Title

COMPLEX REGIONAL PAIN SYNDROME (CRPS) AND THE ROLE OF SYMPATHECTOMY IN ITS MANAGEMENT: A REVIEW

by

Suman Mewa Kinoo

Student number

993216384

submitted for the degree of

Master of Medicine (MMed) Surgery

supervised by

Professor Bhugwan Singh

in the

Department of Surgery

Nelson R Mandela School of Medicine

University of KwaZulu Natal

2012

ACKNOWLEDGEMENTS

I would like to convey my sincere gratitude to the following persons:

- My mentor and supervisor Professor Bhugwan Singh for all his encouragement, guidance, assistance and supervision in preparing this thesis
- My wife Doctor Shirelle Assaram for her support, sacrifice and patience during the preparation of this thesis
- My parents Mr V Mewa Kinoo and Mrs L Mewa Kinoo for their wisdom and support always
- My friend Doctor Sumayyah Ebrahim for her ever willing assistance
- Doctor SS Ramklass for supervising the process of submission for this thesis

ABSTRACT

Complex Regional Pain Syndrome (CRPS) is an extremely debilitating condition, characterized by chronic pain with associated trophic changes. The 1st description of this condition dates back to 1864. The condition has been variously described over the years as "causalgia", "Sudeck's dystrophy" and "reflex sympathetic dystrophy". In 1993 the International Association for the Study of Pain (IASP) introduced the term Complex Regional Pain Syndrome (CRPS) with diagnostic criteria that are currently used. CRPS was subdivided into type I and type II. CRPS type I is diagnosed when there is no obvious nerve injury, whereas CRPS type II refers to cases with nerve injury. It follows that the present diagnostic criteria depend solely on meticulous history and physical examination without any confirmation by specific gold standard tests. The pathophysiology of this pain syndrome is poorly understood; however there is growing evidence for an inflammatory or sympathetic cause. It is therefore not surprising that there is no uniform approach to its management. Therapy is often based on a multi-disciplinary team approach with use of non – pharmacological therapy (physiotherapy and occupational therapy), pharmacological therapy (analgesics, neuroleptics, bone metabolism drugs), and invasive therapy (stellate ganglion blocks and sympathectomy).

This review acknowledges the humble beginnings of this condition, and provides an understanding for the evolution of its terminology. It objectively reviews the current IASP diagnostic criteria, challenging its efficacy and sensitivity. Despite its pathophysiology remaining an enigma, the latest pathophysiological advances are reviewed in the endeavour to better understand this condition and enhance treatment options. The role of surgical sympathectomy for this condition is reviewed, highlighting its importance and underappreciated success in the management of CRPS.

LIST OF ABBREVIATIONS

ACE:	Angiotensin converting enzyme
Ca:	Calcium
CGRP:	Calcitonin-gene related peptide
CNS:	Central Nervous System
CRPS:	Complex / Chronic Regional Pain Syndrome
CRPS-NOS:	Complex / Chronic Regional Pain Syndrome - not otherwise specified
DMSO:	Dimethylsulfoxide
ETS:	Endoscopic Thoracic Sympathectomy
fMRI:	functional Magnetic Resonance Imaging
GABA:	γ-aminobutyric acid
IASP:	International Association for the Study of Pain
IL:	Interleukin
IVIG:	Intravenous Immunoglobulin
MCS:	Motor Cortex Stimulation
MEG:	Magneto-encephalographic
MRI:	Magnetic Resonance Imaging
NAC:	N-acetyl-cysteine
NDMA:	N-methyl-Daspartate

NO:	Nitric Oxide
NSAID:	Non-steroidal anti-inflammatory drug
PET:	Positron Emission Tomography
PNS:	Peripheral Nerve Stimulation
RSD:	Reflex Sympathetic Dystrophy
sCRPS:	spontaneous CRPS
SCS:	Spinal cord stimulation
SGB:	Sympathetic ganglion block
SI:	Somatosensory
SIP:	Sympathetically Independent Pain
SMA:	Supplementary motor area
SMP:	Sympathetically Mediated Pain
SS:	Surgical sympathectomy
SSRI:	Selective Serotonin Reuptake Inhibitors
TCA:	Tricyclic antidepressant
tCRPS:	trauma related CRPS
TMS:	Trans-cranial Magnetic Stimulation
TNFα:	Tumour Necrosis Factor alpha
VAS:	Visual Analogue Scale
VLAS:	Visual Linear Analogue Scale

LIST OF TABLES

LIST OF FIGURES

CONTENTS

CHAPTER ONE

INTRODUCTION

INTRODUCTION

1.1 INTRODUCTION

Complex regional pain syndrome (CRPS), as the name suggests, is a complicated pain condition involving a constellation of symptoms. It is an extremely debilitating condition and has been ranked 42 out of 50 on the McGill pain index, making it one of the most painful chronic syndromes that exist to date. To the untrained eye, diagnosis may be difficult and more often than not, missed. As a result of this patients are often subjected to numerous and varied medical interventions that, not surprisingly, are mostly unsuccessful.

The entity of complex regional pain syndrome dates back to the 17th century, and although the terminology has evolved, the initial description of symptomatology and presentation remains the same. This condition was as intriguing and mind boggling to health care providers then, as it is now. This is evident from the description made by Silas Weir Mitchell in 1864:

"We met with a small number of men who were suffering from a pain which they described as burning or mustard red-hot or as red-hot fire rasping the skin…….The part itself is not alone subject to an intense burning sensation, but becomes exquisitely hyperaesthetic, so that a touch or tap of the fingers increases the pain. Exposure to the air is avoided with a care which seems almost absurd…" Silas Weir Mitchell, 1864.

Since its first description, enormous amount of effort was dedicated to better understand this condition, and despite this effort, no definite conclusions have been drawn. However, in current medical practice we have guidelines to making its diagnosis, cite a list of possible theories, and suggest reasonable management options.

1.2 PROBLEM STATEMENT

CRPS is an extremely challenging pain condition for the patient and may be more challenging for the health care practitioner. Diagnosis is often difficult to make and part of this maybe due to the unawareness of this condition to the health care practitioner. Furthermore, this type of pain is often treated with a protracted long drawn trial and error use of physiotherapy & pharmacology, mostly unsuccessful, with referral to the general surgeon as a last resort.

1.3 SIGNIFICANCE OF STUDY

Making a diagnosis of CRPS is a challenge which often leads to failure of promptly recognizing and appropriately treating CRPS. This may result in a complicated clinical course with irreversible changes, as well as a missed opportunity for relief by sympathectomy. Furthermore in the era of minimal access surgery, sympathectomy can be performed safely with minimal morbidity. This warranted a necessary review of this topic and provided optimum treatment approaches for overall better patient care, relieving this excruciating pain and restoring function to patients, thereby improving quality of life and facilitating reintroduction into society. The rationale for sympathectomy by the general surgeon and the timing of this approach in the management of CRPS also merited review. This review also identified short falls in the literature and made recommendations for future research.

1.4 AIM OF STUDY

This review aimed to provide a critical overview of the current literature, thus ensuring a better understanding into this condition, outlined the latest evidence based pathophysiological theories, and management strategies, as well as provided a background on this subject. The study emphasized that early recognition and swift appropriate referral to the general surgeon can relieve pain and restore function. The study focused on the unappreciated therapeutic value of sympathectomy in its management, prompting early referral to the general surgeon.

1.5 SPECIFIC OBJECTIVES

The objective of the study was to:

- define CRPS and give a brief history of how this terminology has evolved
- establish the criteria for diagnosing CRPS, and determine its efficacy
- describe the criteria for staging CRPS
- describe the postulated pathogenesis of CRPS
- describe the nonsurgical management options, and its effectiveness
- establish the role of the general surgeon in sympathectomy.

CHAPTER TWO

METHODS

METHODS

2.1 ETHICAL CONSIDERATIONS

Ethical approval for this study was waived on 17/01/2012 by the University of KwaZulu- Natal (UKZN) Biomedical Research Ethics Committee (BREC), E 242.11. On 18/04/2012, the Postgraduate Education Committee at UKZN ratified the study (Appendix 1 and 2).

2.2 STUDY DESIGN

The study consisted of a literature review of relevant published material. A total of 1260 relevant articles were identified from the year 2000 to present date. Of these 1260, 234 fulfilled the inclusion criteria and were found to be suitable for review.

2.2.1 Search strategy

A collective review of the literature using the relevant search engines and search terms (as listed below) was undertaken.

Search engines and electronic databases:

- UKZN Primo search
- Biomed central
- Science Direct
- Cochrane library
- EBSCO host
- Google scholar
- MD consult

- Medline/ Pubmed

An experienced medical librarian was consulted to improve general approaches for conducting a comprehensive search of the above databases.

Relevant search terms included the following keywords and MeSH terms as applicable:

- CRPS (Chronic / Complex regional pain syndrome)
- Chronic pain
- Causalgia
- Reflex sympathetic dystrophy
- Sudecks dystrophy
- Sympathectomy / thorascopic sympathectomy

2.2.2 Inclusion and exclusion criteria

The inclusion criteria were:

- Human subjects
- Adults (>18 years old)
- English language text
- Period: Year 2000 to 2012
- Studies from both developed and developing countries

The exclusion criteria were:

- Literature published before the year 2000
- Foreign language publications

- Paediatrics

2.2.3 Data collection methods

Various publications, including academic journals on the subject were used to collect the relevant data. Information was gathered from studies that included randomized controlled trials, review articles, case reports and systematic reviews. Only literature published after the year 1999 (*ie* year 2000 onwards) was used for this review. Studies meeting the above inclusion criteria were assessed for its inclusion. Microsoft Excel was used to summarise and categorise the main results and sub groups e.g. sympathectomy.

