressure pain was bilateral, indicating activation of endogenous net inhibitory mechanisms interacting bilaterally. We found no influence of pain intensity on somatosensory thresholds restricted to the referred pain area and light touch was the only affected modality in the referred pain area only. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

Keywords: referred pain, muscle pain, quantitative sensory testing, pressure algometry, endogenous pain regulation.

INTRODUCTION

Pain from muscles is usually perceived in the area of activated nociceptive afferents but, not infrequently, also at a distance from this area, i.e., referred pain (Kellgren, 1938; Lewis & Kellgren, 1939; Feinstein et al., 1954). Despite the fact that the existence of referred pain from deep somatic structures has been recognised for at least a 100 years, the underlying pathophysiological mechanisms remain largely unknown. There is evidence that ongoing nociceptive input from the site of injury is the only prerequisite to induce referred pain, since pain can be referred to a phantom limb (Harman, 1948), and to areas with complete sensory loss due to spinal cord injury (Whitty & Willison, 1958) or anaesthetic block (Kellgren, 1938; Feinstein et al., 1954).
Furthermore, the ongoing nociceptive barrage from the primary pain focus seems to be necessary to maintain the sensation of referred pain, which is illustrated by the fact that both local and referred pain can be abolished by anaesthetising the site of injury (Whitty & Willison, 1958; Hockaday & Whitty, 1967; Vecchiet et al., 1993). In addition, a significant positive correlation between the pain intensity in the primary pain focus and the appearance of referred pain (Inman & Saunders, 1944; Sinclair et al., 1948; Torebjörk et al., 1984; Falace et al., 1996; Graven-Nielsen et al., 1997a,b), the intensity of referred pain (Graven-Nielsen et al., 1997a,b) and the size of the referred pain area (Graven-Nielsen et al., 1997a,b) has been reported.

While the importance of afferent input from the primary pain focus for the sensation of referred pain is obvious, little is known about the influence on the latter of afferent input from the referred pain area itself. The relation between the intensity of referred pain and the afferent input from the referred pain area can be studied in two principally different ways. One is by withdrawing normal input by anaesthetising the referred pain area and the second is by stimulating the referred pain area with different kinds of somatosensory stimuli and to assess the sensitivity qualitatively or quantitatively. Both approaches have been tried and have led to conflicting results. Anaesthesia of the referred pain area has been reported to reduce or eliminate the referred pain (Whitty & Willison, 1958; Hockaday & Whitty, 1967; Laursen et al., 1997), or to leave the intensity of referred pain unaffected (Kellgren, 1938; Feinstein et al., 1954; Whitty & Willison, 1958). Signs of somatosensory abnormalities in the referred pain area have been reported (Kellgren, 1938; Lewis & Kellgren, 1939; Graven-Nielsen, 1997c; Leffler et al., 2000a) and like the referred pain itself, they depend on the ongoing nociceptive barrage from the site of injury, since they can be abolished by anaesthetising the primary pain focus (Hockaday & Whitty, 1967; Vecchiet et al., 1993). However, conflicting results regarding somatosensory perception in the referred pain area have been found, illustrated by reports of increased (Kellgren, 1938; Feinstein et al., 1954), unaffected (Steinbrocker et al., 1953; Leffler et al., 2000a), and decreased (Graven-Nielsen et al., 1997c, 1998) sensitivity to pressure pain, as well as increased (Klingon & Jeffreys, 1958), unaffected (Leffler et al., 2000a), and decreased (Graven-Nielsen et al., 1997c) sensitivity to heat pain. Different methodologies, quantitative only in recent studies, have been used to assess somatosensory perception which makes the results difficult to interpret. Furthermore, to our knowledge, no previous study has systematically assessed the sensitivity to somatosensory stimuli in relation to pain intensity in the local and referred pain area. If pain intensity can influence the profile of sensory aberrations in the referred pain area this may explain the contradictory results regarding somatosensory perception in the referred pain area reported in previous studies. A better survey of the relation between the intensity of referred pain and somatosensory function in the referred pain area may increase our understanding of the pathophysiology of referred pain.

In clinical practice patients with musculoskeletal pain disorders do not infrequently report a diffuse distribution of referred pain with both deep and superficial components and, in addition, numbness and/or paresthetic and/or pricking sensations. Furthermore, sensory aberrations at quantitative examination have been reported in the referred pain area in patients with musculoskeletal pain (Leffler et al., 2000b). These symptoms and signs may to some extent mimic what is found in neuropathic pain states and may be confounding factors in the diagnostic evaluation of chronic pain patients. The diagnosis of neuropathic pain rests heavily on the findings of neuroanatomically correlated distribution of pain and somatosensory disturbances (Hansson, 1993). The latter may be assessed by quantitative sensory testing (QST) using the contralateral painfree side as an intra-individual control. Therefore, it is important to characterise the profiles of sensory aberrations found in the referred pain area in musculoskeletal pain and to learn what factors are important to induce and maintain these changes. It is our clinical experience that somatosensory aberrations in patients with musculoskeletal pain are more variable over time regarding their presence, distribution, and profile, than in patients with neuropathic pain. The reason for this variability remains unknown. However, since pain intensity, i.e., the activity in the nociceptive system, often changes over time.
Statistical methods

LTTs, CTs, WTIs, HPTs, and PPTs were analysed using a two-way ANOVA with repeated measures on two factors. The within factors were SIDE with the two levels ‘painful site’ and ‘contralateral site’ and CONDITION with the four levels ‘baseline’, ‘mild local pain’, ‘mild referred pain’, and ‘moderate referred pain’. Differences between levels of the within factor condition were evaluated by the post-hoc Tukey test if the sphericity condition was tenable, otherwise specific contrasts were applied with correction of p-values according to Bonferroni. In case of significant interaction between the factors, simple effects were examined, i.e., effects of one factor holding the other factor fixed. The simple effects procedure produces a very large significance test. Therefore, the p-values have been corrected according to the Bonferroni procedure. The distribution of the variables was inspected by box plots and by skewness, a measure of symmetry of the distribution of values. If the distribution is symmetrical, the skewness is equal to zero. A value greater than +1 indicates that the variable is positively skewed. The distribution for some variables was skewed. Such data have been log-transformed to meet the requirements for an adequate ANOVA. For ANOVA F-values and degrees of freedom are presented as ‘F (df effect, df error) = x’. Data are presented as medians of absolute values. Comparisons between different conditions with respect to VAS ratings and differences in intensity of the i.m. electrical stimulation were analysed using Friedman’s test with appropriate post-hoc analysis (Siegel & Castellan, 1988). Medians and ranges are presented. Differences in means of the touch perception threshold at the site of stimulation before and following EMLA cream were analysed with Students’ two-tailed t test, means, and SEMs are presented.

RESULTS

Amplitude of i.m. electrical stimulation

The median amplitude of intramuscular electrical stimulation during QST assessments was 4.2 V (range 0.3–10.4 V) to maintain ‘mild local pain’, 4.7 V (range 0.9–43.3 V) to maintain ‘mild referred pain’ and 7.7 V (range 1.4–53.2 V) to maintain ‘moderate referred pain’ (Friedman's test; p < 0.001). Post-hoc analysis showed no statistically significant difference between the amplitude of intramuscular electrical stimulation during maintenance of ‘mild local pain’ and ‘mild referred pain’ (p > 0.05). The amplitude during ‘moderate referred pain’ was significantly higher than during ‘mild local pain’ (p < 0.001) and ‘mild referred pain’ (p < 0.001), respectively.

