Referred Muscle Pain and Hyperalgesia from Viscera: Clinical and Pathophysiological Aspects

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Abstract

Referred muscle pain, i.e., pain perceived in a musculoskeletal area other than the site of the noxious stimulation, is seen frequently in the clinical setting. Referred pain from viscera is the most paradigmatic form of this phenomenon and is frequently accompanied locally by secondary hyperalgesia. In patients with different diseases of internal organs (gastrointestinal and urinary tracts, female reproductive organs) this muscle hyperalgesia, testified by a pain threshold decrease, proves to be an early process, proportional in extent to the number and intensity of visceral pain episodes and prolonged in duration. Referred muscle pain with hyperalgesia is normally attributed to processes of central sensitization which, as shown by electrophysiological studies on animal models of this condition, take place in the Central Nervous System, triggered by the massive afferent visceral barrage upon convergent viscero-somatic neurons. The visceral barrage, however, is also likely to activate a reflex arc towards the periphery (afferent branch: visceral afferent fibers, efferent branch: somatic efferences towards the muscle) resulting in sustained muscle contraction and subsequent local sensitization of nociceptors. This hypothesis is supported by the results of recent studies in the area of referred muscle hyperalgesia caused by an artificial ureteric stone in rats, where positivity was found for a number of morphofunctional indices of skeletal muscle contraction (decrease in I band length/sarcomere length ratio and in 3H-ryanodine binding, increase in Ca^{2+} - ATPase activity and muscle cell membrane fluidity). These changes were proportional to the degree of the hyperalgesia behaviorally monitored in the animals.

Key words: referred muscle pain, hyperalgesia, viscera, central sensitization, muscle contraction.

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Muscle pain is a very common occurrence in life [27]. It can derive from algogenic processes taking place directly in the muscle structure (*primary muscle pain*) or be the result of noxious events occurring at a distance, either in other deep somatic structures (e.g., another muscle, a joint) or, more often, in visceral structures (*secondary or referred muscle pain*). Referred muscle pain from viscera is the most paradigmatic form of the phenomenon of pain referral (i.e., pain perceived in an area other than that of the primary painful focus)[18] and is a prominent symptom in clinical practice, given the very high number of algogenic pathologies affecting internal organs [9,21]. In the referred area, a condition of hyperalgesia of the muscle very often arises, i.e., the musculoskeletal tissue is the site of an increased sensitivity to painful stimuli and also of a decreased pain threshold as measured via different kinds of stimuli (mechanical, electrical) [7, 22]. This hyperalgesia, which is called secondary as it occurs in an area different from the site of the primary injury, is most often accompanied by a state of sustained contraction of the muscle and, in long-lasting painful processes, by real trophic changes of the tissue, i.e. a tendency to atrophy, as revealed by a decreased thickness and section area of the muscle belly [4,8]. In spite of their notable clinical impact, the phenomena of referred pain and hyperalgesia/trophic changes in muscles are still incompletely understood as far as their mechanisms are concerned and have been the subject of active investigation, especially in recent years [3,6]. The following sections intend to provide the reader with an overview of the present knowledge about the clinical and pathophysiological aspects of the described

phenomena, as derived from relevant clinical and experimental studies performed in the field.

Clinical aspects

The process of pain referral occurs constantly in visceral nociception [22]. After a transitory phase in which visceral pain is perceived as a direct symptom, in fact, (the so-called "true visceral pain", always felt along the midline, whatever the viscus in question, accompanied by marked neurovegetative signs and emotional reactions), the sensation is "transferred" to somatic areas of the body wall which differ according to the specific viscus and which are generally located within the relative metameric field [17]. As already mentioned in the introduction, in these areas secondary hyperalgesia may arise (referred pain with and without hyperalgesia). This hyperalgesia may involve all three parietal somatic tissues - skin, subcutis and muscle - but is most often localized at muscle level, where it is frequently accompanied by a state of sustained contraction [21].

The phenomena of referred muscle pain and hyperalgesia in the course of a visceral algogenic process are extremely frequent in the clinical setting.