2.3 DATA ANALYSIS

Studies were evaluated through content analysis, as meta-analyses were not feasible due to the vast variety of study designs and variables used in this study. The study focused only on quantitative research designs.

The study was analysed by comparing and contrasting content related to:

- Proposed pathogenesis
- Aspects of diagnosis
- Areas affected
- Management/ treatment strategies
- Success of sympathectomy

The data obtained was categorised and then cross checked against the inclusion and exclusion criteria. The findings were then evaluated and conclusions drawn from this information. Absences and gaps in the existing literature were highlighted and recommendations for future research or clinical advancement were suggested.

CHAPTER THREE

HISTORICAL

OVERVIEW

HISTORICAL OVERVIEW

The earliest description of chronic pain syndromes, probably dates back to the 17th century when Ambroise Pare's described persistent pain and contractures in King Charles IX after a "bloodletting" procedure (1). However the first documented description was in 1864 in a paper published by Silas Weir Mitchell (figure 3.1), a neurologist, entitled "Gunshot wounds and other injuries of nerves" (2). Mitchell called this condition causalgia which meant "burning pain" from the Greek words *kausis* (fire), and *algos* (pain) (3), a term, that was given to him by his friend Robley Dunglison. Mitchell noticed soldiers during the American civil war complaining of burning pain, hyperaesthesia, oedema, and decreased motor function in limbs following injury. His graphic description of causalgia (burning pain) remains the best depiction of the clinical presentation of CRPS as we know today.

Figure 3.1: Silas Weir Mitchell (1)

In 1900, Paul Sudeck described a similar condition following trauma that resulted in patchy bone demineralization. Some years later in his honour, this condition was referred to as "Sudecks dystrophy" by traumatologists (3).

In 1947 Evans described a reflex sympathetic arc as a possible cause for these symptoms and called it Reflex Sympathetic Dystrophy (RSD) (1). Extrapolation from the possible

sympathetic origin of the as described by Evans prompted the use of sympathetic blockage to treat this condition by Roberts in 1986. He suggested that this pain condition be referred to as sympathetically mediated pain (SMP). However not all patients with the classic features of RSD responded to sympathetic blockage. Campbell, in 1992, suggested 2 types of RSD *viz* those that responded to sympathetic blockage referred to as sympathetically mediated pain (SMP) and those that did not respond to sympathetic blockage referred to as sympathetically independent pain (SIP) (1).

Increasingly, the role of the sympathetic nervous system in chronic pain became questionable. In 1993 a special task force subgroup of the International Association for the Study of Pain (IASP), called "The Pain and the Sympathetic Nervous System group" was designed to clarify the terminology of this condition. A consensus was reached to call this condition Complex Regional Pain Syndrome (CRPS), with RSD and causalgia as subtypes.

In 1994 the IASP revised the subgroups describing the classic RSD as Type I CRPS, and classic causalgia as Type II CRPS (4).

In 1996 Stanton-Hicks described the reasons for calling this pain syndrome CRPS (5):

- **Complex** expresses the varied clinical features within a single person over time, as well as the features of inflammation, autonomic, cutaneous, motor, and dystrophic changes.
- **Regional** reflects that most cases involve a particular region of the body; pain can expand beyond the area of the initial lesion.
- **Pain** is essential to the diagnosis of CRPS; pain can be either spontaneous pain or evoked, such as allodynia or hyperalgesia.
- **Syndrome** indicates that the signs and symptoms of CRPS are a series of distinct correlated events.

The evolution of the terminology pertinent to chronic pain is summarised in table 3.1.

YEAR	AUTHOR	NAME GIVEN TO CRPS
17th century	Ambroise Pare's	No specific name
1864	Silas Weir Mitchell	Causalgia
1900	Paul Sudeck	Sudecks Dystrophy
1947	Evans	Reflex Sympathetic Dystrophy
1986	Roberts	SMP
1992	Campbell	Subdivided RSD, SMP&SIP
1993	Consensus conference*	CRPS type RSD & Causalgia
1994	IASP	CRPS type I & II

RSD: Reflex sympathetic dystrophy; SMP: sympathetically mediated pain; SIP: sympathetically independent pain; CRPS: Complex regional pain syndrome; IASP: International Association for the Study of Pain
* IASP "The Pain and the Sympathetic Nervous System group"

Table 3.1: Evolution of CRPS terminology

CHAPTER FOUR

CLINICAL PRESENTATION

OF

CRPS

CLINICAL PRESENTATION

The clinical presentation of CRPS is always preceded by a history of a noxious initiating event that triggers the onset of a symptom complex. It is described that the preceding initiating event may or may not result in an injury to a nerve. If the pain syndrome is pursuant to damage or injury to a nerve, this is regarded as CRPS type II; when the pain syndrome is pursuant without any nerve injury, this is regarded as CRPS type I. The initiating noxious event in CRPS type II is often the result of iatrogenic injury, tumour infiltration or trauma. The initiating events in CRPS type I, are vast and can range from trauma or surgery, to a stroke or myocardial infarction, and may even be produced after an intramuscular injection. Table 4.1 outlines examples of stimuli implicated in the development of CRPS.

TRAUMA	
Accidental	Sprains, minor cuts, contusions, dislocations, fractures, crush injuries, traumatic amputation, burns
Surgical	Tight plaster casts Tissue or nerve damage from any procedure (*eg* Mastectomy*)
Occupational	Repetitive strain injury, for example pneumatic tools, typing
DISEASES	
Visceral	Myocardial infarction
Neurological	Cerebrovascular accident resulting in post hemiplegic dystrophy Nerve damage by tumour invasion, nerve infection (Herpes*)
Vascular	General angiopathies, frostbite, thrombosis

* Anecdotally reported (5)

Table 4.1: Examples of stimuli implicated in the development of CRPS(6)

The onset of the symptom complex in CRPS is usually within hours or days following the initiating noxious event, but may be delayed for several weeks or even months. This symptom complex includes a combination of the following classic triad of symptoms (see figure 4.5):

1 Sensory symptoms
2 Motor symptoms including "neglect like motor symptoms" / body perceptual disturbances
3 Autonomic symptoms including trophic, sudomotor and vasomotor features

4.1 SENSORY SYMPTOMS

The hallmark of this feature is pain. Pain may be described by patients as being burning, like electric shocks, aching or of a throbbing nature. Pain may be divided into 2 main categories (see figure 4.1.), *ie* sensory gain or sensory loss (3).

Sensory gain is the most prevalent presentation. Sensory gain is categorised by an increase response or decrease threshold to pain. It is often referred to as hyperaesthesia. This category includes allodynia (pain following usually non painful stimuli *ie* a decrease threshold to pain) and, hyperalgesia (strong hypersensitivity to mild painful stimuli *ie* an increase response to pain) (7).

Sensory loss is categorised by a decrease response or increase threshold to pain. It is often referred to as hypoaesthesia. This category includes hypoalgesia (decrease pain to normal painful stimuli). A less common category characterised by an abnormal reaction to pain stimuli can occur with sensory loss or gain and is referred to as hyperpathia.

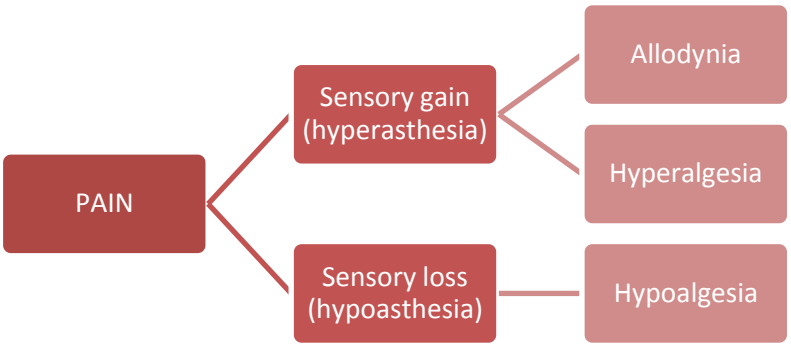


Figure 4.1: Categories of pain

The pain experienced in CRPS has the following documented classic features:

a. It is out of proportion of the initiating event(4)
b. It is more frequently located in deeper structures such as muscle and bone (in 68% of cases), and skin (in 32% of cases) (3)
c. It is increased by orthostasis, anxiety, exercise or temperature changes and may be more pronounced at night (3)
d. It is not confined to the area of injury in up to 50% of patients, and may spread proximally and involve the entire half of the body or upper quadrant, face and also to the contralateral side (so called the mirror image symptom) (8)
e. It has the tendency of distal generalization, for example, the hand is affected more than the forearm (2)

Despite the different descriptive types of CRPS, the presentation of pain is similar. However a study conducted by Bruehl et al (9) where nerve conduction velocity testing was used to distinguish CRPS type I from type II, found that type II exhibited a higher frequency of neuropathic pain characteristics (*ie* allodynia and hyperalgesia) when compared to type I.

4.2 MOTOR SYMPTOMS

Motor symptoms include (8):

- Decreased active range of movement
- Increased amplitude of physiological tremor
- Decreased active motor force
- Dystonia (10% of patients)

Impaired motor function is common after most injuries but generally resolves as the patient recovers. However, in CRPS susceptible patients develop marked movement disorders. Dystonia is the most prevalent movement disorder in CRPS. It is defined as a movement disorder that causes the muscles to contract and spasm involuntarily. In CRPS it is characterised by persistent flexion postures of the fingers and wrist in the arm, and by plantar flexion and inversion of the foot, with or without clawing of the toes in the leg (10), (see figure 4.2).

Figure 4.2: CRPS patient with dystonia

It is unlikely that these motor changes are a result of a peripheral process and more likely as a result of a central process. The decreased range of movement in the acute stages may be due to

pain or oedema and later by contractures and fibrosis (11). Complex movements such as first closure or finger thumb apposition are restricted and only rarely possible under visual control. Nerve conduction and electromyography (EMG) studies are normal, except in patients in the chronic and advanced stages(2).