Perception of pain during i.m. electrical stimulation

When the subjects were requested to set the electrical stimulation intensity to elicit ‘mild local pain’, referred pain was also experienced 9 out of 24 times. By a further small (statistically insignificant) increase in the intensity of the electrical stimulation, ‘mild referred pain’ was induced in all 12 subjects, without a statistically significant increase in the local pain intensity, and there was no statistically significant difference between the local and referred pain intensity rated on the VAS. When the electrical stimulation was increased to induce ‘moderate referred pain’, VAS ratings of pain intensity increased in the local and referred pain area, again without a statistically significant difference between these sites. All subjects reported a diffuse distribution of referred pain, i.e., had difficulties to exactly define the borders of the referred pain area. In addition, the sensation of referred pain was reported to have both superficial and deep components. No statistically significant differences were found between VAS ratings before and following QST, therefore these data were pooled. There was a statistically significant overall difference in VAS ratings of pain intensity during the various intensities of i.m. electrical stimulation (Friedman’s test; p < 0.001). The median VAS ratings of pain intensity in the stimulated area (m. infraspinatus sinister) were 5 mm (range 1–12 mm) during ‘mild local pain’, 5 mm (range 0–38 mm) during ‘mild referred pain’, and 20.5 mm (range 3–45 mm) during ‘moderate referred pain’. Post-hoc analysis did not reveal a statistically significant difference in pain intensity in the local area.
between 'mild local pain' and 'mild referred pain' stimulation, but the rated pain intensity during 'moderate referred pain' was significantly higher than during 'mild local pain' (p < 0.001) and 'mild referred pain' (p < 0.001), respectively.

The median VAS ratings of pain intensity in the referred pain area were 0 mm (range 0–9 mm) during 'mild local pain', 5.5 mm (range 1–15 mm) during 'mild referred pain', and 19 mm (range 6–25 mm) during 'moderate referred pain'. Post-hoc analysis revealed that the rated pain intensity was higher during 'mild referred pain' compared to 'mild local pain' (p < 0.001) and during 'moderate referred pain' compared to 'mild referred pain' (p < 0.001) (as well as 'mild local pain' (p < 0.001)).

The effect of local anaesthetic cream (EMLA)

The mean perception threshold to von Frey filaments was 0.72 g (SEM ± 0.24 g) before EMLA cream and 5.23 g (SEM ± 1.13 g) following EMLA cream (p < 0.001). All subjects could successfully discriminate the sharp and blunt end of a needle at both sides before EMLA. This ability was lost in all subjects following EMLA cream.

Quantitative sensory testing (QST)

Light-touch perception thresholds (LTTs) (Fig. 1)

A statistically significant effect was seen for factors condition (p < 0.001, F(3, 33) = 8.3) and side (p = 0.005, F(1, 11) = 12.4), as well as a statistically significant interaction between these factors (p = 0.026, F(3, 33) = 3.5). In the painful side, compared to baseline, LTTs were higher during 'mild local pain' (p < 0.007), 'mild referred pain' (p < 0.002), and 'moderate referred pain' (p < 0.001), while no differences were seen between the various stimulation conditions. No statistically significant differences were seen contralaterally. There was no statistically significant difference in LTTs between sides at baseline or during 'mild local pain', while LTTs were higher on the painful side during 'mild referred pain' (p < 0.02) and 'moderate referred pain' (p < 0.05), respectively.

Perception thresholds to innocuous cold (CTs) (Fig. 2)

A statistically significant effect was seen for the factor condition (p < 0.001, F(3, 33) = 24.6), while no such significant effect was present for the factor side (p = 0.910, F(1, 11) = 0.01), and there was no statistically significant interaction between the factors (p = 0.667, F(3, 33) = 0.5). Compared to baseline, CTs were bilaterally higher during 'mild local pain' (p < 0.001), 'mild referred pain' (p < 0.001), and 'moderate referred pain' (p < 0.001), while no differences were seen between the various stimulation conditions.

Perception thresholds to innocuous warmth (WTs) (Fig. 3)

A statistically significant effect was seen for the factor condition (p = 0.002, F(3, 33) = 6.0), while
no such effect was present for the factor side (p = 0.276, F(1,11) = 1.3), and there was no statistically significant interaction between the factors (p = 0.214, F(3,33) = 1.6). Compared to baseline, WTs were bilaterally higher during ‘mild local pain’ (p < 0.003), ‘mild referred pain’ (p < 0.03), and ‘moderate referred pain’ (p < 0.02), while no differences were seen between the various stimulation conditions. Statistically significant differences compared to baseline (p < 0.001).

Heat pain thresholds (HPTs) (Fig. 4)

No statistically significant effect was seen for the factors condition (p = 0.943, F(3,33) = 0.1) and side (p = 0.217, F(1,11) = 1.7), and there was no statistically significant interaction between these factors (p = 0.545, F(3,33) = 0.7). Power calculations indicate that to have a 80% power (standard deviation of differences of 2.2 °C, two-tailed significance level of 0.05) a sample size of 12 is needed to detect a difference in means of 2 °C.

Perception thresholds to cold pain (CPTs)

Eight subjects did not perceive pain during cold stimulation to 10 °C, three subjects reported cold pain at one stimulation each and only one subject consistently reported a cold pain sensation. Due to the limited number of subjects perceiving cold pain no statistical analysis was possible.

Pressure pain thresholds (PPTs) (Fig. 5)

A statistically significant effect was seen for the factor condition (p < 0.001, F(3,33) = 15.7), while no such effect was present for the factor side (p = 0.161, F(1,11) = 2.3), and there was no statistically significant interaction between the factors (p = 0.830, F(3,33) = 0.3). Compared to baseline, PPTs were bilaterally higher during ‘mild local pain’ (p < 0.02), ‘mild referred pain’ (p < 0.002), and ‘moderate referred pain’ (p < 0.001). The PPTs were higher during ‘moderate referred pain’ compared to ‘mild local pain’ (p < 0.008) and ‘mild referred pain’ (p < 0.05).
FIG. 4. Heat pain thresholds (HPTs) (°C). Data are presented as box plots. Horizontal lines indicate medians with 75th percentile at the top and 25th percentile at the bottom of the boxes; 90th and 10th percentiles are presented as whiskers. No statistically significant effect was seen for the factors side and condition and there was no statistically significant interaction between these factors. MLP = mild local pain, MRP = mild referred pain, MoRP = moderate referred pain.

while no statistically significant difference was seen between the latter two.

DISCUSSION

Methodological considerations

The present study has a number of limitations that should be kept in mind when interpreting the data. First, the referred pain was induced by i.m. electrical stimulation in m. infraspinatus (myotome C4-6), while the QST assessments were performed within the area of referred pain at the dorsolateral part of the upper arm (myotome C6-8; dermatome C5). Thus, while the assessed dermatome overlapped with the electrically stimulated segments, there was only a partial overlap for the myotomes which could have a bearing on the pressure algometry results (see discussion below). Furthermore, since no technique is available using a natural stimulus to reliably quantify intramuscular pain sensitivity, we turned to pressure algometry. Pressure algometry has been shown to be reliable (Kosek et al., 1993), and, although it mostly reflects deep sensitivity, PPTs are also influenced by the sensitivity of overlying skin (Kosek et al., 1999). Since we were interested in assessing cutaneous as well as deep sensitivity in the referred pain area, no anesthesia of skin that would have eliminated the skin component during pressure algometry could be used in the present study. Due to the limited number of QST assessments that can be performed in one session (to avoid fatigue), no distal site was included and thus the distinction between segmental and plurisegmental effects on sensitivity is outside the scope of this study. Furthermore, no suprathreshold painful stimuli were used during QST to avoid peripheral sensitisation. Instead, we chose to study stimulus-response relations for suprathreshold stimuli in the referred pain area during various intensities of referred pain in a separate study using one modality (Kosek &
Hansson, manuscript in preparation). For ethical reasons, the conditioning pain stimulus was kept at a low intensity. Therefore, the present results do not necessarily apply to higher pain intensities.

