Reversibility of central neuronal changes in patients recovering from gallbladder stones or acute cholecystitis

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INTRODUCTION

Cholecystectomy in patients with gallstone disease usually relieves the symptoms. However, it has repeatedly been demonstrated that 5%-10% of the patients still suffer from severe pain, and even more patients (25%-40%) have milder symptoms[6-8]. The explanations for continuing symptoms are multiple. An underlying organic disorder can be demonstrated in some patients, but no well-defined diagnosis can be identified in a substantial number of patients. Previous studies have shown that some of the patients suffer from sphincter of Oddi dysfunction (SOD). This condition can be relieved by endoscopic sphincterotomy[11-13]. Others have suggested a more generalized intestinal motor disorder in which SOD may be a component[6-8]. In previous studies we have demonstrated that patients with uncomplicated gallstone disease or acute cholecystitis have an increased sensibility in the referred pain area (RPA), probably reflecting neuroplastic changes and hyperexcitability in the central nervous system[9,10]. Animal studies have shown that such changes are frequently persisting even though the initial cause is eliminated[11]. We therefore hypothesized that continuing central neuronal changes could be the cause of continuing pain in some of the patients. However, we were not able to support this hypothesis in subsequent investigations[10]. Since these studies were carried out shortly after cholecystectomy, the possibility still remains that neuroplastic changes could occur at a later point of time.

Accordingly, the aim of the present study was to evaluate the sensibility in the referred pain area in patients who underwent cholecystectomy some years earlier, and to correlate possible abnormalities to the clinical condition of the patients.

MATERIALS AND METHODS

Patients

Two groups of Fifty-five patients were included in this study and divided into two groups. These were patients from the previous gallbladder stones and acute cholecystitis studies[6-8]. The first group consisting of 36 patients was tested prior to their cholecystectomy and then approximately 4 wk following the surgery. These patients were contacted and asked to participate in the follow-up study. Twenty-five entered the study, one man and 24 women, with a median age of 48 years (range 25-68 years). The reason for not entering the study was either that they did not want to (six patients) or we were not able to locate

Abstract

AIM: To investigate the referred pain area in patients 2-7 years after cholecystectomy in order to test the hypothesis that neuroplastic changes could give rise to post cholecystectomy pain.

METHODS: Forty patients were tested. Twenty five were cholecystectomized due to uncomplicated gallbladder stones and 15 because of acute cholecystitis. Sensitivity to pinprick, heat, cold, pressure and single and repeated electrical stimulation was studied both in the referred pain area and in the control area on the contra lateral side of the abdomen.

RESULTS: Five patients still intermittently suffered from pain. But in the objective test of the 40 patients, no statistical significant difference was found between the referred pain area and the control area.

CONCLUSION: This study does not support the hypothesis that de novo neuroplastic changes could develop several years after cholecystectomy.
Protocol

The patients were interviewed focusing on any relevant pain or medication. Each patient was asked to express the degree of pain during any attacks similar to what they knew as gallstone-attacks from their experience prior to the cholecystectomy. The pain was described in terms of intensity, localization, number of attacks, duration, physical activity, accompanying symptoms, and use of the visual analogue scale (VAS) anchored at 0 (no pain) to 10 (worst imaginable). After the interview the patients were tested with the same equipment to evoke pain as in the previous studies\(^1\),\(^2\). For testing of somatosensory sensitivity the patients were asked to assign the area under the right curvature/epigastrium where the pain was referred to during the previous disease. This area was assumed to be the area of initial referred pain (RPA). Then a symmetrical area was marked under the left costal margin to represent the control area (CA). The subsequent sensory assessment was performed at the centre of these areas. The experimental sensory testing with different modalities (see below) was used for measuring superficial/deep and sensory/pain thresholds in the RPA and CA. The sensory testing was first applied in the CA and then in the RPA.

Pinprick

The sensitivity to touch was determined using a Von Frey hair with a bending force of 6.6 g (SenseLab, Somedic AB, Stockholm, Sweden), which was pressed against the skin until bending of the hair occurred. The two skin areas were stimulated consecutively, and the patients were asked if it was painful or if they felt any difference between the two areas. The perception of the pinprick was rated as 'similar', 'greater', or 'painful'.

Pinching

The sensitivity of pain to the pinching stimulation was determined bilaterally using an electronic pressure algometer (Somedic AB, Stockholm, Sweden) mounted with a 1 cm\(^2\) probe, connected to a plastic clamp. A skin fold was placed and pinched between the clamp. The pinching was gradually increased at 10 kPa/s, and the patients pushed a stop button when the pain detection threshold was reached. The mean of three trials, with an interval of a minimum of 20 s between each trial, was used in the subsequent calculations.

Thermal stimuli

The sensitivity to thermal stimuli was tested in the two areas using two 4 cm\(^2\) metal rollers, which prior to testing were placed in water baths with temperatures of 0°C and 40°C, respectively. The cold and warm rollers were held in contact with the skin for 3 s in the two areas, and immediately after the stimulus the patients were asked to rate possible differences in sensation (lesser, similar, greater, or painful) between the two zones. The cold stimulus was applied first.