4.2.1 Motor "neglect like" symptoms / body perception disturbance

It would be expected that due to intense pain experienced by patients, constant attention will be paid to the affected limb. However two large studies by Galer *et al* and Lewis *et al* demonstrated that this is not the case; instead patients tend to neglect the affected limb (12). The description of classic, "neurological neglect symptoms" occur in stroke patients where everything about their affected side of their body is regarded as non-existent. Patients with CRPS however experience a paradox of symptoms. On the one hand they experience reduced visual spatial sensory awareness in a neglect manner and on the other hand they experience hyper-vigilance to touch and pain. Due to this paradox of symptoms, Galer *et al* labelled this phenomena "neglect like symptoms" (13). However, Lewis *et al* in 2007 suggested that this term does not accurately reflect patient symptoms and that "body perception disturbance" is the more appropriate term to describe this phenomenon (12). In this study 27 patients with CRPS were interviewed; the following 6 common themes were recognised:

1. Hostile feelings – for example, a feeling of frustration, hate and disgust with limb.
2. Spectrum of disassociation (referred to as cognitive neglect by Galer) – for example, requesting an amputation of the affected limb.
3. Disparity between what is apparent and what is felt - for example, the affected arm felt bigger than it really is.
4. Distorted mental image of affected part – for example, descriptions of affected limb differed whilst looking at limb and when eyes were closed.

5. Awareness of limb position – for example, they were conscious of its presence due to the pain but paradoxically expressed difficulty in knowing its position.
6. Conscious attention (referred to as motor neglect by Galer) – for example, they consciously distracted their attention away from the limb.

Pain intensity, illness duration and the extent of sensory deficits may be related to the development of these symptoms (14). Brain imaging studies have shown that those with CRPS have a disrupted cortical map of the affected body part (15). There is an incongruence between peripheral sensory input and central motor output (16). This is confirmed by the use of mirror visual feedback, where visual input to the brain from moving the unaffected limb can be re-established with resultant motor execution (17). These findings suggest a complex interaction between pain, body perception disturbance and central remapping. Further studies are thus advocated to use treatments that target cortical areas, which may reduce body perception disturbance and pain.

4.3 AUTONOMIC SYMPTOMS

Autonomic symptoms include a combination of:

1. vasomotor changes
2. sudomotor changes
3. trophic changes

4.3.1 Vasomotor changes

Vasomotor symptoms include skin temperature and colour changes (11). A 1^0C difference between the affected and non- affected limb is regarded as a significant temperature difference. In CRPS, patients invariably exhibit temperature differences greater than 1^0C. The affected limb may be warmer than the normal limb, which occurs in up to 75% of

patients and is more commonly seen in the acute stages; the affected limb may be cooler in up to 25% of patients, commonly seen in chronic stages (2). Skin colour changes mirror temperature changes as the underlying mechanism is not dissimilar. In the acute stages skin appears red and with time it turns to a paler shade with a bluish tinge.

4.3.2 Sudomotor changes

Sudomotor changes include a degree of sweating and swelling. 60% of patients experience hyperhidrosis (see figure 4.3) and 20% hypohidrosis (2). Swelling and oedema starts within hours to weeks of the initiating event and occurs in 80% of cases (18). It lasts beyond the expected time to recovery and is exacerbated by immobilization as well as overzealous physiotherapy (3).

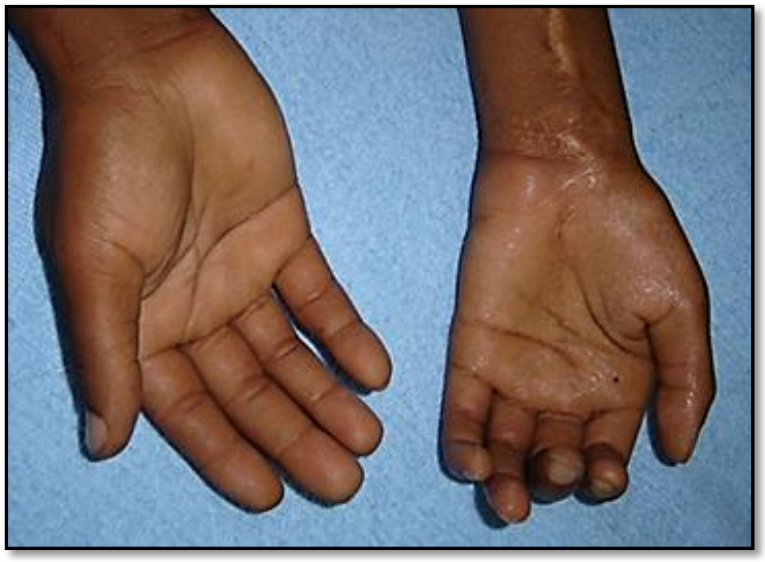


Figure 4.3: Left hand CRPS with sudomotor changes (hyperhidrosis)

4.3.2 Trophic changes

Trophic changes include changes to skin and bone and to hair and nail growth. Skin usually atrophies with time, and bone demineralizes and patients may present with osteoporosis(6), (see figure 4.4). Hair and nail growth increase in acute stages and then decrease in later stages.

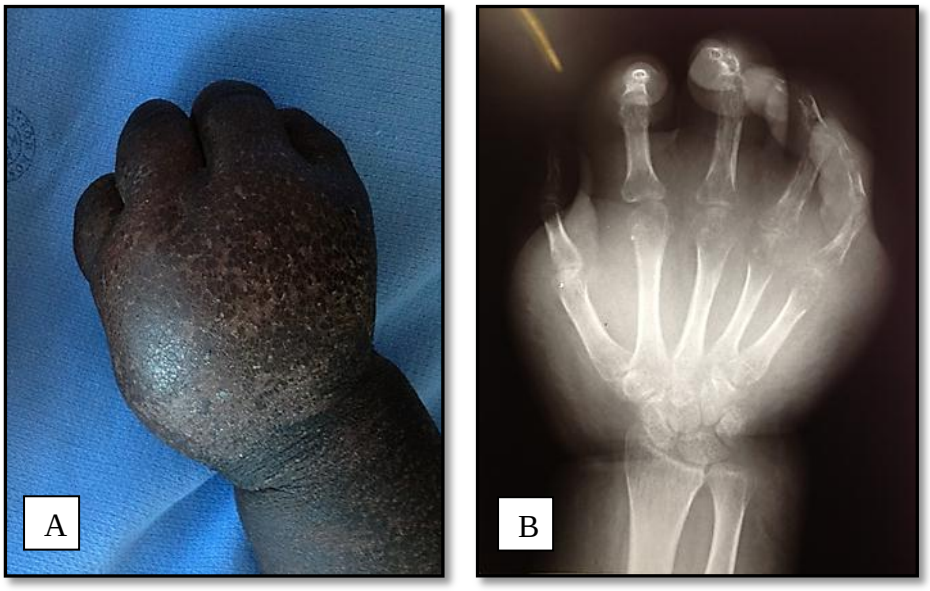


Figure 4.4: Type I CRPS with trophic changes [skin changes (A) and osteoporosis (B)]

Psychological symptoms often accompany the classic triad of sensory, motor and autonomic symptoms of CRPS. They are a result of CRPS disease process and not a cause. Patients often have feelings of anger and depression due to anxiety of their disease process. The symptoms of motor neglect and body perceptual disturbance may also be due to the psychological response to the disease (19).

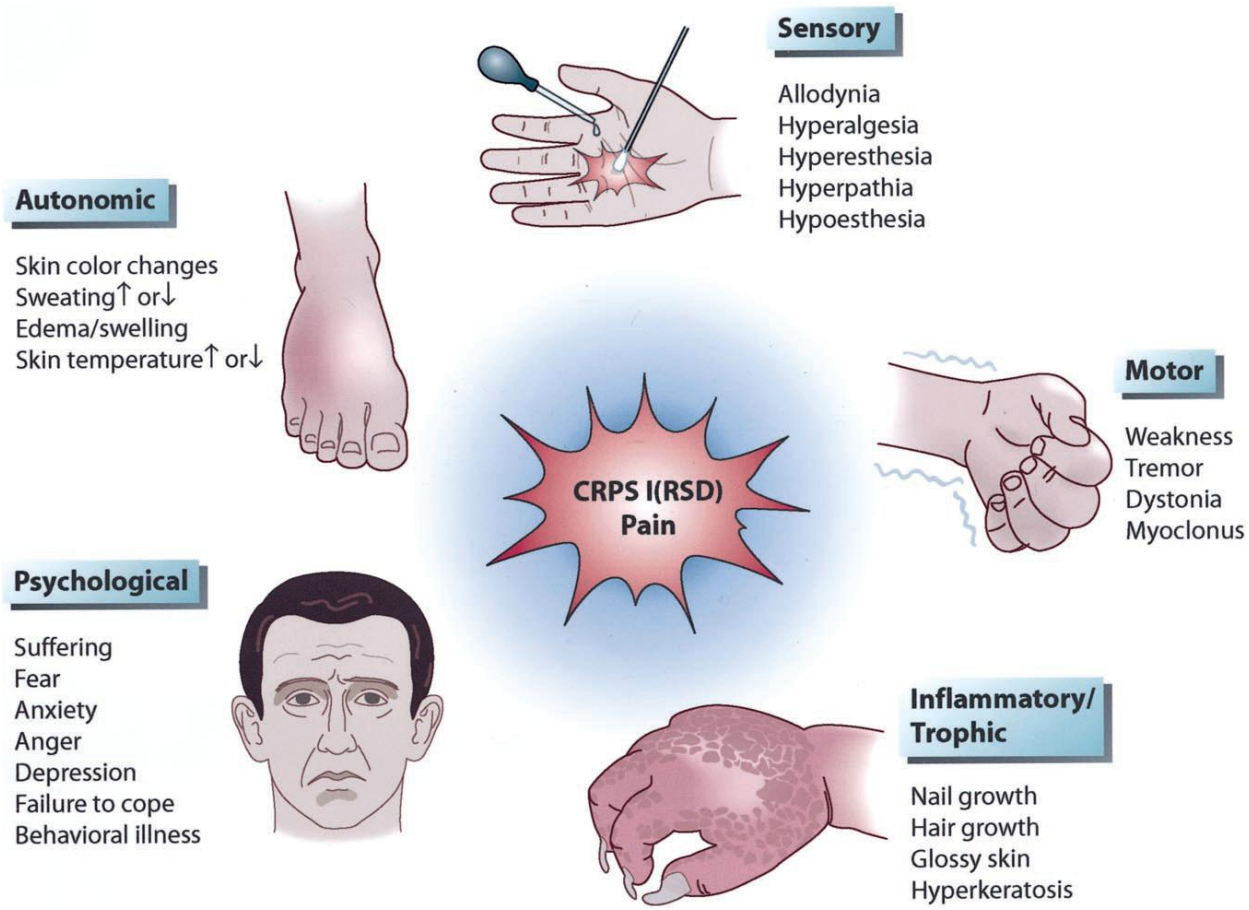


Figure 4.5: Summary of clinical presentation (19)