Potential mechanisms underlying the sensation of referred pain in the present study

Findings from studies using intraneural microstimulation of nerve fascicles supplying muscle show that by increasing the stimulus intensity the focal pain can be projected over a broader and less well-localised area (Marchettini et al., 1996) and pain is referred to areas not innervated by the stimulated nerve (Torebjörk et al., 1984). Further increase in pain intensity in the primary pain focus results in an increase in the area of referred pain (Torebjörk et al., 1984; Marchettini et al., 1996; Graven-Nielsen et al., 1997a,b). Several theories advocate that referred pain is due to a misinterpretation of the origin of inputs from an injured region, because input from the injured and referred pain regions to some extent converge on the same cells in the dorsal horn of the spinal cord or supraspinally (Ruch, 1949; Codere & Katz, 1997). However, in accordance with previous studies (Graven-Nielsen et al., 1997a) our subjects reported local pain only, and with increasing stimulus intensities local and referred pain. This is difficult to fully explain by convergence of input from the injured and referred pain regions onto the same cells, since it would require the neurones receiving the convergent input to change their projected fields with increasing input frequency. Rather, the topographic organisation of the primary somatosensory cortex (S1) (Dykes, 1978) has been taken to imply that localisation of a stimulus depends on the activated region of the S1. Thus, separate loci in the somatosensory cortex would be expected to be activated when pain is experienced concomitantly at separate sites of the body. As pointed out by Torebjörk et al. (1984), this would require, rather than convergence, divergence of pathways at some point in the CNS. If we accept this hypothesis, then low frequency afferent input from the injured area would excite only neurones with projected fields in the injured area and the subject would feel pain limited to that area. However, with increasing stimulus intensity/impulse frequency neurones with projected fields in the referred pain area would be activated which is perceived as referred pain by the subject. Thus, due to divergence, a larger pool of neurones would be firing when the local pain is accompanied by referred pain.

Other theories of referred pain are based on the assumption that afferent input from the injured area in different ways facilitates input from the referred pain area. According to the 'axon-reflex theory' referred pain depends on impulses arising in the injured deep tissue region producing a sensitisation of the referred pain area by means of an axon reflex mechanism (Sinclair et al., 1948). If this theory is correct, we would expect to find allodynia/hyperalgesia in the referred pain area related to the intensity of referred pain. The same finding would be expected according to the convergence-facilitation theory (Mackenzie, 1893) and the 'central sensitisation theory' (Mense, 1994), explaining referred pain by facilitation or excitation of neurones with nociceptive input in the spinal cord, at which axons from the local as well as the referred pain area terminate. In the present study, allodynia was not found for any assessed modality. Instead, a bilateral increase in PPTs related to the intensity of referred pain was found. Theoretically, facilitatory mechanisms could be counteracted by activation of endogenous inhibitory mechanisms and thus masked. However, referred pain was only perceived unilaterally. Thus, if facilitatory mechanisms would be of importance for the perception of referred pain, an increased sensitivity to somatosensory stimuli in the referred pain area as compared to the contralateral side would be expected. No such difference was seen in the present study. Therefore, based on assessment of perception thresholds to different stimulus modalities, our results do not support the notion that afferent input from the primary pain focus facilitates input from the referred pain area in the setting of experimentally induced pain. It should be pointed out, however, that assessment of perception thresholds only provides limited insights into mechanisms related to referred pain, and therefore no definite conclusions can be drawn from this study. In a study where sensitivity to suprathreshold stimuli in the referred pain area were assessed,
modality-specific somatosensory changes were found (i.e., increased sensitivity to electrotactile stimuli, decreased sensitivity to cutaneous radiant heat and pressure and no effect on sensitivity to contact heat stimuli) (Graven-Nielsen et al., 1997c). Further, net facilitation could be relevant for perception of referred pain in chronic pain patients as indicated by findings of increased sensitivity to threshold heat pain in patients with lateral epicondylalgia (Leffler et al., 2000b) and pressure pain in patients with trapezius myalgia (Leffler et al., submitted).

Quantitative sensory testing in the referred pain area

The bilaterally increased pressure pain thresholds, increasing further with increased local and referred pain intensity can only be explained by activation of segmental (bilateral) or plurisegmental inhibitory mechanisms. In the present study, we cannot distinguish between segmental and plurisegmental effects since QST has not been performed in body areas remote from the conditioning stimulus. In addition, there was only a partial overlap between the myotomes used for conditioning stimulation (C4-6) and sensory testing (C6-8), and so the pressure pain assessment was not performed in an area with complete overlap between the myotomes. Segmental inhibitory effects on noxious sensory neurones following stimulation of A delta and C fibers have been reported (Woollf, 1983; Chung et al., 1984a,b). The inhibitory effects were stronger when the intensity of the conditioning stimulation increased (Chung et al., 1984b). Powerful and selective widespread inhibition of wide dynamic range (WDR) neurones in the dorsal horn of the spinal cord by heterotopic noxious conditioning stimulation (HNCS) has been described as 'diffuse noxious inhibitory controls' (DNIC) (Le Bars et al., 1979a,b; Dickenson et al., 1980). DNIC-like effects in man have been shown to involve supraspinal structures (Roby-Brami et al., 1987; De Broucker et al., 1990) and heterotopic painful stimuli have been reported to increase pressure pain thresholds in humans (Kosek & Hansson, 1997; Graven-Nielsen et al., 1998), presumably by activation of DNIC. Following injection of hypertonic saline into m. tibialis anterior in healthy subjects, Graven-Nielsen et al. (1998) found increased PPTs in a heterotopic control site (atm) as well as in the referred pain area (ankle), and the degree of increased PPTs was positively correlated to the intensity of ongoing muscle pain. This is in accordance with our results and could be interpreted as activation of DNIC since, in addition, a significant positive correlation has been found between noception and activation of DNIC in animal studies (Le Bars et al., 1979a; Willer et al., 1984, 1989). Furthermore, recent results indicate the existence of a supraspinally mediated negative feed-back loop modulating the excitability of spinal cord dorsal horn neurones, triggered only when a critical area of the skin was subjected to noxious stimulation (Bouhassira et al., 1995). The authors reported that the responses of these spinal cord convergent neurones to noxious stimulation decreased progressively when the area of noxious skin stimulation reached, and then exceeded, a critical size. If we hypothesise that a larger number of spinal and supraspinal neurones are activated due to divergence, during perception of referred pain (see above), this supraspinally mediated negative feedback loop may be activated, explaining the bilateral increase in PPTs. The activation of endogenous pain inhibitory mechanisms affecting the referred pain area and the contralateral non-painful side alike, does not support theories arguing that the perception of referred pain would depend on facilitation of input from the referred pain area. On the contrary, our results indicate activation of endogenous inhibitory mechanisms interacting bilaterally.

In agreement with previous results no effect was seen on HPTs (Graven-Nielsen et al., 1997c; Leffler et al., 2000a) in the referred pain area, which is in accordance with the failure to alter HPTs during HNCS in humans (Kosek & Hansson, 1997; Kosek & Ordeberg, 2000b). However, the possibility of a statistical type II error must also be kept in mind.

