

ROLE OF NEUROPEPTIDES IN PATHOGENESIS OF REFLEX SYMPATHETIC DYSTROPHY

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In 1993, a study was undertaken at the Hand Clinics of Loyola University Medical Center in Chicago to investigate the role of the neuropeptides in the pathogenesis of Reflex Sympathetic Dystrophy. All of the patients had recurrent or continuous pain, swelling, and stiffness of one or both extremities following either acute trauma or surgical intervention.

All of the patients showed a markedly increased level of bradykinin as well as calcitonin gene-related peptide. The levels of bradykinin were four times as high as the controls. A few showed increased levels of the other neuropeptides. With these results, we agree with Veldman, Goris and others who consider Reflex Sympathetic Dystrophy to be an exaggerated regional inflammatory disorder.

Keywords : reflex sympathetic dystrophy ; neuropeptides.

Mots-clés : algodystrophie ; neuropeptides.

In 1993, a study was undertaken at the Hand Clinics of Loyola University Medical Center in Chicago to investigate the role of neuropeptides in the pathogenesis of reflex sympathetic dystrophy (5).

There were 61 patients in the study, 47 female and 14 male. Their ages ranged from 20 to 71 with the majority being between 33 and 48 years of age (average : 40 years). All of the patients had recurrent or continuous pain which was worse with use. In addition, they had swelling or stiffness in all or parts of the extremity. Twenty-three had muscle spasm in various parts of the extremity. In addition to the above symptoms, they were also classified according to severity : mild (23), moderate (18), and severe (20).

ONSET

Thirty-seven had an acute traumatic event which was mild such as a sprain or contusion to severe which included crush injuries of the hand. Twenty-two had a gradual onset which was related to repetitive tasks. Some of the above had surgical intervention.

The most common associated diagnosis in addition to the reflex sympathetic dystrophy was :

- Carpal Tunnel Syndrome (26)
- Ulnar Nerve Neuropathy (16)
- Crush Injury of the Hand (8)
- Sprained Joints of the Hand (4)
- Synovitis, Tenosynovitis of the Hand (10).

METHOD

Blood samples were drawn from these patients. The neuropeptides studied included bradykinin, neurokinin A&B, neurokinin Y, calcitonin-gene related peptide, vaso active intestinal peptide, and substance P. Levels were determined using commercial available Elisa (Enzyme linked immuno absorbent assay) and RIA (radio-immuno-assay, Peninsula Laboratories, Belmont, California). There were 20 controls.

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VIP Levels In Patients With Reflex Sympathetic Dystrophy

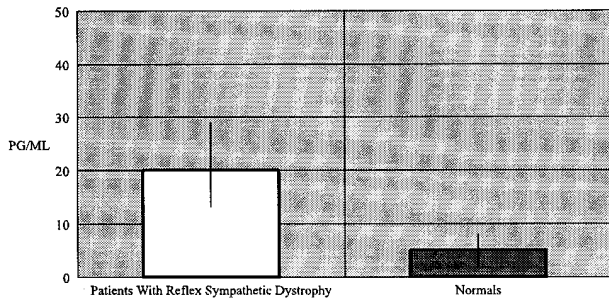


Fig. 1. — VIP levels in patients with reflex sympathetic dystrophy.

Bradykinin Levels In Patients With Reflex Sympathetic Dystrophy

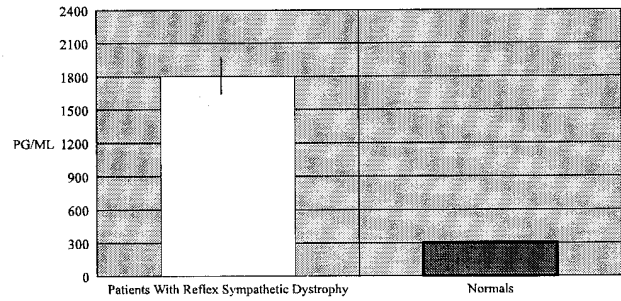


Fig. 3. — Bradykinin levels in patients with reflex sympathetic dystrophy.

Neurokinin Y Levels In Patients With Reflex Sympathetic Dystrophy

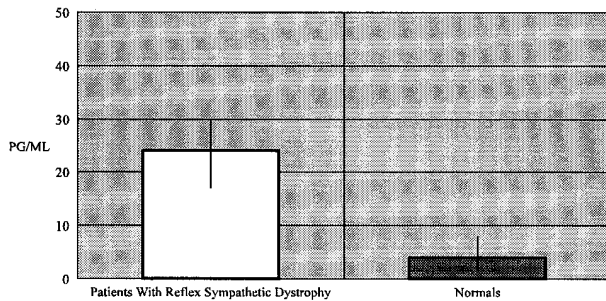


Fig. 2. — Neurokinin Y levels in patients with reflex sympathetic dystrophy.