CHAPTER FIVE

DIAGNOSIS

AND

DIAGNOSTIC CRITERIA

FOR

CRPS

DIAGNOSIS & DIAGNOSTIC CRITERIA

Despite numerous trials investigating diagnostic modalities on CRPS patients ranging from plain x-rays to MRI scans, no single investigation to date has been shown to confidently confirm a diagnosis of CRPS. Due to the difficulties in confirming the diagnosis using standard investigative modalities, the attendant clinician is compelled to recourse to the evaluation of symptoms and signs in the endeavour to make this challenging diagnosis.

5.1 IASP DIAGNOSTIC CRITERIA

In an attempt to facilitate the diagnosis of CRPS and improve the clinical recognition of the disorder, the first IASP diagnostic criteria for CRPS were published in the International Association for the Study of Pain's Taxonomy monograph in 1994 published by Stanton-Hicks in 1995(20) (see table 5.1).

CRPS type 1 (previously called Reflex Sympathetic Dystrophy)
1. The presence of an initiating noxious event, or a cause of immobilization. 2. Continuous pain, allodynia, or hyperalgesia with which the pain is disproportionate to any inciting event 3. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain 4. The diagnosis is excluded by the existence of conditions that would otherwise account for the degree of pain and dysfunction. *Note : Criteria 2-4 must be satisfied*
CRPS type 11 (previously called Causalgia)
1. The presence of continuing pain, allodynia, or hyperalgesia after a nerve injury, not necessarily limited to the distribution of the injured nerve. 2. Evidence at some time of oedema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain. 3. This diagnosis is excluded by the existence of a condition that would otherwise account for the degree of pain and dysfunction. *Note : All three criteria must be satisfied*

Table 5.1: IASP diagnostic criteria for CRPS (21)

5.2 BRUEHL AND HARDEN DIAGNOSTIC CRITERIA

Notwithstanding the detailed diagnostic criteria for CRPS as defined by the IASP, Bruehl and Harden challenged the IASP diagnostic criteria in 1999 with the use of pilot work by Galer from 1998. They identified a lack in specificity and inability to distinguish CRPS from non-CRPS neuropathic pain (*eg* diabetic neuropathy and post-Herpetic neuropathy) in the IASP criteria.

Their reported specificity and sensitivity of the IASP diagnostic criteria was 0,98, and 0,36 respectively and found that a positive diagnosis of CRPS was likely to be correct in as few as only 40% of cases, leading to over diagnosis of CRPS (22).

Bruehl and Harden proposed a set of research diagnostic criteria for CRPS, based upon results of their study and previous factor analysis research. Their criteria appeared to be more specific than the IASP criteria, and substantially improved the ability to discriminate accurately between CRPS and other types of neuropathic pain.

They have suggested criteria requiring at least two of four sign categories and four symptom categories to positively maximize diagnostic accuracy across the widest range of CRPS prevalence rates. Also, their criteria did not discriminate between CRPS type I and type II as it was thought that it was unlikely that the presence or absence of nerve injury would have a significant impact on diagnosis and management.

They concluded that their modified criteria, provides data-based guidelines for future revisions of the criteria proposed by the IASP taxonomy committee, (see table 5.2).

1. Continuing pain which is disproportionate to inciting event

2. Must report at least one symptom in each of the four following categories:

Sensory:	reports of hyperesthesia
Vasomotor:	reports of temperature asymmetry and / or skin colour changes and / or skin colour asymmetry
Sudomotor:	reports of oedema and / or sweating changes and / or sweating asymmetry
Motor / trophic:	reports of decreased range of motion and / or motor dysfunction (weakness, tremor, dystonia) and / or trophic changes (hair, nail, skin)

3. Must display at least one sign in two or more of the following categories:

Sensory:	evidence of hyperalgesia (to pinprick) and / or allodynia (to light touch)
Vasomotor:	evidence of temperature asymmetry and / or skin colour changes and / or asymmetry
Sudomotor:	evidence of oedema and / or sweating changes and / or sweating asymmetry
Motor / trophic:	evidence of decreased range of motion and / or motor dysfunction (weakness, tremor, dystonia) and / or trophic changes (hair, nail, skin)

Table 5.2: Revision of CRPS diagnostic criteria proposed by Breuhl and Harden (21)

5.3 BUDAPEST DIAGNOSTIC CRITERIA

In 2003 a “closed” workshop (by invitation only) was held in Budapest, Hungary to discuss the above proposed revision of CRPS diagnostic criteria. Thirty five pain specialists discussed issues surrounding the IASP diagnostic criteria similar to issues addressed by Breuhl and Harden. They concluded that for clinical purposes, sensitivity is extremely important and on the other hand, specificity is critical in the selection of research samples. Thus, the proposed revision to the CRPS criteria endorsed by the Budapest group resulted in two similar sets of diagnostic criteria (see table 5.3), differing only in the decision rules employed to optimize their use for clinical *vs* research purposes.

General definition of the syndrome
CRPS describes an array of painful conditions that are characterized by a continuing (spontaneous and/or evoked) regional pain that is seemingly disproportionate in time or degree to the usual course of any known trauma or other lesion. The pain is regional (not in a specific nerve territory or dermatome) and usually has a distal predominance of abnormal sensory, motor, sudomotor, vasomotor, and/or trophic findings. The syndrome shows variable progression over time.

To make the clinical diagnosis, the following criteria must be met:

1. Continuing pain, which is disproportionate to any inciting event

2. Must report at least one symptom in three of the four following categories:

Sensory:	Reports of hyperesthesia and/or allodynia
Vasomotor:	Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry
Sudomotor:	Reports of oedema and/or sweating changes and/or sweating asymmetry
Motor/Trophic:	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

3. Must display at least one sign at time of evaluation in two or more of the following categories:

Sensory:	Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement)
Vasomotor:	Evidence of temperature asymmetry (>1°C) and/or skin colour changes and/or asymmetry
Sudomotor:	Evidence of oedema and/or sweating changes and/or sweating asymmetry
Motor/Trophic:	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)

4. There is no other diagnosis that better explains the signs and symptoms

For research purposes, diagnostic decision rule should be at least one symptom in all four symptom categories, and at least one sign (observed at evaluation) in two or more sign categories.

Table 5.3: The Budapest criteria(21)

The interpretation of the Budapest criteria (table 5.3) includes the following(22):

For clinical use: At least 1 symptom in 3 categories & 1 sign in 2 categories

Sensitivity 0.85, specificity 0.60

For research use: At least 1 symptom in 4 categories & 1 sign in 2 categories

Sensitivity 0.70, specificity 0.96

The distinction between CRPS type I and type II, although questioned at the Budapest conference in terms of diagnosis and management validity, was unchanged as per the original IASP diagnostic criteria. With the use of the Budapest criteria, approximately 15% of patients previously diagnosed with CRPS would now be without a diagnosis. A third diagnostic subtype called CRPS-NOS (CRPS – not otherwise specified) was recommended that would categorize those patients who did not fully meet the new clinical criteria, but whose signs and symptoms could not be better explained by another diagnosis.

The diagnostic criteria recommended by the Budapest group, was proposed to the Committee for Classification of Chronic Pain (of the IASP), for inclusion in future revisions of their formal taxonomy and diagnostic criteria for pain states. Pressure is also mounting from other population groups (23), for a more individualised diagnostic criteria tailored to individual population groups to increase the sensitivity as there may be evidence of a genetic contribution to pain perception in CRPS that has been reported from patients across the world (24). This suggestion seems farfetched and unjustifiable and defeats the purpose of common global diagnostic criteria of CRPS.

To date the IASP diagnostic criteria from 1994 remains the official diagnostic criteria used for diagnosis of CRPS despite reproducible evidence that the Budapest criteria is superior (20). In order to improve the diagnostic accuracy of the IASP diagnostic criteria Lankford suggested certain secondary characteristics (listed below) to aid making a diagnosis of CRPS (4):

1. Demineralization and osteoporosis are the most classic findings in late CRPS.

2. Sudomotor changes that vary from hyperhydrosis to dryness of the skin.

3. Temperature difference between affected and unaffected extremities may be marked but is usually measurable at some point in time.

4. Vasomotor instability most commonly is manifested as decreased capillary refill.

5. Erythema may be a sign of increased capillary refill and should be compared with refill in unaffected extremity.

6. Skin may develop a glossy shiny appearance. In late stages, trophic changes may involve a decrease in subcutaneous tissue.