We found increased perception thresholds to cold and warmth bilaterally, without a relation to the intensity of referred pain. In a previous study using HNCS, a temporal discrepancy in the elevation of innocuous thermal perception thresholds and PPTs was found (Kosek & Hansson, 1997), indicating the involvement of complex mechanisms. The complexity of these mechanisms was also illustrated.
by Pertovaara et al. (1982) who found that HNCS elevated dental pain thresholds in a naloxone-independent fashion and increased cutaneous perception thresholds to innocuous heat and cold in a partially naloxone-dependent fashion. Such obscure and complex interaction may explain why, in the present study, the sensitivity to innocuous thermal stimuli did not correlate with pain intensity, while the sensitivity to pressure pain did.

Even though HNCS has been shown to induce increased LTTs (Kosek & Ordeberg, 2000b), this was not found in the present study. Light touch was the only modality where the change in perception threshold was restricted to the area of referred pain (i.e., unilateral). This is in accordance with our previous findings of increased LTTs in the area of referred pain during pain provocation by injection of hypertonic saline (Leffler et al., 2000a), as well as during increased referred pain intensity following exercise in patients with unilateral lateral epicondylalgia (Leffler et al., 2000b). In patients with a variety of chronic pain conditions (Nathan, 1960) and patients with pain due to osteoarthritis of the hip (Kosek & Ordeberg, 2000a), improved sensitivity to tactile stimuli following pain relief has been reported. These results are in line with the 'touch gate' concept proposed by Apkarian et al. (1994), suggesting that nociceptive input may have an inhibitory effect on the perception of touch. Furthermore, while it is our clinical experience that patients rarely, if ever, report a sensation of cold/warmth in the referred pain area, paresthesias, numbness and pricking sensations are common. In the present study, subjects volunteered the information that they perceived paresthesias during i.m. stimulation even when no or only mild pain in the referred pain area was experienced. Thus, it is possible that the sensation of pain and/or other sensations in the referred pain area made it more difficult to distinguish the light touch stimuli, explaining the greater LTT variability and the increase in LTTs in the present study.

Clinical applications

The present study confirmed our previous findings of a rather constant inter-individual pattern of referred pain when stimulating a defined site in m. infraspinatus in healthy individuals. This is in accordance with the empirical knowledge that different muscles have characteristic patterns of pain referral (Travell & Rinzler, 1952) which could be useful for diagnostic and treatment purposes. Musculoskeletal pain conditions with referred pain to superficial and deep structures and concomitant signs of cutaneous sensory aberrations can be difficult to distinguish from neuropathic pain states. Therefore, it is of great clinical relevance to examine whether nociceptive pain give rise to characteristic patterns of sensory aberrations. Such insights may be useful for diagnostic purposes. QST may be used to assess patients when neuropathic pain is suspected. In these cases, the healthy contralateral side is often used as an intra-individual control. When compared with the contralateral side only an increase in LTT was seen in the referred pain area in the present study which is in accordance with previous results (Leffler et al., 2000a). Even though such a unimodal and minute change in sensitivity is rarely seen in patients with neuropathic pain conditions (Hansson, 1994; Lindblom, 1994), studies of patients with chronic long-term pain need to be performed to elucidate if profiles of somatosensory aberrations useful for diagnostic purposes can be identified.

In conclusion, during electrical i.m. stimulation in the left m. infraspinatus we found increased light touch thresholds in the referred pain area and a bilateral increase in perception thresholds to innocuous cold and warmth as well as to pressure pain. Pressure pain was the only modality influenced by the intensity of the local and referred pain. The decreased sensitivity to innocuous cold, warmth, and pressure pain indicated activation of endogenous inhibitory mechanisms acting bilaterally. We found no influence of pain intensity on somatosensory thresholds restricted to the area of referred pain and light touch was the only modality that was affected in the referred pain area only.

ACKNOWLEDGMENTS

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The association between psychological factors and oro-facial pain: a community-based study

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OBJECTIVE
To examine the hypothesis that psychological factors of psychological distress, maladaptive response to illness and perception of happiness in childhood, are associated with self-reported oro-facial pain (OFP).

METHOD
A cross-sectional population-based study was conducted in South-East Cheshire, UK. The adjusted participation rate was 74%, and 2504 adults aged 18–65 years participated in the study.

RESULTS
A report of not having had a happy childhood was associated with risk of 1.6 (95% CI 1.4–2.0) of reporting OFP. An increased propensity to report symptoms associated with OFP was seen for those individuals with higher levels of psychological distress measured using the general health questionnaire (GHQ) with the risk of 2.7 (95% CI 2.3–3.2) in the highest category. All components of the illness behaviour questionnaire (IBQ) were associated with presence of OFP. There was a linear increase in risk (test for trend, \( P < 0.01 \)) associated with the report of OFP for general hypochondriasis, disease conviction, affective inhibition, affective disturbance, and irritability. However, there was a significant decrease in risk with a high score for perception of illness (0.6; 95% CI 0.6–0.7) and denial (0.6; 95% CI 0.5–0.7). None of the factors showed significant change in estimates when adjusted for age and gender.

CONCLUSIONS
This large cross-sectional community-based study showed significant association for all of the factors considered. The obtained data raise interesting questions of cause and effect for which further, longitudinal studies are required to establish temporal relationship between these factors and the onset, cause, and treatment of OFP. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

KEYWORDS: oro-facial pain, general population, general health questionnaire, illness behaviour questionnaire, psychological factors, childhood events.

INTRODUCTION

It is now generally recognised that psychological factors play an important role in chronic pain (Gamsa, 1994a,b; Asmundson & Norton, 1999; Vlaeyen & Linton, 2000). Specific type of pain, oro-facial pain (OFP), can be defined as oral (pain within the mouth) and/or facial, which includes pain whose origin is below the orbitomental line,
above neck, and interior to the ears (Zakrzewska & Hamlyn, 1999). While the majority of studies investigating the role of psychological factors in aetiology of oro-facial pain involved people attending clinics, who may be different from general population (Drangsholt & LeResche, 1999; Zakrzewska & Hamlyn, 1999), a number of population-based cross-sectional studies reported relationships between psychological factors and OFP (Szentpetyery et al., 1987; Duckro et al., 1990; Egermark-Eriksson et al., 1990; Wanman & Agerberg, 1990; Vimpari et al., 1995). Systematic review of population-based epidemiological studies of oro-facial pain (Macfarlane et al., 2001) showed that there is need for conducting good quality population-based studies of oro-facial pain, and there is lack of studies in the UK, as the majority of the studies were conducted in Scandinavia. There have been no population-based studies of OFP, which specifically investigated the role of psychological factors (Macfarlane et al., 2001) in aetiology of oro-facial pain.

This study aims to examine the hypothesis that psychological distress, maladaptive response to illness, and retrospective perception of happiness in childhood are each individually associated with self-reported OFP.

MATERIALS AND METHODS

A simple random sample of 4000 people aged 18–65 years was selected from a General Medical Practice in South-East Cheshire (Borough of Congleton, North West England) of whom 2504 responded to the postal questionnaire (adjusted participation rate 74%, after exclusion of those that had moved, died, or who were not able to complete the questionnaire due to disability and did not understand English). The majority of the population of the UK (95%) are registered with a general medical practitioner. In addition, the Borough of Congleton has a socio-economic structure similar to England and Wales, therefore the participants can be considered representative of the general population. Non-respondents were followed up successively with a postcard reminder, a further postal questionnaire, and a short-version of the questionnaire. Those who had still not returned a completed questionnaire and had not declined to participate were contacted by telephone and offered a short interview. The survey commenced in October 1997 and was terminated at the end of July 1998. Ethical approval for the survey was granted by the local research ethics committee. The study was registered under the Data Protection Act.