Electrical stimuli

A constant current electrical stimulator controlled by a computer (Aalborg University, Denmark) was attached to two electrodes (Neuroline, Disposable Neurology Electrodes, type: 720-01-K; Medicotest A/S, Ølstykke, Denmark). The electrodes were applied to the RPA and CA. Five constant currents, 1ms rectangular pulses applied at 200 Hz, were defined as a ‘single burst stimulus’. When this single stimulus was repeated five times at 2 Hz, it was defined as a ‘repeated burst stimulus’. This repeated paradigm was used to measure temporal summation\(^13\)\(^-\)\(^15\). The patients were instructed to indicate when the single and repeated stimuli could be felt (sensation threshold), and when pain was perceived (pain detection threshold). The stimulation was started at 0.2 mA, and the current was gradually increased in steps of 0.1-1.0 mA until the actual threshold was reached. The patients could interrupt the stimulation at any time during the experiment.

Pressure stimuli

The sensitivity of pain to the pressure stimulation was determined bilaterally using an electronic pressure algometer (Somedic AB, Stockholm, Sweden) mounted with a 1 cm\(^2\) probe. The pressure was gradually increased at 50 kPa/s, and the patients pushed a stop button when the pain detection threshold was reached. The mean of three trials, with an interval of a minimum of 20 s between each trial, was used in the subsequent calculations.

General hypersensitivity

Hypersensitivity in general was defined as three or more pain-modalities showing hypersensitivity in the RPA compared to the CA and no modalities demonstrating hypersensitivity in the CA compared to the RPA. All patients were tested in the pain free period.

Statistical analysis

Data were described as median (range). For comparison of the sensation to pinprick, heat and cold in the RPA and CA, the McNemar test for dichotomous paired data was used. The sensation and pain thresholds for pinching, electrical and pressure stimuli in the two areas were compared using the Mann-Whitney test. Correlation analysis was performed with Pearson's test. \(P < 0.05\) was considered statistically significant.

Ethics

The study was conducted in accordance with the Helsinki Declaration. All patients gave their verbal and written consent following verbal and written information.

RESULTS

The median time interval between cholecystectomy and the investigation was 35.6 (27.7-58.1) mo for the first group.
of patients and 74.9 (62.2-87.8) mo for the second group. The majority of patients no longer had pain in the relevant region. Five patients (12.5%) still intermittently suffered from pain similar to the pain they remembered during the precholecystectomy period localized to the original region (Table 1). The general picture showed some diversity in terms of pain description. One patient had daily attacks of pain and another only two to three attacks every year. One patient had attacks lasting seconds and in another case the duration of pain was days. The mean VAS-score under attacks was 6.6.

Only three patients had general hypersensitivity in the RPA compared to the CA (Table 2). There were no overlaps between the five patients informing of actual intermittent pain and the three patients who had generalised hypersensitivity in the RPA.

**Sensory test**

Using Von Frey hair the presence of increased sensitivity in the RPA was detected in three patients (7.5%) but three other patients (7.5%) experienced increased sensitivity in the CA (P > 0.05). No patient had allodynia (painful response to a stimulus that does not normally provoke pain).

When cold stimulation was applied increased sensitivity was found in the RPA in 12.5% of the cases and again 12.5% experienced increased sensitivity in the CA (P > 0.05). No patient had allodynia. Using heat stimulation, increased sensitivity was found in the RPA in 10% of the cases and 12.5% experienced increased sensitivity in the CA (P > 0.05). None of these patients reported that pain was evoked.

**Quantitative assessment**

The pinching pain threshold was 176.5 kPa (4-1057 kPa) in the RPA and 213.5 kPa (7-660 kPa) in the CA (P > 0.05).

**Sensation to electrical stimuli:** The sensation detection threshold for single burst electrical stimuli was 0.6 (0.3-2.5) mA in the RPA and 0.6 (0.2-1.4) mA in the CA (P > 0.05). The pain threshold for single burst electrical stimuli was 9 (1.0-30.5) mA in the RPA and 9.3 (0.9-35.4) mA in the CA (P > 0.05).