7. In CRPS of the hand, nodules and thickening of the palmer fascia may develop.

As mentioned at the beginning of this chapter, a gold standard in the form of an objective test is not available despite many efforts. However Harden (25), suggested that the use of measurement techniques and laboratory testing may further improve the specificity of diagnostic criteria. Some of these techniques include:

1. The use of 100 mm visual analogue scale for quantifying pain
2. Measuring temperature allodynia using a Peltier type device / infrared thermography
3. Measuring mechanical allodynia using von Frey testing
4. Measuring vasomotor tone using laser doppler flowmetry
5. Measuring oedema using volumetry
6. Measuring osteoporosis using x-ray
7. Measuring vascular bone changes using triple phase bone scintigraphy

Of all the above-mentioned investigative modalities triple phase bone scintigraphy, requires a special mention, since it has the most promising results in terms of aiding in a diagnosis of

CRPS. It is most accurate early on, (in the first year after trauma). Band shape increase radionuclide accumulation in metacarpo- phalangeal and inter phalangeal joints during the mineralization phase is a specific diagnostic criteria (2). Bone scans appear to be sensitive to treatment and may therefore be used both for initial diagnosis and for monitoring response to treatment. Pankaj et el (26) and Wuppenhorst et al (27) showed 100% sensitivity in delayed 3rd phase of bone scan in patients presenting within 3 months of the onset, (see figure 5.1).

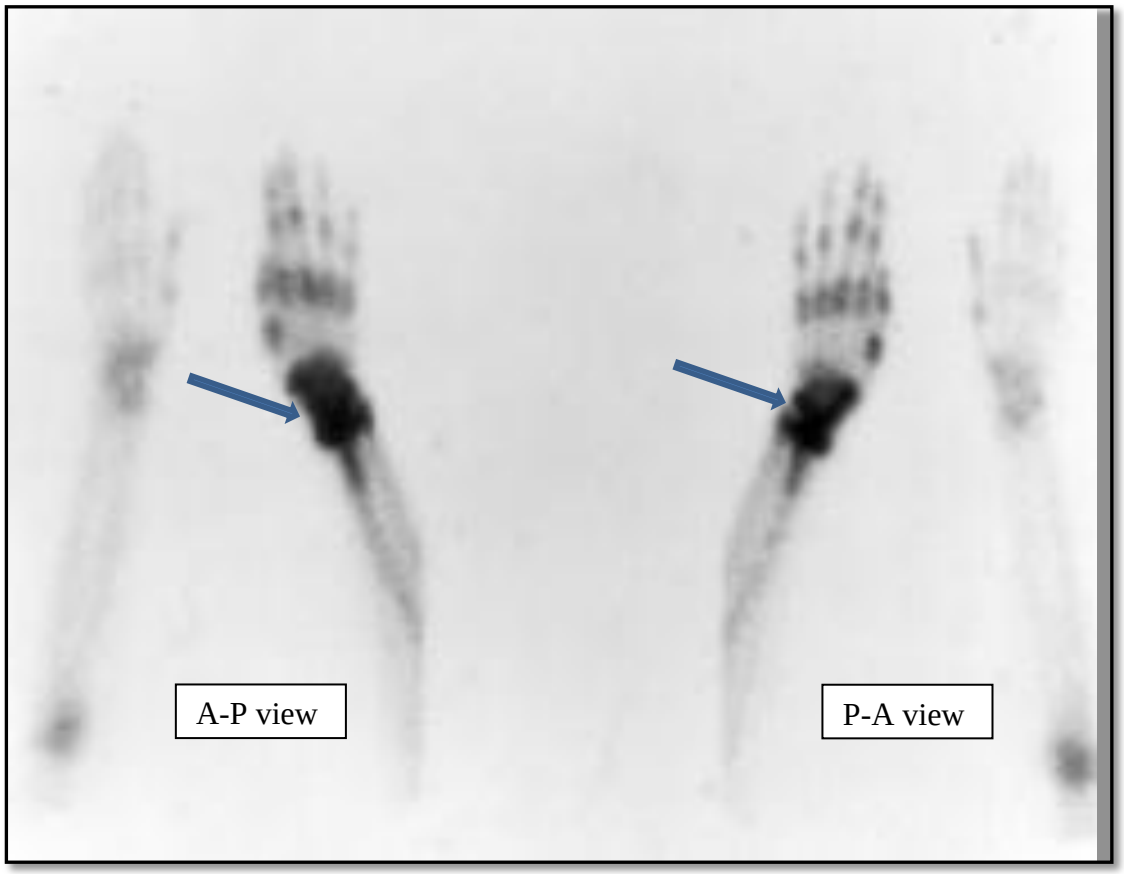


Figure 5.1: Three-phase bone scan in acute CRPS showing increase in tracer-uptake in digital joints, indicated by arrow(4)

The ever increasing range of diagnostic investigations preferred for making the diagnosis of CRPS suggests that no one test is universally applicable and that use of such tests suggests institutional bias, rather than their universal applicability. In addition, many of these diagnostic tests are not widely available, nor accessible to the general practitioner.

CHAPTER SIX

TYPES

AND

STAGES

OF

CRPS

TYPES AND STAGES OF CRPS

CRPS may be classified into types according to presence or absence of nerve injury, according to aetiology, or according to symptomatology extrapolated from previously accepted stages. Of these 3 classification types, only the type according to presence or absence of nerve injury is currently accepted by the IASP.

6.1 TYPES ACCORDING TO PRESENCE OR ABSENCE OF NERVE INJURY

In 1994 the IASP, classified CRPS into two types, *viz* CRPS type I (previously called reflex sympathetic dystrophy) and CRPS type II (previously called causalgia). CRPS type I is diagnosed when there is no obvious nerve injury, whereas CRPS type II refers to cases associated with a nerve injury. Currently this is the only accepted criteria for classifying CRPS. CRPS type II is a true neuropathic condition as there is always documentation of a nerve injury. This nerve injury may be complete, partial or confined to its branches. Majority of CRPS type II cases are due to partial or nerve branch injury and only 5% of CRPS cases are a result of complete nerve injury (28). (See table 6.1).

	TYPE I	**TYPE II**
PREVIOUS TERMINOLOGY	Reflex Sympathetic Dystophy	Causalgia
NERVE INJURY	No	Yes
NERVE CONDUCTION	Often normal	Often abnormal
SYMPATHETIC CHANGES	Less common	More common

Table 6.1: Differences in CRPS type I and type II

Furthermore there is evidence that sympathetically maintained changes occurs more commonly in CRPS type II (29), and of the peripheral nerves involved, the median, ulnar, sciatic and tibial nerves are responsible for these sympathetic changes as they are thought to carry a higher sympathetic burden when compared to peripheral nerves such as the radial nerve (28) (see figure 6.1).

Figure 6.1: Ulnar nerve injury resulting in CRPS of right hand

Although there is evidence for possible differences in clinical presentation this clinical significance in respect of treatment strategies is yet to be established.

6.2 TYPES ACCORDING TO AETIOLOGY

CRPS often develops following a noxious stimulus or an initiating event. However CRPS may develop spontaneously. This so called spontaneous presentation of CRPS has been reported up to 3-11% of cases (30). When comparing the two groups, *ie* the classic post-trauma related CRPS (tCRPS), and spontaneous CRPS (sCRPS), the gender, side of the body, upper and lower limb presentation rates are equal in the 2 groups, as well as the signs and symptoms. What is significantly different is the onset of symptoms (9 year earlier average) in sCRPS

compared to tCRPS, and a poorer prognosis in sCRPS. The younger onset is possibly related to a genetic cause and the poorer prognosis is most probably attributed to the late presentation, or delay in diagnosis due to absence of an initiating event (30). These differences are summarized in table 6.2.

	sCRPS	**tCRPS**
Eitology	? Genetic	Post traumatic
Age	9 years younger	9 years older
Site	Similar	Similar
Signs	Similar	Similar
Symptoms	Similar	Similar
Prognosis	Worse	Better

Table 6.2: Differences between sCRPS and tCRPS types

6.3 TYPES ACCORDING TO CLINICAL PRESENTATION

Earlier reports suggested that CRPS is a progressive condition that evolves with time. These reports date as far back as 1937 and hypothesised that the condition progresses in symptomatology with time, and thus can be divided in to distinct stages. In an attempt to define treatment rationale, Drucker *et al* (1959) arbitrarily categorised CRPS (then, in the pre-IASP era, called causalgia) into three stages which were partially based on time, and partially based on symptom severity (26). Since then the descriptions of these stages differed somewhat in detail by the different authors; however they all conformed in general to the stages described by Bonica in 1990. Stage 1 was from onset to 3 months and was characterised by burning pain and oedema, stage 2 was from 3-6 months from onset and characterised by increased pain with motor and trophic changes, and stage 3 was greater than 6 months from onset and characterised

by intractable pain, with atrophic muscles and contracture formation (9), (see figure 6.1). A summary of the 3 stages of CRPS is shown below (table 6.3)

Stage	Sensory	Motor	Autonomic trophic	Autonomic vasomotor
1 Hyperaemic (0-3 months)	burning pain	muscle spasm limited mobility joint stiffness	increased hair nail growth hyperhidrosis	soft oedema hyperthermic skin
2 Dystrophic (3-6 months)	increase in pain intensity	muscle atrophy joint thickening	decreased hair growth weak nails and bones	brawny oedema cooler skin
3 Atrophic (> 6 months)	intractable pain	muscle wasting with contracture formation	hair &nails may regrow sweat may return	irreversible skin changes atrophic skin

Table 6.3: Summary of stages(4)