The main question concerning OFP consisted of nine items (Locker & Slade, 1988) about various types of pain experienced over the past month at any moment. Oro-facial pain (OFP) was defined as present if the respondent had experienced pain during the past month in at least one of the following: in the jaw joint; in the area just in front of the ear; in or around the eyes; when opening the mouth wide; in the jaw joint when chewing food and in and around the temples. OFP was also recorded if there had been tenderness of muscles at the side of the face; prolonged burning sensation in the tongue or other parts of the mouth or shooting pain in the face or cheeks.

In view of suggestions that psychological stress in adult life is influenced by childhood experience, a dichotomous question ‘Did you have a happy childhood?’ was included in the questionnaire.

Participants completed the 12-item general health questionnaire (GHQ-12) (Goldberg, 1978), as the measure of psychological distress. This self-complete questionnaire was used to identify the recent onset of symptoms of psychological distress. It concentrates on two main areas: inability to continue normal functions and the appearance of new problems of a distressing nature, and is a screening instrument for mental disorder which has been successfully validated against a standard psychiatric interview in community, primary care, and tertiary clinic settings (Henderson et al., 1979; Tarnopolsky et al., 1979; Banks, 1983; Benjamin et al., 1991). Each item within the questionnaire consists of asking the subject whether they have recently (during the past few weeks) experienced a particular symptom, on a 4-point Likert scale.

The 30-item illness behaviour questionnaire (IBQ) (Pilowsky & Spence, 1983) was used to measure maladaptive responses to illness. This questionnaire was chosen because it was previously used on oro-facial pain patients (Speculand et al., 1981; Goss et al., 1990). Pilowsky (1967) defined abnormal illness behaviour as ‘an inappropriate or maladaptive mode of experiencing, evaluating, or
acting in relation to one’s own state of health, which persists, despite the fact that a doctor (or other recognised social agent) has offered accurate and reasonably lucid information concerning the person’s health status and the appropriate course of management (if any), with provision of adequate opportunity for discussion, clarification, and negotiation. The questions are grouped in seven dimensions: general hypochondriasis; disease conviction; psychological versus somatic perception of illness; affective inhibition; affective disturbance; denial; and irritability. Questions were modified to accommodate the general population. At the beginning of the questionnaire the following phrase was used: ‘Here are some questions about you and your facial/mouth pain, or an illness that you have had’. The phrase ‘When you are ill...’ was inserted into each question about illness. Due to administrative error one of the items of the IBQ (scale 6, denial) was omitted, therefore the maximum score was 2.

The magnitude of association between an exposure and OFP was described by the relative risk (RR). Continuous variables were categorised using percentiles (quartiles, tertiles, or median) of the overall distribution. Cox regression (Cox, 1972; Lee, 1994) was used to estimate relative risk adjusted for potential confounders (age and gender).

RESULTS

Description of study participants

The mean age of the participants was 44 (SD 13) years, of whom 55% were women. The prevalence of self-reported oro-facial pain was 26%. The one-month period prevalence decreased with age and was the highest in the age group 18–25 years (30%) and lowest in the age group 56–65 years (22%) (χ² test for trend, P = 0.007). The prevalence was higher in women than in men (30% versus 21%) (χ² test, P < 0.001).

Relationship between psychological factors and OFP

A report of not having had a happy childhood was associated with risk of 1.6 (95% CI 1.4–2.0) of reporting OFP and this result did not change after adjusting for age and gender (Table 1).

An increased propensity to report OFP was seen for those individuals with higher levels of psychological distress (Table 1); persons in the highest category of GHQ questionnaire were at almost three-fold increase in risk (2.7; 95% CI 2.3–3.2) and there was a significant trend of increase in RRs with increase of score (P < 0.001).

All components of the IBQ were associated with presence of OFP, with significant trend (P < 0.01) of increase in RRs with increase of score when there were more than two categories. None of the factors showed significant change in estimates when adjusted for age and gender.

The lowest crude risk in the highest score category was 1.3 (95% CI 1.1–1.6) for scale 4 (affective inhibition) and the highest 2.4 (95% CI 2.0–3.0) for scale 5 (affective disturbance). However there was a significant decrease in risk with a high score for scale 3 (perception of illness) (0.6; 95% CI 0.5–0.7) and scale 6 (denial) (0.6; 95% CI 0.5–0.7) (Table 1).

Relationship between perception of happy childhood, GHQ, and IBQ

There was significant relationship (P < 0.001) between the perception of a happy childhood, GHQ score, and all sub-scales of IBQ (Table 2). For example, only 5% reported an unhappy childhood among those with no psychological distress (GHQ score 0) while those who had highest GHQ score had a prevalence of unhappy childhood of 18% (test for trend, P < 0.001). Similar relationships were seen for all seven sub-scales of IBQ (P < 0.001) except scale 3 and scale 6, where the inverse relationship was found. Similarly, there was significant relationship between total GHQ score and all sub-scales of IBQs (P < 0.001) (Table 2).

DISCUSSION

The epidemiological data produced in this study stimulate potentially important hypotheses about the cause-and-effect relationships between levels of psychological distress, illness perceptions and behaviours, and current perceptions of oro-facial
TABLE 1. Association of psychological factors with OFP

<table>
<thead>
<tr>
<th>Factor</th>
<th>% with OFP</th>
<th>Total number in group</th>
<th>Crude RR (95% CI)</th>
<th>Adjusted for age and sex RR (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Happy childhood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
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<td>1955</td>
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<td>1.00</td>
</tr>
<tr>
<td>No</td>
<td>40.6</td>
<td>192</td>
<td>1.63 (1.35–1.96)</td>
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<td>GHQ</td>
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<td>0</td>
<td>16.6</td>
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<tr>
<td>1</td>
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<td>272</td>
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<td>2–4</td>
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<td>IBQ</td>
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<td>1</td>
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<td>2–8</td>
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<td>497</td>
<td>1.72 (1.45–2.04)</td>
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<td>Scale 2 (disease conviction)</td>
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<td>784</td>
<td>2.23 (1.77–2.81)</td>
<td>2.16 (1.67–2.80)</td>
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<td>Scale 3 (perception of illness)</td>
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<td>1589</td>
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<td>1.28 (1.08–1.51)</td>
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<td>29.3</td>
<td>533</td>
<td>1.30 (1.08–1.56)</td>
<td>1.37 (1.11–1.69)</td>
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<tr>
<td>Scale 5 (affective disturbance)</td>
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<td>17.8</td>
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<tr>
<td>1</td>
<td>31.4</td>
<td>491</td>
<td>1.76 (1.47–2.11)</td>
<td>1.71 (1.39–2.12)</td>
</tr>
<tr>
<td>2</td>
<td>36.5</td>
<td>329</td>
<td>2.04 (1.69–2.47)</td>
<td>1.96 (1.54–2.47)</td>
</tr>
<tr>
<td>3</td>
<td>43.2</td>
<td>213</td>
<td>2.42 (1.98–2.95)</td>
<td>2.30 (1.79–2.96)</td>
</tr>
<tr>
<td>Scale 6 (denial)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>36.1</td>
<td>595</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>22.2</td>
<td>1566</td>
<td>0.61 (0.53–0.71)</td>
<td>0.63 (0.53–0.74)</td>
</tr>
<tr>
<td>Scale 7 (irritability)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21.6</td>
<td>1038</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>29.4</td>
<td>574</td>
<td>1.36 (1.15–1.62)</td>
<td>1.37 (1.12–1.67)</td>
</tr>
<tr>
<td>2–3</td>
<td>32.8</td>
<td>481</td>
<td>1.52 (1.28–1.81)</td>
<td>1.54 (1.26–1.90)</td>
</tr>
</tbody>
</table>

Numbers do not add up to the total due to missing values.