**DISCUSSION**

In the present study, no evidence for long lasting or _de novo_ central neuronal changes were found 2-7 years after uncomplicated gallbladder stones or acute cholecystitis. Somatosensory hyperalgesia in the referred pain area (RPA) has previously been reported in different groups of patients. The phenomenon is the result of direct or indirect convergence of nerve fibres from visceral and somatic tissue at the spinal and/or even the supraspinal levels, and the RPA therefore, most likely, reflects central changes in neurons receiving convergent afferent information from both the visceral and somatic systems. Hyperexcitability of neurons in the central nervous system (CNS) may theoretically explain why some patients suffer from pain although the original disease has resolved. In other words, continuous visceral pain stimuli can lead to a hypersensitive cutaneous area, where a stimulus that does not usually cause pain is perceived as painful (allodynia). This central sensitization is characterized by neuroplastic findings such as increased spontaneous activity, decreased firing threshold, and expansion of the receptive fields of pain.
spinal neurons. The primary objective of this study was to investigate a group of patients who tested twice during and after acute cholecystitis or uncomplicated gallbladder stones. We searched for any persisting changes in the RPA reflecting central hyperexcitability in exactly the same way as in the initial studies shortly after surgery. In these studies, hyperalgesia in the RPA was found and the abnormal sensation disappeared after surgery. Other studies have shown that muscular hyperalgesia tends to persist for a long time, outlasting the duration of the initial pain and that muscular hyperalgesia in the RPA could be experienced several years after elimination of renal stones. These findings by Italian colleagues were not confirmed in our work, where the experimental findings in the RPA in patients with uncomplicated gallstone disease in the pain free period were not dependent on intensity or duration. The statistical analysis showed no significant correlations between the pain thresholds to single and repeated electrical or mechanical stimuli in the RPA. This absence of correlation between hyperalgesia in the RPA in the pain free period, can therefore be caused by too short duration and relatively low intensity of the painful episodes. The duration of the pain attacks was much shorter and the intensity was lower than in above-mentioned studies with unilateral renal/ureteral colics (where the duration was around 5-10 d with high intensity). An alternative explanation for the lack of correlation could be that our method was insufficient for measuring chronic pain caused by neuroplastic changes at the supraspinal level. The method was, however, sufficient to demonstrate abnormalities prior to surgery.

All but five patients no longer suffered from pain similar to the pain they remembered during the preoperative interval. These patients were classified as having postcholecystectomy syndrome. In these patients no evidence for hyperalgesia in the RPA was found, reflecting that any neuronal changes at the spinal cord level have resolved. Hence the reason for their symptoms could be either peripheral changes relating to the surgical incision of the nerves or more complex supraspinal changes as reorganization in the CNS which have been demonstrated in patients suffering from chronic pancreatic pain. The pathogenesis of chronic pain is poorly understood, but there is a growing body of evidence that neuroplastic changes as seen in neuropathic pain and other chronic pain disorders may be of importance in understanding chronic pain disorders, including post cholecystectomy syndrome.

In conclusion, initial studies in this patient group showed that hypersensitivity is present in the RPA after acute cholecystitis and gallbladder stones. After the immediate recovery from the cholecystectomy the hypersensitivity returns to normal. The current study has confirmed that the hypersensitivity does not reappear, which does not support the hypothesis that the occurrence of neuroplastic changes could explain pain some years after cholecystectomy. Since five patients in the present study suffered from pain, central changes in a small subset of patients with post cholecystectomy syndrome cannot be ruled out. Therefore, in the future, it would be interesting to study a large group of patients with post cholecystectomy syndrome. Further studies with more advanced equipment for measuring peripheral changes and reorganization in the CNS, along with alternative ways of testing, should be carried out to further explain post cholecystectomy syndrome.

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COMMENTS

Background
Cholecystectomy in patients with gallstone disease usually relieves the symptoms. However, it has repeatedly been demonstrated that 5%-10% of the patients still suffer from severe pain, and even more patients (25%-40%) have milder symptoms. Accordingly, the aim of the present study was to evaluate the sensitivity in the referred pain area in patients who underwent cholecystectomy some years earlier, and to correlate possible abnormalities to the clinical condition of the patients.

Research frontiers
In previous studies we have demonstrated that patients with uncomplicated gallstone disease or acute cholecystitis have an increased sensitivity in the referred pain area (RPA), probably reflecting neuroplastic changes and hyperexcitability in the central nervous system. Animal studies have shown that such changes are frequently persisting even though the initial cause is eliminated. Could this increased sensitivity indicate a later development into post cholecystectomy syndrome?

Innovations and breakthroughs
There is no indication that changes in the central nervous system persist in patients treated with cholecystectomy after several years of follow-up.

Applications
This study strips away the hypothesis that central neuronal changes may be responsible for the post cholecystectomy syndrome. Although it does not give sufficient information on the post cholecystectomy syndrome, it is definitely a future puzzle.

Terminology
Referred pain: Physical pain in a location other than the site of origin. Somatosensory sensitivity: The somatosensory system includes multiple types of sensation from the body-light touch, pain, pressure, temperature, and joint and muscle position sense (also called proprioception). However, these modalities are lumped into three different pathways in the spinal cord and have different targets in the brain.

Peer review
In order to test the hypothesis that neuroplastic changes give rise to post cholecystectomy pain, the referred pain area after cholecystectomy was studied in 40 patients. However, no statistical significant differences were found between the referred pain area and the control area. Thus, this study does not support the hypothesis that de nova neuroplastic changes cause post cholecystectomy syndrome. The description of materials and methods is sound. However, a major drawback of this study is the small number of patients.