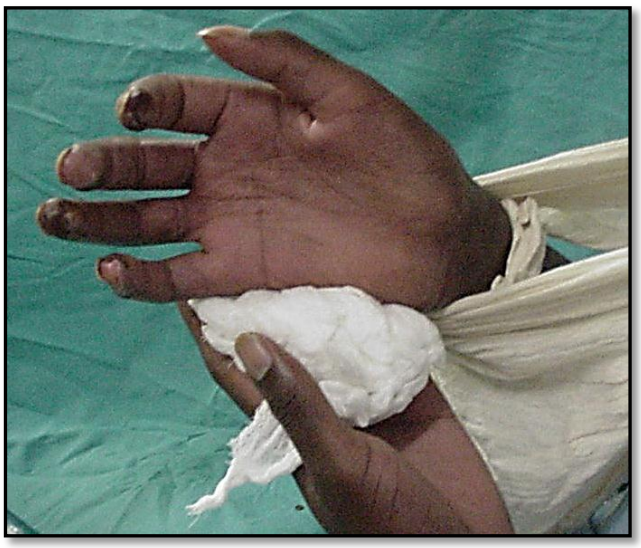


Figure 6.2: Atrophic stage of CRPS with skin changes

The early reports suggesting distinct stages were widely accepted until a large multicentre cluster analysis was performed by Bruehl et al (9). The clinical presentation was classified into 3 subgroups based along the arbitrary stages referred to. There was lack of pain duration difference between the subgroups and therefore they strongly refuted the traditional view of progressive stages of the disease. The results of this study showed pain duration to be greatest in subgroup 2, the briefest in subgroup 3 and intermediate in subgroup 1. The motor and trophic changes were the same in subgroup 1 and 2 and twice as prevalent in subgroup 3. However, what this study did show was a statistically difference in the subgroups despite refuting the traditional view of progressive stages. They concluded that CRPS can be divided into the following 3 subgroups:

1. A relatively limited syndrome in which vasomotor signs predominate
2. A relatively limited syndrome in which neuropathic pain/ sensory abnormalities predominate. Nerve conduction studies showed that this group may well be CRPS type II patients.
3. Florid CRPS, similar to ‘‘classic RSD’’ descriptions. This group featured the highest levels of motor and trophic signs and possible disuse-related changes (osteopenia) on bone scan, despite having the briefest pain duration of the three groups.

CHAPTER SEVEN

SPREAD

OF

CRPS

SPREAD OF CRPS

It is well known and indeed widely described in literature over the past 7-8 decades that CRPS symptoms may be experienced in parts of the body other than that of the initial CRPS presentation. This phenomenon is called CRPS spread. There is paucity of data studying patterns and possible etiological aspects of spread. To date only 2 large publications tackle this issue by Maleki *et al* (31) and Van Rijn *et al* (32). A review of their findings follows.

7.1 MALEKI PATTERNS OF SPREAD – see table 7.1 (31)

Maleki described three patterns of spread:

1. Contiguous spread: gradual enlargement of the area affected initially
2. Independent spread: appearance of CRPS in a location that was distant and non-contiguous with the initial site
3. Mirror image spread: appearance of symptoms that closely matches size and location of the initial presentation but on the opposite side

In this study, 19% of patients experienced contiguous spread alone, 81% experienced contiguous spread together with either independent spread or mirror image spread, and less than 1% experienced all 3 types of spread.

All patients in their review presented with contiguous spread over an average period of 78 days from initial presentation. Spread occurred both proximally and distally from initial site, with distal spread greater than proximal spread. In 26% of these patients there was no identifiable precipitating factor (true spread), whereas 74% was related to a therapeutic intervention *eg* splinting.

Seventy percent of patients presented with independent spread over an average period of 2.6 years from initial presentation. In 26% of these patients there was no identifiable precipitating factor (true spread), whereas 74% was related to either therapeutic intervention, *eg* epidural blocks, a second injury or compensatory overuse of the limb.

Fifteen percent of patients presented with mirror image spread over an average period of 2.5 years from initial presentation. In 25% of these patients there was no identifiable precipitating factor (true spread), whereas 75% of patients were related to circumstances similar to that mentioned in independent spread.

It can be seen that the majority of cases are associated with an event that can be reasonably thought to have been causative and thus cannot represent true spread. However a significant amount of patients (averaging 25-26% in each group) where no causative relationship could be established with confidence may represent true spread.

The postulated aetiology for contiguous spread was an abnormal inflammatory response that is exaggerated in magnitude that does not resolve when tissue heals. Independent spread was thought to be due to an aberrant CNS regulation of neurogenic inflammation. Mirror image spread possibly involved spread across commissural pathways in the dorsal root ganglia.

However these theories are difficult to reconcile with the frequent long intervals between the initial CRPS presentation and the onset of spread.

TYPE OF SPREAD	PRESENTATION (%)	TIME TO PRESENTATION
CONTIGUOUS	100%	78 DAYS
INDEPENDENT	70%	2.6 YEARS
MIRROR IMAGE	15%	2.5 YEARS

Table 7.1: Maleki patterns of spread

7.2 VAN RIJN PATTERNS OF SPREAD - see table 7.2 (32)

Van Rijn et al also described 3 patterns of spread:

1. Contralateral spread: Spread from arm to arm or leg to leg
2. Ipsilateral spread: Spread from arm to leg or leg to arm on same side
3. Diagonal spread: Spread from arm to leg on opposite side or vice versa

This study focused on true spread (where no precipitator to spread was identifiable). Certain patterns were identified in this study and were regarded as hazards. The greater the number of limbs involved, the greater the risk of spread to other limbs. Left side onset had a higher risk of spread compared to right side onset.

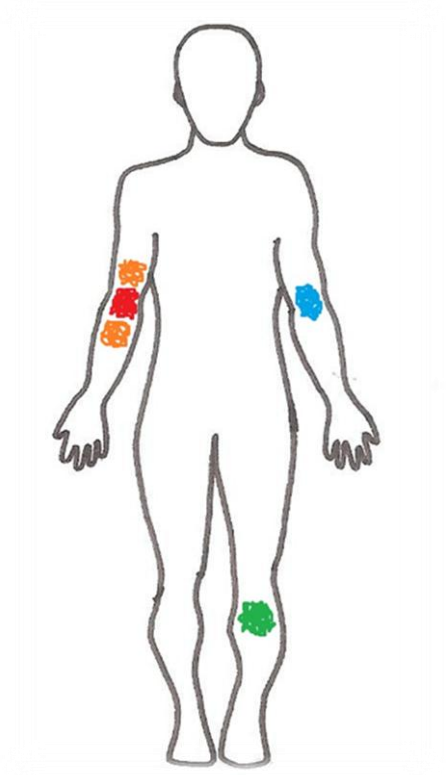
The dominant pattern of spontaneous spread observed in this study strongly suggested that CRPS does not spread according to some systemic vulnerability but is more likely to spread via spinal or cortically mediated mechanisms; however, the evidence for this remains is lacking.

A comparison of spread patterns described by Maleki and Van Rijn can be seen in figure 7.1.

TYPE OF SPREAD	PRESENTATION (%)	TIME TO PRESENTATION
CONTRALATERAL	63%	21 MONTHS
IPSILATERAL	34%	19 MONTHS
DIAGONAL	3%	10 MONTHS

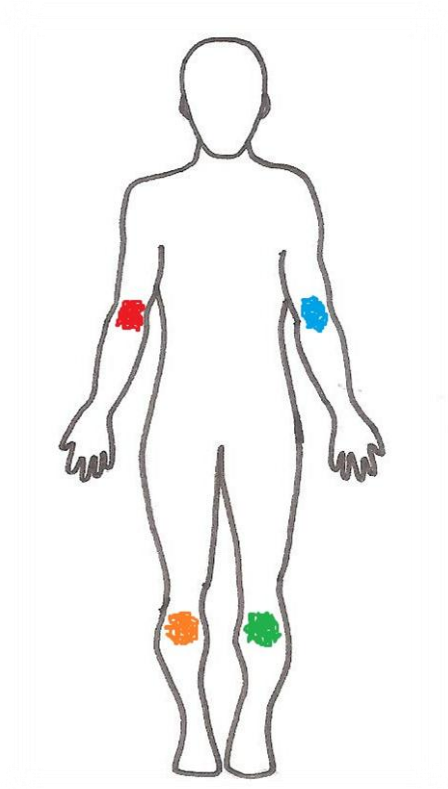
Table 7.2: Van Rijn patterns of spread

MALEKI



PRIMARY SITE
CONTIGIOUS SPREAD
MIRROR SPREAD
INDEPENDENT SPREAD

VAN RIJN



PRIMARY SITE
CONTRALATERAL SPREAD
IPSILATERAL SPREAD
DIAGONAL SPREAD

Figure 7.1: Comparisons of patterns of spread

CHAPTER EIGHT

RISK FACTORS

AND

PREDISPOSITION

TO

CRPS

RISK FACTORS AND PREDISPOSITION

Almost every person will experience some sort of trauma in their lifetime, ranging from the most minor of traumas to the most extensive. However not all people develop CRPS. Why is this? It should make sense then that there has to be a certain predisposition in certain individuals. But is there? Several studies using this understanding have attempted to seek risk factors and predisposing factors for the development of CRPS. The following are considered:

1. Psychological
2. Genetic
3. Behavioural
4. Epidemiological

8.1 PSYCHOLOGICAL

Anxiety and depression are known proven psychological problems as a result of CRPS. However the presumption that anxiety and depression presence before trauma as a risk factor for the development of CRPS has not been demonstrated in 2 large trials(33, 34). However, other psychological aspects may be related and merit investigation.