A typical example is provided by myocardial infarction. In the early phases, true visceral pain is perceived in the lowest sternal or epigastric areas and sometimes also in the interscapular region; the symptom has only vague localization, an oppressive and constrictive quality, and is generally accompanied by pallor, sweating, nausea and vomiting, with associated strong alarm reactions (such as a feeling of impending death). After 10 minutes to several hours, however, the pain reaches the structures of the body wall. It becomes sharper in quality, tends to be located in the thoracic region, either anteriorly or posteriorly, and very often extends to the upper limbs (most often the left one)(referred pain). Hyperalgesia, usually at muscle level, often accompanies the symptom, so that additional stimuli exerted on the area of referral increase the pain. Hyperalgesia most often involves the pectoralis major and muscles of the interscapular region and forearm. The trapezius and deltoid muscles are less frequently involved [9].

Another typical and frequent example of referred muscle pain from viscera is represented by renal/ureteral colics from calculosis. The symptom is perceived in the lumbar region of the affected side, with radiation towards the ipsilateral flank and anteriorly towards the groin. Tenderness characteristically affects muscles of the lumbar and flank area (*quadratus lomborum*, oblique muscles). Patients with biliary calculosis, another very frequent pathology from internal organs, report pain in the upper right quadrant of abdomen with radiation towards the back [2]. Exquisite tenderness of the *rectus abdominis*, at the level of the cystic point (level of junction of the 10th rib with the outer margin of the same muscle) is a typical finding in these patients. Lastly, women suffering from recurrent/chronic pain from their reproductive organs (e.g., dysmenorrhea, or painful menstruation) complain of diffuse pain in the lower abdomen, perineum and sacral region, with radiation towards the groin and upper part of the thighs. Tenderness typically affects the lowest part of the *rectus abdominis* and muscles of the pelvic region [12].

Muscle hypersensitivity in the referred pain zones can be detected by either clinical means (manual compression) or instrumental procedures (evaluation of pain thresholds to different kinds of stimuli). Regarding the latter, our group has long been employing the technique of pain threshold measurement to electrical stimulation. Numerous studies were performed in patients with various pathologies of the internal organs, particularly of the urinary tract, biliary tract and female reproductive organs. The main aim of these studies was to characterize the referred muscle hyperalgesia in relation to the algogenic potential of the visceral focus, i.e., the spontaneous painful symptoms.

In patients with *symptomatic calculosis,* muscle pain thresholds to electrical stimulation were significantly lower than normal in the referred pain area (lumbar region for urinary calculosis, cystic point for biliary calculosis), a result testifying hyperalgesia [7, 24]. This threshold decrease was already detectable after a few painful visceral episodes (colics), accentuated with the repetition of the colics (more pronounced in patients who had suffered from many and/or particularly intense colic episodes than in those experiencing a small number) [25] and outlasted the spontaneous pain (hyperalgesia was detected in the pain-free interval). Sometimes muscle hyperalgesia even outlasted the presence itself of the primary focus in the viscus; in patients with urinary calculosis who had previously suffered from colics and had eliminated the stone a long time prior to examination, a threshold decrease was still detectable in a high percentage of cases [14,26].

In patients with *asymptomatic calculosis* (both at renal and biliary level), in whom the stone had been detected by chance during x-rays and or ultrasound examinations performed for other medical reasons, no threshold decrease was present at muscle level in the expected area of pain referral (no hyperalgesia) [7,8].

In contrast, in patients suffering from visceral pain motivated by dysfunction (and thus not sustained by any organic pathology), such as *biliary colics without calculosis* (painful dysfunction of gallbladder) hyperalgesia was clearly detectable in the referred muscle pain area [7].

Similar results were found in visceral diseases of the female reproductive organs. In a previous study by our group [12], the impact of *primary dysmenorrhea* was examined on the sensitivity of parietal tissues at the abdominal level, that is the area of pain referral (within the uterine viscerotomes, 2 symmetrical abdominal sites

4 cm lateral to the navel), in different phases of the menstrual cycle. Pain thresholds to electrical stimulation of the rectus abdominis were significantly lower than normal in dysmenorrheic women than in nondysmenorrheic women. Although this lowering was particularly evident in the perimenstrual (painful) period, it was present throughout the cycle, thus also outside the phase of spontaneous pain. This result testified once more that referred muscle hyperalgesia is a long lasting phenomenon. Further studies in different groups of women who had suffered from dysmenorrhea for a progressively higher number of years (which corresponds to a progressively higher number of painful visceral episodes, given the recurrent nature of this condition) showed that muscle hyperalgesia at the abdominal level was more accentuated if dysmenorrhea had started a long time prior to examination rather than recently [8]. Here, again, the result of muscle hyperalgesia accentuating in parallel with the repetition of the visceral algogenic input was confirmed.