Continuous variables were categorised using percentiles of the overall distribution.

Test for trend, $P < 0.001$.

Test for trend, $P = 0.003$.

pain. Where oro-facial pain is associated with significant psychological distress the most obvious two possibilities are either that the pain itself may produce the distress or that the existence of the psychological distress, whatever its cause, may lead to a high level of perception or reporting of oro-facial pain.

A large cross-sectional study that investigated association between physical and psychological morbidity (Stanfield et al., 1993) reported that overall health status and self-reported physical symptoms were strongly associated with psychiatric disorder (measured using GHQ questionnaire), and the authors suggested that psychiatric disorder is likely to be secondary to the pain. Two large prospective studies in the US (Magne et al., 1994) and UK (Hotopf et al., 1998) found that there is a relationship between psychological distress and
Studies of other regional pains (back pain, shoulder pain) demonstrated a relationship with psychological distress, which shows that there are similarities between regional pains (Croft et al., 1995; Pope et al., 1997).

The current study is the first population-based study of OFP and associated factors in the UK. Overall, 26% of adults reported OFP during the past month, which is similar to that reported previously in other countries (Agerberg & Carlsson, 1972; Locker & Grushka, 1987; Salonen et al., 1990; Locker et al., 1991). The study achieved a satisfactory participation rate and is comparable to the 75% achieved in two previous studies of chronic pain in the North-West of England (Croft et al., 1993; Hunt et al., 1999). While the non-response bias may influence the estimate of prevalence rate, it is unlikely that it has affected the actual relationship between psychological factors and OFP.

Overall, the current cross-sectional study highlights a number of important features involving the occurrence of OFP. It showed that participants who reported not having had a happy childhood had an increased risk of reporting OFP compared to those with a happy childhood. Assuming that adverse childhood events determine the happiness of childhood, the results support the findings of other studies, while caution is necessary. It is not possible to fully validate such reports, and they may be susceptible to differential recall between those who currently have and do not have pain. Hypotheses have been proposed relating to the childhood origins of increased levels of psychological distress, to adult psychiatric illness (Mullen et al., 1993; Kessler et al., 1997; Fillingham et al., 1999), and fibromyalgia (a pain disorder) in patients attending clinic (Schuessler & Konermann, 1993; Boisset Pioro et al., 1995). In addition, somatisation, which is also associated with reports of adverse childhood events, has also been associated with fibromyalgia (Kellner, 1994). It has also been demonstrated that reports of adverse events in childhood, such as the separation or death of parents or abuse, and perceived paternal overprotection, or lack of care are strongly associated with a high tender point count (McBeth et al., 1999).

Another factor found to be an important correlate of self-reported OFP is psychological dis-

---

**TABLE 2. Relationship between GHQ, IBQ, and perception of happiness in childhood**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Happy childhood (N (%) with no happy childhood)</th>
<th>GHQ (N (%)) with high score (5-12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58 (5.1)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>21 (7.9)</td>
<td></td>
</tr>
<tr>
<td>2-4</td>
<td>47 (13.7)</td>
<td></td>
</tr>
<tr>
<td>5-12</td>
<td>63 (18.2)</td>
<td></td>
</tr>
<tr>
<td>IBQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale 1 (general hypochondriasis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>66 (6.3)</td>
<td>111 (10.6)</td>
</tr>
<tr>
<td>1</td>
<td>47 (9.8)</td>
<td>86 (17.7)</td>
</tr>
<tr>
<td>2-8</td>
<td>61 (12.6)</td>
<td>135 (27.4)</td>
</tr>
<tr>
<td>Scale 2 (disease conviction)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (5.3)</td>
<td>27 (5.9)</td>
</tr>
<tr>
<td>1</td>
<td>44 (6.2)</td>
<td>75 (10.8)</td>
</tr>
<tr>
<td>2-6</td>
<td>58 (12.9)</td>
<td>222 (28.7)</td>
</tr>
<tr>
<td>Scale 3 (perception of illness)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>70 (13.7)</td>
<td>124 (23.9)</td>
</tr>
<tr>
<td>2-4</td>
<td>113 (7.3)</td>
<td>220 (14.1)</td>
</tr>
<tr>
<td>Scale 4 (affective inhibition)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>56 (6.6)</td>
<td>93 (10.9)</td>
</tr>
<tr>
<td>1</td>
<td>64 (9.0)</td>
<td>139 (19.4)</td>
</tr>
<tr>
<td>2</td>
<td>66 (12.7)</td>
<td>117 (22.2)</td>
</tr>
<tr>
<td>Scale 5 (affective disturbance)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>50 (4.6)</td>
<td>57 (5.2)</td>
</tr>
<tr>
<td>1</td>
<td>41 (8.6)</td>
<td>88 (18.1)</td>
</tr>
<tr>
<td>2</td>
<td>40 (12.7)</td>
<td>101 (30.8)</td>
</tr>
<tr>
<td>3</td>
<td>53 (26.2)</td>
<td>102 (49.0)</td>
</tr>
<tr>
<td>Scale 6 (denial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>101 (17.5)</td>
<td>186 (32.0)</td>
</tr>
<tr>
<td>2</td>
<td>90 (5.9)</td>
<td>169 (11.0)</td>
</tr>
<tr>
<td>Scale 7 (irritability)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>67 (6.6)</td>
<td>118 (11.6)</td>
</tr>
<tr>
<td>1</td>
<td>55 (9.8)</td>
<td>100 (17.6)</td>
</tr>
<tr>
<td>2-3</td>
<td>62 (13.1)</td>
<td>128 (25.9)</td>
</tr>
</tbody>
</table>

pain, which appears to operate both ways. A high level of psychological distress at baseline was a predictor of the onset of future pain, and the presence of pain at baseline was associated with future psychological distress.

The work of Melzack and Wall (1965) suggested that emotional state can influence the perception of pain and cause individuals to develop new symptoms. Recent evidence has suggested that psychological problems can manifest as somatic symptoms, sometimes referred to as 'masked depression' or in extreme cases, somatisation and these symptoms are not restricted just to the face.
tress, measured here by the GHQ questionnaire. This supports the results of other cross-sectional (Szentpetery et al., 1987; Von Korff et al., 1988; Duckro et al., 1990; Wanman & Agerberg, 1990; Vimpari et al., 1995) and case-control (Fine, 1971; Marbach et al., 1988; Gerke et al., 1990; Beaton et al., 1991; Niimi et al., 1993; De Leeuw et al., 1994) studies that showed an association between different measures of psychological distress and oro-facial pain.

No other population-based study of OFP has investigated maladaptive response to illness, and the results strengthen the findings of hospital-based case-control studies of OFP and other types of pain (Pilowsky et al., 1977; Speculand et al., 1981, 1983; Gerke et al., 1990; Bassett et al., 1990; Goss et al., 1990).