8.2 GENETIC

The occurrence of CRPS in siblings of patients with CPRS suggests a genetic predisposition to its development (35). Hence, the research into its possibility exits. Population based studies reveal no overall increased risk of developing CRPS for siblings of CRPS patients but a significantly increased risk in siblings younger than 50 years, which may indicate that genetic factors play a more pronounced role in this subgroup (36). Genetic studies of CRPS have identified polymorphisms in the tumour necrosis factor alpha (TNFα) gene and to a lesser degree the angiotensin converting enzyme (ACE) gene (37). However these findings have yet

to be reproduced in independent studies. Also, a significant elevation of HLA II DR15 has been found in CRPS patients and HLA II DR13 in patients with multifocal or generalized tonic dystonia. The exact relations between HLA features and CRPS are also not clear. However these findings suggest possible genetic factors for the manifestation of CRPS (38).

8.3 BEHAVIOURAL

Certain post injury behaviour patterns or treatment responses such splinting and immobilisation of limbs in an attempt to produce healing may in fact promote the development of CRPS (39). In a study of healthy persons, voluntary splinting and immobilisation of limbs produced mild features of CRPS except pain which were reversed once mobilisation commenced indicating that behavioural responses such as immobilisation may be a risk factor for CRPS (40). No correlation to smoking or alcohol has been found (41).

8.4 EPIDEMIOLOGICAL

The use of angiotensin converting enzyme (ACE) inhibitors at the time of trauma or a history of migraine or asthma may be associated with an increased risk of developing CRPS (42, 43). The common denominator in these epidemiological factors is inflammation. Migraine and asthma share an underlying mechanism of neurogenic inflammation whereas ACE inhibitors increase substance P and bradykinin which are mediators of inflammation.

It can thus be appreciated that research into predisposing factors can have a potentially invaluable contribution to CRPS, as this can curb the management for better outcome in patients at risk for CRPS, and implement preventative measures to help pacify this aggressive and morbid disease process.

CHAPTER NINE

EPIDEMIOLOGY

OF

CRPS

EPIDEMIOLOGY OF CRPS

The exact incidence and prevalence of CRPS is unknown due to obvious multiple confounding factors. There is a vast epidemiological difference in published data and this may well be attributed to differences in ethnicity, socio-economics and different diagnostic criteria.

The two largest population based studies to date were undertaken in the USA and the Netherlands. The USA study reported an incidence of 5,5per 100 000 persons at risk and a prevalence of 21 per 100 000 persons in CRPS type I. Type II CRPS was reported as an incidence of 0,8 per 100 000 persons at risk and a prevalence of 4 per 100 000 (44).

The Netherlands study reported an incidence of 26,2 per 100 000 in CRPS in general (45).

Overall, CRPS type I is more prevalent than CRPS type II. The female to male ratio ranges from 2-4:1. The mean age of peak diagnosis is 37-50 years and the highest incidence is at 61-70 years (44, 45).

With regards to sites that are involved, the extremities are most commonly affected; the upper extremity is almost twice as more affected than the lower extremity. Fractures are the most common trigger accounting for 45% of cases (46), followed by sprains (18% of cases) and elective surgery (12% of cases) (45).

Brain lesions account for 12% of CRPS cases and myocardial infarctions about 5% (8). Breast CRPS and CRPS following Herpes have only been anecdotally reported (see figure 9.1). The incidence of spontaneous CRPS has been reported as being < 10% (30).

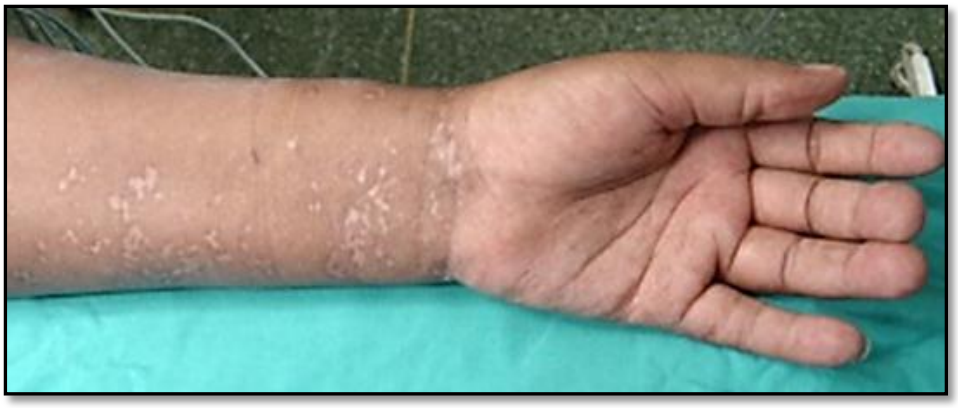


Figure 9.1: CRPS of left hand following Herpes Simplex Virus

CHAPTER TEN

PATHOGENESIS

OF

CRPS

PATHOGENESIS OF CRPS

Despite intense research into this phenomenal condition, the pathogenesis of CRPS is still not well understood. What we have today are numerous postulated theories for its remarkable presentation, most of which provides us with an understanding today for reasons of specific presentations and symptoms, but none accounting for the disease process. The pathogenesis of each symptom complex will be discussed separately.

10.1 PATHOGENESIS OF SENSORY ABNORMALITIES

There is increasing evidence that one of the underlying causes of sensory abnormalities is changes in the central representation of somatosensory sensations in the thalamus and cortex. Central sensitisation at the level of the spinal cord has also been recently implicated. The idea of sympathetically mediated pain is still supported today as one of the oldest theories of pain and sensory abnormalities in CRPS to date.

10.1.1 Central representation: Cortico-thalmic reorganisation theory

Magneto-encephalographic (MEG) and functional magnetic resonance imaging (fMRI) studies of patients with upper limb CRPS demonstrated a shrinkage of the hand representation in the primary sensory cortex (postcentral gyrus) *ie* a shortened distance between little finger and thumb representations and a total shift of hand representation towards the lip on the painful side of the primary somatosensory (SI) cortex (15, 47, 48). This cortical reorganisation has been reported to correlate linearly with the intensity of CRPS pain and to reverse following pain relief (48, 49). This is a clear indication that on-going pain results in cortico-thalmic reorganisation in the brain which influences somatosensory output or interpretation, and prevention of this reorganisation may curb symptomatology.

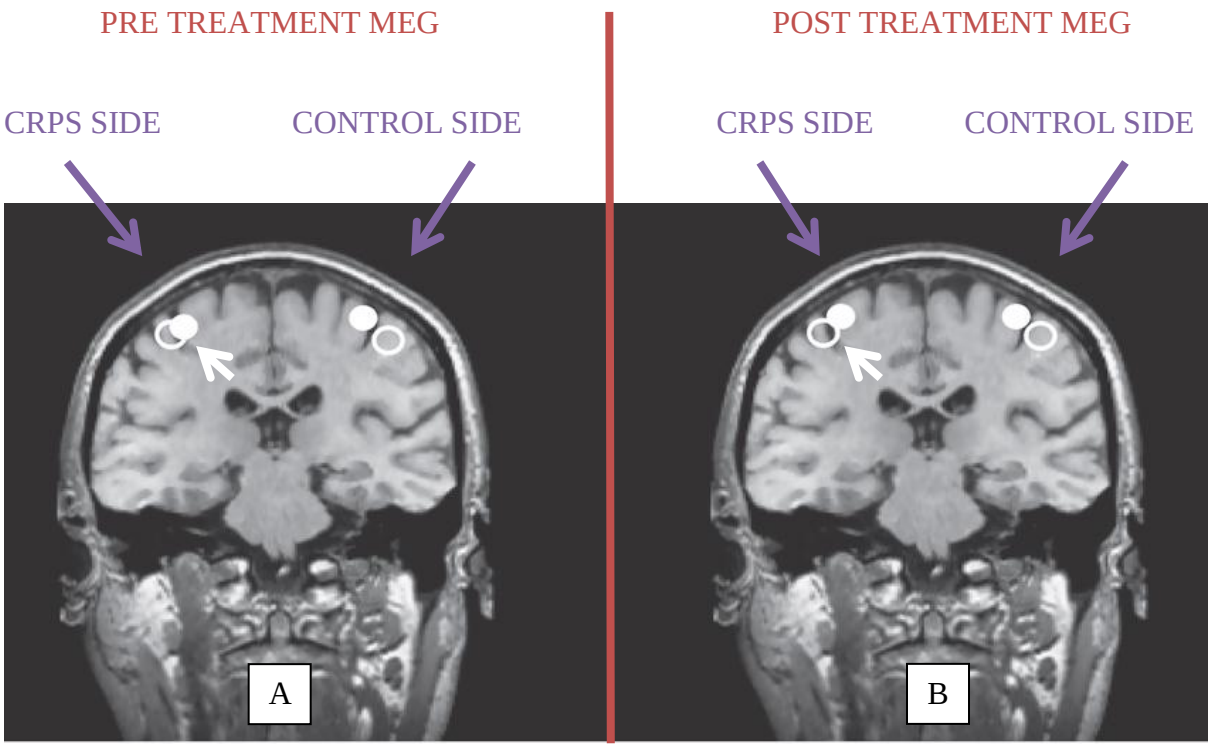


Figure 10.1: Pre-treatment (A) and Post treatment (B) MEG imaging (39)

Image indicating distance between 1st digit (filled circle) and 5th digit (open circle), of affected CRPS side of brain (indicated by arrow) compared to unaffected side. There is a shortened distance between the thumb and little finger cortical representation of the affected CRPS side witch normalizes after treatment.

Other evidence of centrally mediated effects include adaptive changes in the thalamus and increases SI responses on the affected side noted on positron emission tomography (PET) (50) and sensory and motor hyper excitability noted with the central nervous system trans-cranial magnetic stimulation (TMS) studies (51). Central sensitization permits normally non painful stimuli such as light touch or cold to activate nociceptive pathways (allodynia) and results in exaggerated responses to nociceptive stimuli (hyperalgesia).

10.1.2 Central sensitisation theory

Central sensitization is reflected in the increased excitability of nociceptive neurons in the spinal cord. This is thought to be a result of persistent or intense noxious input resulting from tissue damage or nerve injury which results in the release of neuropeptides, such as substance P and bradykinin (52).