Thus, in summary, clinical studies in patients show that referred muscle hyperalgesia from viscera is related to the pain perceived, independently of the underlying organic visceral pathology. It is an early process, as it tends to manifest as early as the first visceral episodes, that is accentuated in extent by the repetition of the visceral pains and lasts for a long time, i.e., it not only outlasts the spontaneous pain from the internal organ, but sometimes also the presence itself of the primary focus in the viscus.

In the same patients, together with hyperalgesia the muscle in the areas of pain referral often presents trophic changes, as testified by a decreased thickness and section area upon ultrasound examination. These changes were documented in the case of symptomatic calculosis both at the urinary and gallbladder levels; muscle thickness was significantly lower on the ipsilateral than on the contralateral side. In contrast, no changes were observed in patients with asymptomatic gallbladder or urinary stones [9]. Thus, also trophic changes accompanying referred hyperalgesia appear as a function of the algogenic potential of the primary visceral focus.

In recent years, a new line of clinical studies has been devoted to the characterization of the referred muscle phenomena in patients who are affected with more than one algogenic condition of the internal organs at the same time. Referred muscle hyperalgesia/trophic changes in a specific body area, in fact, can also be the result of concurrent algogenic processes in two different visceral domains which share part of their central sensory projection. e.g., female reproductive organs and urinary tract (T10-L1), or heart and gallbladder (T5) (phenomena of viscero-visceral hyperalgesia) [5,8]. In this case, it has been shown that the extent of the hyperalgesia is notably enhanced, as happens, for instance, in the oblique musculature of calculosis female patients who also suffer from dysmenorrhea [15].

Pathophysiological aspects

Mechanisms underlying referred muscle pain from viscera are still not completely known, in spite of an exponential rise in the number of studies in the field in recent years [2,3,6]. Interpretive problems regard, in particular, the form of referred muscle pain with hyperalgesia.

Simple referred pain (without hyperalgesia) is, in fact, relatively easy to account for, given the extensively documented phenomenon of viscero-somatic convergence in the central nervous system (at both spinal and supraspinal level). At the spinal level, in particular, neurons receiving convergent input from deep somatic structures (including muscles) and visceral structures appear located in the deep layers of the dorsal horn [4]. The pain would be directly referred to the muscle instead of to the viscera because of a misinterpretation on behalf of the higher brain centers [*see* 17, 21].

Regarding referred muscle pain with hyperalgesia, the most credited hypothesis attributes the phenomenon to a process of central sensitization taking place in the Central Nervous System (CNS), triggered by the massive afferent visceral barrage upon convergent viscero-somatic neurons [3, 19].

An example is reported here of an animal model of referred muscle hyperalgesia from viscera (set up by this group) in which the central phenomena have been shown via electrophysiological studies, i.e., an animal model of urinary colics from calculosis.

The characteristics of the referred hyperalgesia from urinary stones have been reproduced in animals (rats) with an artificial stone formed in the upper third of one ureter by injection of dental cement [16]. Stone-implanted animals develop hypersensitivity of the ipsilateral obliquus externus (the same muscle as in humans), as shown by a decrease in the vocalization threshold to electrical muscle stimulation. This hypersensitivity appears on the first day after stone implantation and, although particularly pronounced during the first 3-4 days, usually lasts for more than a week.

Along with the muscle hyperalgesia, and as shown by long-term non-stop videotape recordings, stone-implanted animals also show complex behavioural episodes, similar in nature to the writhing behaviour characteristic of noxious visceral stimulation in animals. These episodes are never manifested in sham-operated rats or rats subjected to non-algogenic ureteric interventions. The episodes, which are mostly visible during the first 3-4 days, vary in frequency and duration, their number and duration decreasing significantly and linearly with time after the operation. In addition, the number, duration and complexity of the

episodes are significantly reduced in a dose-dependent fashion by chronic treatment with morphine.

All these observations together support the notion that this behaviour is an index of perceived visceral pain and thus the equivalent of urinary colics in humans. These visceral episodes show a precise and constant relationship with referred muscle hyperalgesia. In fact, a significant direct linear correlation exists between the number of episodes and the extent of the ipsilateral muscle threshold decrease, so that hyperalgesia is more accentuated in rats displaying a high number of visceral episodes than in those with a smaller number. Furthermore, the hyperalgesia is still detectable one week after stone implantation, even in rats which, upon autopsy, prove to have expelled the stone spontaneously.