Mechanic and Volkart first introduced the term ‘illness behaviour’ in 1960 (Mechanic & Volkart, 1960). The concept of illness behaviour provides a useful way of understanding and describing the many psychological influences that affect how people monitor their bodies, define and interpret their symptoms, come to view themselves as sick and disabled, take remedial action, and use lay and professional sources (Mechanic, 1978). This concept draws on psychological theories of perception, cognition, and meaning attribution and on theories of social relationships. There is a difference between the concepts of disease and illness. While disease refers to a specific physiological or psychological dysfunction, illness is a subjective state of a person who feels aware of being ill (Last, 1995). Therefore, illness behaviour is a dynamic response to changing bodily sensations. It reflects not only the individual’s psychological predisposition, but also broader socio-economic and cultural contexts within individual’s views.

If we assume that the psychological distress leads to a high level of perception or OFP, then the presentation of oro-facial pain could be interpreted as a specific variant of somatisation which might in principle be amenable to psychological therapeutic intervention. The assumption that the pain itself may produce the distress should not however be seen as ruling out the relevance of psychological interventions, and a combined dental/psychological intervention might be appropriate.

In either case a combined dental/psychological assessment process, even if not intervention, is probably going to be needed for those individuals for whom the intensity or duration of their oro-facial pain produces a continuing health problem.

Relationships between pain, psychological distress, and maladaptive response to illness or cognition may help to inform the type of psychological interventions of value in this context. If particular patterns of maladaptive response to illness are seen to be correlated with higher levels of pain or distress these may need to be the focus of psychological interventions attempting to change behaviour. The use of cognitive psychological strategies to clarify and alter attributions or to enhance perceptions of self-efficacy in pain control could be useful in this respect.

The limitation of cross-sectional study design is that it cannot differentiate temporal cause of events, i.e., whether psychological distress precedes pain or whether it is consequence of it. Therefore to fully understand aetiology, it is necessary to conduct prospective studies. An important next step in this work would be the collection of longitudinal data on these variables within the present or similar populations. This should help to clarify cause-and-effect relationships and to refine psychological models that could then be used in a therapeutic, randomised controlled trials framework, for individuals whose oro-facial pain problems justified such clinical interventions.

In summary, this cross-sectional community-based study adds important information on the relationship between psychological factors and OFP, showing a positive association for all of the factors considered. It is possible that these characteristics contribute to the development of OFP, however further longitudinal studies are required to establish temporal relationships.

ACKNOWLEDGMENTS

The authors are grateful to staff and patients of Lawton House Surgery for their help with the study and Dr. A. Jones for advice on aspects of the questionnaire design.
REFERENCES


Prevention of postherpetic neuralgia with varicella-zoster hyperimmune globulin

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Recovery after an acute attack of herpes zoster is followed by postherpetic neuralgia (PHN) in 9–14% of all patients. Depending on the patient's age, the severity of the acute attack of herpes zoster and the dermatome involved, the incidence of PHN may be as high as 65%. The purpose of our study was to ascertain the incidence of PHN after a prophylactic intravenous injection of varicella-zoster hyperimmune globulin (VZV-IG) (Varitact Biotech Pharma). For this double-blind placebo-controlled randomised investigation we defined PHN as pain confined to the dermatome previously affected by herpes zoster, and we required a pain intensity of at least 15% points on a visual analogue scale (VAS) for this dermatome. The inclusion criteria were the dermatological diagnosis of herpes zoster together with age over 50 years. On Day 1, 20 patients received a single intravenous infusion of VZV-IG in a dose of 2 mL/kg body weight, 20 patients (control group) received a single infusion of human albumin 5% in a dose of 2 mL/kg body weight. All patients received acyclovir intravenously in a dose of 15 mg/kg body weight per 24 h for 5 days. The patients were followed up for a total of 42 days. The incidence of PHN at Day 42 was selected as the main outcome criterion for assessing the efficacy of prophylaxis. On reaching a significant difference between the groups (t test; z < 0.05) in favour of the active treatment group, prophylaxis of PHN by VZV-IG was assessed as effective. Pain was assessed on a VAS and a NAS. As auxiliary outcome criteria, we used the McGill Pain-Rating Questionnaire in its German version, the revised multidimensional pain scale (RMSS) and the Freiburg symptom list (FBL). All results were assessed by the t test (z < 0.05). The frequency of PHN in the placebo group was 70% (14/20), in the active treatment group it was 35% (7/20) at Day 42. The results of the McGill test showed the variability of the perception of pain in the placebo group significantly greater. No significant group differences were found in the FBL. Being tested with the RMSS, the patients of the placebo group assessed their pains as significantly 'more obstinate' (p = 0.047). The results can be summed up by saying that VZV-IG not only reduces the incidence of PHN, but also that in certain respects the patients' assessments of their pain experience were different. In our study we found a 50% reduction in PHN incidence. However, the outcome time point of our trial was so close to the acute phase of the zoster illness that spontaneous remissions of PHN still have to be taken into account. Despite the widely varied approaches to the problem, reliably effective therapy, let alone 100% prevention of PHN, is still not feasible. © 2002 European Federation of Chapters of the International Association for the Study of Pain. Published by Elsevier Science Ltd. All rights reserved.

KEYWORDS: postherpetic neuralgia, immune globulin, varicella-zoster virus, prophylaxis, double-blind placebo-controlled randomised investigation.

INTRODUCTION

Recovery after an acute attack of herpes zoster is followed by postherpetic neuralgia (PHN) in
9–14% of all patients. Depending on the patient's age, the severity of the acute attack of herpes zoster and the dermatome involved, the incidence of PHN may be as high as 65% (Loeser, 1986; Portenoy et al., 1986; Watson & Evans, 1986; Wood, 1991). This chronic painful condition may persist for years or even decades and the pain may be extremely intense. The pain is typically burning in character, and is frequently associated with dysesthesia, hyperalgesia, hypoalgesia, hypaesthesia, disorders of sympathetic function and, in up to 80% of patients, with alldynia (Baron & Sagué, 1993; Dworkin & Schmader, 2001; Hugler et al., 1992; Nurminsko et al., 1990, 1991).

The cause of pre-zoster and peri-zoster pains may be the acute inflammatory reaction (Mumenthaler, 1985; Wassilew, 1988; Wood, 1991). These pains can be relieved with anti-inflammatory drugs, by sympathetic nerve block or by blocking sensory nerves (Wassilew, 1988; Wood, 1991).

The pathogenesis and pathophysiology of PHN are discussed in detail in the current literature, but no satisfactory explanation has yet been given (Chen, 1991; Nurminsko et al., 1991; Wulf & Baron, 1997; Zenz et al., 1994).

The question of prophylaxis against PHN is posed by nearly all authors, but up to the present time the necessary scientific investigations in the form of double-blind prospective studies are lacking for almost all the conceivable treatments, with the exception of virustatic therapy (Wulf & Baron, 1997). The pre-emptive use of amitriptylin is the only evidence-based treatment: a randomised, double-blind, placebo-controlled trial showed a reduction in the incidence of PHN from 35.3% to 15.8% at 6 months (Bowsher, 1997). Although the pathophysiological mechanisms involved in PHN are still largely unknown, it seems reasonable to assume that there are lesions of the peripheral afferent pain pathways and inflammation-induced damage to afferent ganglia in the spinal cord.

The purpose of our study was to ascertain the incidence of PHN after a prophylactic intravenous injection of varicella-zoster hyperimmune globulin (VZV-IG) (Varitent Biotest Pharma).