CGRP Levels In Patients With Reflex Sympathetic Dystrophy

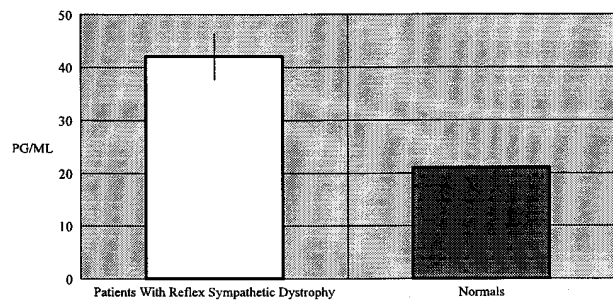


Fig. 4. — CGRP levels in patients with reflex sympathetic dystrophy.

RESULTS

There was no increase in the levels of neurokinin A&B or substance P. Half of the patients showed an elevation of the vaso active intestinal peptide (fig. 1) and neuropeptide Y (fig. 2). The most notable effects were noted with bradykinin and calcitonin gene-related peptide.

The bradykinin levels in controls were 246.0 ± 37.8 pg-ml and in the reflex sympathetic dystrophy patients 1842.8 ± 270.9 pg-ml (fig. 3). The calcitonin gene-related peptide levels in controls were 27.7 ± 3.7 pg-ml and the reflex sympathetic dystrophy patients, 44.5 ± 10.8 pg-ml (fig. 4).

DISCUSSION

Schott (12) recently questioned the sympathetic role and alluded to neurogenic inflammatory

mediators as playing a possible role in the disorder. Neurogenic inflammation has also been discussed by Levine *et al.* (3-6) and others to account for some of the painful disorders of the extremities.

The International Association for the Study of Pain decided to reclassify and use different terminology of reflex sympathetic dystrophy (11). They had decided to call it a complex regional pain disorder. Veldman and Goris (14) in their discussion of reflex sympathetic dystrophy in 1993 recommended that it be called an exaggerated regional inflammatory disorder. They discussed the inflammatory aspects of the disorder and considered that the mechanisms of injury were related to oxidative stress.

Keeping with the inflammatory role, our study found elevated bradykinin and calcitonin-gene related peptides. It has been noted that bradykinin is one of the most potent substances known for inducing pain and vascular permeability (3, 4). It

was found that the bradykinin lowers the mechanical threshold and nociception and produces sensitization (10).

Some patients in our study had cumulative trauma disorders. Some authors, e.g. Sjogaard and Jensen (13) feel that these individuals had developed pain in muscle from muscle ischemia. It has been noted that activation of muscle nociception can occur with release of bradykinin from plasma proteins during ischemia. The above might account for the relationship between cumulative trauma disorders and reflex sympathetic dystrophy (1, 2, 15), there being a spectrum of severity between the above disorders. Both of the above disorders have pain, swelling and variable autonomic manifestations. All the symptoms are increased with use.

SUMMARY

Sixty-one patients with a diagnosis of reflex sympathetic dystrophy were found to have elevated bradykinin and gene-related peptide levels. Because of our findings of these results, we consider reflex sympathetic dystrophy to be an exaggerated regional inflammatory disorder. We also consider that the cumulative trauma disorder may have the same pathophysiological mechanisms in production of symptoms. Further research is needed to elucidate these mechanisms.

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SAMENVATTING

S. J. BLAIR, M. CHINTHAGADA, D. HOPPENSTEHD, R. KIJOWSKI, J. FAREED. De rol van neuropeptiden in de pathogenese van reflex sympathische dystrofie.

In 1993 werd in de Hand Clinics van de Loyola University Medical Center van Chicago een studie gestart naar de rol van neuropeptiden in de pathogenese van de reflex sympathische dystrofie (RSD). Alle patiënten hadden recurrenente of continu pijn met zwelling en stijfheid van één of beide leidematen na een trauma of operatieve ingreep.

Bij alle patiënten werd een verhoogd bradykinine en calcitonine-gen dependente peptide gevonden. De concentraties van bradykinines was 4 maal hoger dan in de controle groep. Enkele vertoonden ook verhoogde concentraties van andere neuropeptiden. Deze bevindingen bevestigen de stelling van Veldman, Goris en anderen om RSD te beschouwen als een overdreven regionale inflammatoire stoornis.

RÉSUMÉ

S. J. BLAIR, M. CHINTHAGADA, D. HOPPEN-STEHD, R. KIJOWSKI, J. FAREED. Rôle des neuropeptides dans la pathogenèse de l'algodystrophie réflexe sympathique.

En 1993, une étude a été entreprise aux Cliniques de Chirurgie de la Main de l'Université Loyola de Chicago, pour investiguer le rôle des neuropeptides dans la pathogenèse de l'algodystrophie réflexe sympathique. Tous les patients souffraient d'une douleur récidivante

ou continue, d'un gonflement, et d'un enraidissement d'un ou plusieurs doigts après un traumatisme aigu ou chirurgical. Tous les patients présentaient une augmentation importante du taux de bradykinine et de «calcitonin gene-related peptide». Les concentrations de bradykinine étaient 4 fois plus élevées que chez les sujets contrôles. Quelques patients démontraient un niveau élevé d'autres neuropeptides. Sur base de ces résultats, les auteurs pensent comme Veldman, Goris et d'autres que l'algodystrophie est une réaction inflammatoire régionale exagérée.