Therefore, this animal model of referred lumbar muscle hyperalgesia from artificial calculosis closely resembles the condition of referred lumbar muscle hyperalgesia observed in humans with urinary colics. As in patients, the phenomenon: a) is mainly localized in muscles of the lumbar region ipsilateral to the affected urinary tract; b) appears at an early stage with respect to the start of the activity of the visceral focus; c) is accentuated by repetition of painful visceral episodes; d) tends to persist for a long time, outlasting the duration of direct pain from the viscus and the presence of the algogenic focus in the urinary tract.

As already mentioned above, electrophysiological experiments performed by this group at spinal cord level in this animal model of referred lumbar muscle hyperalgesia from artificial ureteric calculosis support the involvement of a central component in the production of referred hyperalgesia from viscera [13]. Changes in the excitability and response properties of dorsal horn neurones which receive input from the hyperalgesic muscle in rats with artificial calculi have been found when compared to control animals. A significantly increased percentage of dorsal horn neurons displayed a receptive field in the hyperalgesic muscle, a significantly higher percentage of which also showed ongoing activity. Neurons with muscle input also presented a decreased threshold of activation via mechanical stimuli. These changes were more pronounced in animals that had more visceral episodes and muscle hyperalgesia. Similar results were obtained by Roza et al [23], employing this same model, in electrophysiological experiments in which they examined the characteristics of neurons processing information from the ureter (in calculosis rats versus rats with an intact ureter). These authors concluded that the presence of a ureteric stone evokes excitability changes of spinal neurons (enhanced background activity, greater number of ureter- driven cells, decreased threshold of convergent somatic receptive fields), which likely account for the referred muscle hyperalgesia seen in rats with calculosis. Based on the results of several experimental studies, N-methyl-D-aspartate (NMDA) receptors would seem to play an important role in the generation of these central hyperexcitability changes [3, 19].

The fact that hyperalgesia often outlasts the presence of the "macroscopic" peripheral visceral focus in the clinical setting has led to the hypothesis that the central plastic changes, once established, may persist, becoming relatively independent of the primary triggering event [*see* 8, 21]. However, the results of studies on ureter motility in rats with artificial ureteral calculosis (abnormal hypermotility persisting long after stone elimination) [20] suggest that a number of "clinically inapparent" peripheral visceral changes are likely to outlive the presence of the primary focus and thus maintain the state of central hyperexcitability via persistence of the peripheral drive.

An important role of central neuroplastic changes is also plausible in the case of referred muscle hyperalgesia due to the concomitant presence of two algogenic pathologies in visceral domains which share part of their central sensory projection. As already mentioned in the section devoted to clinical aspects, referred muscle hyperalgesia is notably enhanced in these circumstances. This phenomenon has been reproduced experimentally in animals, i.e., it has been shown that rats with an artificial stone in one ureter which also receive implantation of endometriotic cysts (mimicking the clinical situation of a painful condition from the female reproductive organs: endometriosis – dysmenorrhea) present a much higher degree of referred hyperalgesia in the ipsilateral oblique muscle than do rats with sham endometriosis plus ureteric stone or rats with a ureteric stone alone [11]. This phenomenon of enhanced hypersensitivity is probably contributed to by processes of central sensitization involving viscero-viscero-somatic convergent neurons [8]; viscero-visceral convergences have, in fact, been shown to exist among different internal organs, in addition to viscero-somatic convergence [*see* 9,17]. Future electrophysiological studies on this and similar animal models of viscero-visceral hyperalgesia will hopefully be able to verify this hypothesis experimentally.

Central changes, however, are probably not the sole mechanism involved in referred muscle phenomena, as suggested by the presence of objective (trophic) changes in the muscle. The afferent barrage from the internal organs is likely to activate a number of viscero-somatic reflexes towards the periphery responsible for both the increased sensitivity and the modification of thickness and consistency of deep body wall tissues [17,21,22]. Regarding the muscle, in particular, the "reflex arc activation" would promote reflex muscle contraction, in turn possibly responsible for sensitization of nociceptors locally, which would account for the hyperalgesia [27].