METHODS

Several different definitions of PHN are to be found in the literature (Dworkin & Portenoy, 1994; Dworkin & Schmader, 2001), and these inconsistencies hamper any comparative appraisal of therapeutic or prophylactic measures. The definition of PHN ranges from pain persisting after the rash heals to pain persisting 30 days or 6 months after the onset of herpes zoster (Cunningham & Dworkin, 2000). Some experts consider all pain during and after herpes zoster as a continuum. Therefore it was suggested that this total duration of pain and pain 3 months after onset of herpes zoster be used as endpoints in clinical studies (Dworkin & Portenoy, 1996; Dworkin et al., 1997). In order to recognise early differences we defined PHN as prolonged zoster pain confined to the dermatome previously affected by herpes 42 days after the diagnosis of acute herpes zoster. In addition, we required a pain intensity of at least 15% points on a visual analogue scale (VAS) for this dermatome.

In all, 40 patients, divided into two groups of 20 each, were enrolled for this randomised placebo-controlled double-blind trial. The inclusion criteria were the dermatological diagnosis of herpes zoster together with age over 50 years. Exclusions comprised patients previously treated with immunoglobulins or with blood or plasma products, unless this medication had been discontinued at least 6 weeks before the onset of the attack of zoster. Other reasons for exclusion were pre-existing virustatic treatment, long-term medication with antirheumatics, corticosteroids, nonsteroidal analgesics, anti-inflammatory drugs, adamanine or benzodiazepine derivatives, and also a granulocyte count below 750 mm$^{-3}$, a platelet count below 50,000 mm$^{-3}$, or any impairment of renal function (serum creatinine above 180 μmol/L). Patients with a previous history of psychiatric and/or neurological abnormalities were not accepted.

The study was approved by the Ethics Commission of the Ruhr-University of Bochum. All patients gave their written consent to participation in the trial.

Patients were randomly assigned to receive either VZV-IG or placebo infusion. All persons participating in the trial were 'blinded'. The trial

European Journal of Pain (2002), 6
medication and the control medication were prepared for infusion in the pharmacy of the St. Elisabeth Foundation. Both infusion solutions were concealed by an opaque covering and administered through opaque tubing so that neither the doctor who performed the infusion nor the patient could distinguish between them. The blinding was terminated after the entire study had been completed. The possibility to terminate blinding in individual patients in the event of any symptoms which could conceivably be interpreted as side effects of either the trial or the control medication, was not used. The analysis was performed after unblinding, after all the investigations had been completed.

On their admission to the study (Day 1) not exceeding 48 h after onset of herpes zoster, 20 patients received a single intravenous infusion of VZV-IG in a dose of 2 mL/kg body weight. Twenty patients (control group) received a single infusion of human albumin 5% in a dose of 2 mL/kg body weight on admission to the study (Day 1). All patients received acyclovir intravenously as basic therapy in a dose of 5 mg/kg body weight three times daily (every 8 h) for 5 days.

The patients were followed up for a total of 42 days.

The incidence of PHN at 42 days was defined as the main outcome criterion for assessing the efficacy of prophylaxis. All patients included in the trial would be assessed in terms of the main outcome criterion. If examination on Day 42 was not performed in any patient, he or she would be counted as a case of failed therapy, in other words as a nonresponder.

We defined PHN as subjective pain in the dermatome which had previously shown the changes of zoster. Pain was assessed on a VAS 100 mm long ranging from ‘No Pain’ to ‘The Worst Imaginable Pain’, and had to reach at least 15%. In addition, the subjectively perceived pain intensity was assessed by means of a numerical analogue scale (0–100).

As secondary outcome criteria, we measured the characteristics of the pain with the McGill Pain Rating Questionnaire in its German version (Stein & Mendl, 1988), the revised multidimensional pain scale (RMSS) (Cizkin, 1983) and the Freiburg symptom list (FBL, repetition form) (Fahrenberg, 1975). The results of the McGill test were evaluated by the method devised by Melzack (1975). Dropouts were permitted for the secondary outcome criteria.

All results were assessed by the Student’s t test in order to discover differences between the groups. A significance level of α ≤ 0.05 (towisided) was used. All statistical investigations were performed with the PC-Program SPSS 8.0.0 for Windows.

General experience indicates that in this population PHN is to be expected in some 60% of cases of zoster. Cause of the high costs of this PHN prevention, a legible improvement of this rate was asked for. A difference of 40% points (occurrence of PHN in 20% of the cases) was regarded as clinically relevant. To obtain a maximum power, the t test for independent samples was performed to compare the rates of success. The test is very robust even in the analysis of thus binary criteria (Heeren & D’Agostino, 1987). With the intended numbers of patients, the power of the trial to detect such a difference was 80%.

RESULTS

From 1992 to 1996, 40 patients were randomised into two groups and enrolled in the trial. Each group comprised 11 female and 9 male patients. Their demographic data and the results of examination on enrolment are shown in Figs. 1, 2 and 9.

![FIG. 1. Demographic data of patients in Group 1 (human albumin).](European Journal of Pain (2002), 6)
We found no differences between the groups as regards their preclinical care or symptoms (see Fig. 3).

The parameters for subjective perception of pain intensity, checked on admission to the study, showed no specific differences between the groups, and the same was true of the pain parameters in the McGill test.

The RMSS lays down the following pain perceptions: general pain, pain radiation, chemical pain sensation, electricity-like pain sensations, obstinacy of pain, intensity of pain, distress due to pain, rhythm of pain perception, stabbing pain perception, and thermal pain perception. With the exception of the item ‘rhythm’ there were no conspicuous differences between the groups on admission to the trial.

The FBL formulates and appraises pain-dependent symptoms as items: ‘general’, ‘attention’, ‘cardiovascular’, ‘stomach’, ‘pain’, and ‘total’. In this trial there was a conspicuous difference between the groups for the item ‘stomach’.

Although there were significant differences in one pain criterion of the FBL and in one criterion of the RMSS before the trial began, we consider that the groups are acceptably comparable in terms of the outcome criteria. There were no differences for the direct pain parameters VAS (NAS) or the McGill test, or for the demographic data or the preclinical course. Even the affected dermatomes showed good agreement, although no patients with generalised herpes zoster were included in Group 2 (Fig. 2).

On Day 42, after the start of the study, statements from only 37 patients were available for evaluation. Two patients from the treatment group and one patient from the placebo group had withdrawn from the trial on their own wish. One patient from the treatment group was a Croatian citizen and left Germany before the end of the trial. One patient from each group withdrew while the trial was in progress without giving any reasons, though there was no complaint of pain despite repeated enquiries.

On Day 42 all 40 patients were included in evaluation of the main outcome criterion ‘postherpetic neuralgia’. All patients for whom the outcome criterion ‘postherpetic neuralgia’ was not assessable were counted as nonresponders, i.e., as patients having more than 15% points VAS pain severity.

For the secondary outcome criteria the patients’ actual statements were assessed. Depending on the mode of testing, this therefore means that the entire series of 40 patients was not evaluated by every test.

The patients’ skin lesions had healed on average by Day 7. There was no perceptible difference between the groups ($p = 0.35$).

The mean duration of in-patient treatment for herpes zoster was 8 days. Here too there were no differences between the groups ($p = 0.165$).

There were no adverse reactions or side effects attributable to the VZV-IG infusion.

The inclusion criterion age > 50 was chosen so as to select a group of herpes zoster patients at high risk of PHN. The mean age in Group 1 was 67.65 years and in Group 2 was 71.6 years. This meant that we could confidently expect an incidence of PHN of around 60%.

The frequency of PHN in the placebo group (human albumin 5%) was in fact 70%. At Day 42 13 out of the 20 patients reported more than 15% points on the VAS pain scale; in addition, one patient who had withdrawn from the trial prematurely was assessed as a PHN patient, while six patients (30%) did not reach this pain threshold (Fig. 6). In the active treatment group (VZV-IG) there were five patients with a VAS reading above 15% points on Day 42, and in addition two