This theory had originally been put forward on the basis of the clinical observation of the sustained muscle

contraction that so often accompanies the states of prolonged visceral pain in the area of referral [22]. Recent studies by this group have provided some experimental evidence for this so far theoretic mechanism, by employing the previously described animal model of artificial ureteric calulosis. In stone rats, the possible correlations were investigated between the condition of hyperalgesia of the ipsilateral oblique musculature and some morpho-functional indices of skeletal muscle contraction [10]. Specimens from the *obliquus externus* muscle of both sides were obtained from stone-implanted (left ureter) and from sham-operated rats (2 or 4 days postoperatively). In these specimens, the following parameters were measured: (a) I band length/sarcomere length ratio (as ultrastructural contraction index); (b) muscle cell membrane fluidity; (c) Sarcoplasmic Reticulum (SR) Ca^{2+}-uptake capacity (measured as Ca^{2+}-ATPase activity) and (d) SR- Ca^{2+}release capacity (measured as ryanodine binding).

In sham-controls, no parameters were significantly different on the two sides. In stone rats, parameters of the right obliquus externus muscle (i.e., contralateral to the implanted ureter) did not differ significantly from those of sham controls. On the left (ipsilateral) vs right obliquus externus muscle of stone rats, the following significant changes were found: (a) decreased I band length/sarcomere length ratio; (b) increased muscle cell membrane fluidity; (c) increased Ca^{2+}-uptake capacity (correlated linearly to the number of ureteral "crises") and (d) decreased ryanodine binding. These results suggest the presence, proportional in degree to the activity of the ureteral pain focus, of a state of skeletal muscle contraction in the oblique musculature ipsilateral to the stone, an event which could contribute to the generation of the local hyperalgesia via sensitization of muscle nociceptors.

In a parallel study, c-Fos expression was explored in the spinal cord of calculosis rats versus sham controls [1]. Stone rats were sacrificed two hours after the first ureteral “crisis” and sham controls (no crisis) were suppressed after matching time lapses. All were perfused intracardially; the T9-L3 thoracolumbar spinal cord segment was removed and post-fixed. Frontal frozen sections (40μm thick) were cut and immunostained for c-Fos-like protein. Four-five sections/level/rat were examined under lightfield microscopy to evaluate Fos-positive cell number.

Fos-labeled cells were never observed in sham controls. In stone rats, they were found throughout the dorsal horn (laminae I-VI) bilaterally, but significantly more on the side ipsilateral to the implanted ureter. As expected, most of the Fos expression was in the superficial dorsal horn. Fos-labeled cells, however, were also found in the ventral gray (laminae VII-X), mostly in lamina VII (containing preganglionic sympathetic neurons of the intermediolateral nucleus in segments T1-L3) but also in lamina IX (motoneurons). These results thus suggest that nociceptive input from the ureter in this model activates not only sensory neurons but also efferent neurons in the spinal cord, supporting the notion that reflex arcs are triggered by the visceral focus and that the muscle contraction in the referred site results from a reflex mechanism.

Though further studies will be needed to test this hypothesis more thoroughly, the data so far reported are strongly indicative that referred muscle phenomena from viscera cannot be merely due to central mechanisms but should be also explained on the basis of real changes taking place at the periphery. This seems all the more probable in the light of the clinical evidence that the areas of referred pain from viscera are the site of trophic alterations in addition to the hyperalgesia; these objective changes cannot, in fact, be the result of purely central processes.

Conclusion

Referred muscle pain/hyperalgesia from viscera has definite clinical features, as evidenced by the numerous studies in patients reported in this review.

In clinical practice, detection of simple referred pain (without hyperalgesia) is relatively easy since the absence of tenderness at the site of the symptom immediately indicates that the origin of the algogenic impulses is at a distance. Correct diagnosis of referred muscle pain with hyperalgesia is, instead, much more difficult and represents a major clinical problem since this form is far more frequent than that of simple referred pain. The problem concerns differentiation with respect to primary muscle pain, i.e., that arising in relation to an algogenic pathology primarily affecting the tissue. Only careful study of the clinical history, accurate physical examination, and complete sensory evaluation of the painful areas can help towards a diagnostic orientation.

The pathophysiology of referred muscle pain with hyperalgesia has not yet been clarified from all points of view. Central neuroplastic changes undoubtedly play an important role, but based on the most recent studies in the field, it also seems that the muscle in the referred area is the site of real local changes in terms of both altered functions of nociceptors and of positivity for morphofunctional indices of contraction. These changes are long-lasting and often lead to permanent hyperalgesia and frank atrophy of the tissue. Thus, skeletal muscles in the human body would seem to bear long-term consequences of algogenic processes within the internal organs, which may alter their functionality even for years after the primary occurrence of the visceral painful event. This circumstance conveys the message that every painful condition coming from the internal organs must be identified and treated as early as possible in order to avoid persisting damage in the musculoskeletal domain.

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