10.1.3 Altered cutaneous innervation theory

Skin biopsies obtained from patients with CRPS I (where no clear indication of nerve damage had occurred) has revealed a decrease in C-fibre and Aδ-fibre density in the affected limb (53). Although animal studies have demonstrated that this damage may initiate CRPS symptoms, available human studies cannot determine whether this neural loss is related causally to the injury initiating CRPS.

10.1.4 Sympathetically mediated pain theory

A. Pain may be sympathetically mediated

There are two types of neurogenic pain that exists. Those that are sympathetically mediated, called sympathetically mediated pain (SMP), and those that are not sympathetically mediated, called sympathetically independent pain (SIP). The only way to differentiate between the two is by sympathetic blockade. Those that respond to the blockage are classified as SMP, and those that do not as SIP (8).

B. Sympathetically mediated pain is related to noradrenergic nociceptor sensitivity

There is also evidence that these SMP patients develop noradrenergic nociceptor sensitivity following nerve injury. Evidence for this is as follows:

1. Sympathetic chain stimulation in CRPS type II patients produces pain as opposed to sympathetic chain stimulation in hyperhidrosis patients not producing pain
2. Intra-cutaneous application of norepinephrine into a symptomatic area of SMP patients rekindles spontaneous pain that had been relieved by sympathetic blockade, supporting the idea of noradrenergic nociceptor sensitivity (54).

C. *A link between nociceptor afferents and sympathetic efferents in skin of SMP patients has been described. Evidence supporting this link is:*
    1. The intra-cutaneous norepinephrine re-igniting pain after sympathetic blockade as described above (54).
    2. Physiological stimulation of the sympathetic nervous system in SMP patients by whole body cooling produced intense pain of the affected limb compared to SIP patients (55).

It is very likely that in addition to a coupling in the skin, a sympathetic–afferent interaction may also occur in other tissues, in particular in deep somatic domains such as bone, muscle or joints however there are no studies proving this theory.

For those patients with SIP several theories exist. Two of these theories are:

1. SMP may not be a constant phenomenon and may decrease as disease progresses with time (56).
2. Sympathetic activity may present independent to efferent peripheral pathways and may explain non responsiveness to sympathetic blockade (57).

The above studies suggest increasing evidence that chronic painful stimuli to the brain results in cerebral reorganization and sensitization which in turn leads to sensory and motor deficits. However, the exact mechanism of how this affects changes, both functional and structural to the peripheral nerve system is not known. What can be demonstrated peripherally however is a

sympathetically mediated link to pain with increase nociceptor catecholamine sensitivity over time.

10.2 PATHOGENESIS OF AUTONOMIC ABNORMALITIES

10.2.1 Sympathetic denevation supersensitivity theory

It is reasonable to assume that vasomotor symptoms (temperature and skin blood flow changes), and sudomotor symptoms (alteration in sweating) are being mediated by the sympathetic nervous system (SNS). Early on in the CRPS disease process signs of vasodilatation and increase temperature changes, both indicating a decrease in sympathetic function (sympathetic denervation) are demonstrated. As the condition progresses signs vasoconstriction and decrease temperature changes develop and are thought to be due to increased sensitivity to circulating catecholamines (super sensitivity). However this "sympathetic denevation supersensitivity theory" cannot explain the sudomotor autonomic symptoms *ie* hyperhidrosis (8).

There are 3 reasons for this:

1. In CRPS I there is no overt nerve lesion
2. In CRPS II the autonomic symptoms spread beyond the territory of the injured nerve
3. Unlike blood vessels, sweat glands do not develop denervation super sensitivity and therefore increased sweat production cannot be explained by a peripheral mechanism, and may be better explained by the central autonomic dysregulation theory.

10.2.2 Central autonomic dysregulation theory

This theory holds that the acute presentation of autonomic effects and the on-going sudomotor effects at the periphery are centrally controlled. Central body heating and cooling producing exaggerated temperature changes in the affected CRPS limbs compared to the rest of the body attest to this.

During the warm / acute phase of CRPS central sympathetic reflex measurements by whole body warming and peripheral effector organ output measurements by skin blood flow and temperature infrared thermometry, reveal higher skin temperatures and blood flow compared to the normal side even after massive body cooling (58). This is suggestive of unilateral inhibition of cutaneous sympathetic vasoconstrictor neurons, which leads to a warmer limb in the acute stage. However, when resting sweat output as well as thermoregulatory and axon reflex sweating are tested during this phase an increase is demonstrated, indicating that this phase is centrally controlled phenomena rather than a peripheral denervation (29, 59).

Furthermore, in the cold / chronic phase there is an increase stimulation of cutaneous vasoconstrictor neurons indicating sympathetic activity later on in the disease process, further negating peripheral sympathetic denervation. Increase in alpha adrenoceptors from skin biopsies of affected CRPS limbs may explain this paradox of vasoconstriction and cold limbs later on in the disease process as oppose to earlier vasodilatation and warmer limbs (8). Secondary changes in neurovascular transmission may induce severe vasoconstriction and cold skin but this is thought less likely (60). The finding of increased skin lactate during this phase indicates possible anaerobic glycolysis from chronic tissue hypoxia and is thought to be a result of the vasoconstriction rather than a cause of the vasoconstriction (61).

Thus, although central disturbances in efferent sympathetic outflow seem to be predominant in the acute stage of CRPS, disturbed neurovascular transmission and development of hyper-

reactivity of blood vessels to circulating catecholamines seem to predominate in the chronic stage.

10.2.3 Livingston's vicious circle theory

The interaction of central nervous system with the autonomic nervous system may have been correctly explained by Livingston in 1944 when he described his "vicious circle theory" (4). He postulated that an initial event sends an exaggerated signal to the brain which results in initial inactivity of the sympathetic nervous system. This inactivity reduces the proprioceptive input and its inhibitory effect of pain at the level of the spinal cord, resulting in unopposed hyperactivity of the sympathetic nervous system, causing further vasoconstriction and spasticity (4).

10.2.4 Neurogenic inflammation theory

Classical inflammation in CRPS is not proven, and the reason being that autoimmune antibody concentrations, sedimentation rates, lymphocyte populations, activated T-cell concentrations, antigen titres and blood cell counts are all normal, thus excluding an aberrant inflammatory cellular-mediated immune response (62). However a neurogenic component to inflammation does exist. Trauma results in activation of cytokines and nerve growth factor which causes sensitisation of primary afferents. These primary afferent neurons release neuropeptides [mainly substance P and calcitonin-gene related peptide (CGRP)] which result in the acute CRPS symptoms which resemble inflammation (pain, increased skin temperature, oedema and increased blood flow) (63). This accounts for peripheral neuropeptide release. Peripheral neuropeptide release might also contribute to hyperhidrosis (64). Motor symptoms may be due to central neuropeptide release.

Other evidence supporting this theory includes the following:

- Corticosteroids are often successfully used in acute CRPS (8)
- Radiolabeled immunoglobulin show extensive plasma extravasation in patients with acute CRPS (8).
- Analysis of joint fluid and synovial biopsies in CRPS patients have shown an increase in protein concentration and synovial hyper vascularity (65).
- Higher levels of endothelin-1, interleukin (IL)-6 and tumour necrosis factor α (TNF-α) and diminished levels of nitric oxide (NO) were observed in the involved extremity as compared with the uninvolved extremity (63, 66).
- Analysis of the cerebrospinal fluid in CRPS I and II revealed higher levels of pro-inflammatory IL-1β and -6 when compared to control subjects (67).
- Immunoreactivity to Campylobacter was found in many patients in early stages of CRPS, in particular when the disease was associated with minimal trauma, indicating a post infectious autoimmune basis in some patients (68). More evidence for an autoimmune pathophysiology is that 35% of patients with CRPS express surface-binding autoantibodies against sympathetic and mesenteric plexus neurons (69, 70).

10.2.5 Oxidative stress theory

Indirect proof of on-going oxidative stress in CRPS follows the demonstration, in preliminary studies, of the efficacy of hyperbaric oxygen therapy on pain, oedema and motor dysfunction (71).

The role of the sympathetic nervous system cannot be ignored in the pathogenesis of autonomic symptoms. However the discrepancy in symptomatology and the link to the central nervous system is not well understood and may be still best described by Livingston's theory.

Endothelial dysfunction that was previously linked as a pathogenesis in the cold phase is now thought to be as a result of the free radicals produced due to chronic tissue hypoxia. There is overwhelming evidence of an inflammatory process in CRPS; however this is mainly a neurogenic inflammatory process and only occurs during the acute phases. The exact mechanisms of the initiation and maintenance of these inflammatory reactions remain unclear. However, the way in which the immune and nervous systems interact particularly in the bones, muscles, and connective tissue is still not fully understood and warrants further research.

10.3 PATHOGENISIS OF MOTOR ABNORMALITIES

10.3.1 Central sensitization theory

The evidence for central sensitization theory is listed below:

- Trans-cranial magnetic stimulation (TMS) studies show localised CNS hyper excitability indicating a central origin (51).
- fMRI showed reorganization in the central nervous system, predominantly in the parietal cortices, supplementary motor area (SMA) and primary motor cortex on corresponding affected side (72).
- Repetitive TMS applied to the motor cortex contralateral to the affected extremity in CRPS showed potential to modulate, *ie* decrease pain (47). This has been demonstrated in patients with neglect like symptoms (73).
- Incongruence between central motor output and sensory input has been was demonstrated as an underlying mechanism in CRPS (74, 75).
- A decrease in the afferent sensory input to cortical motor centres in CRPS patients has been demonstrated (76).

Although the peripheral nervous system bares the bulk of the brunt of CRPS affects, most of these studies show a central cause rather than pathology within the peripheral system itself leading to majority of the motor symptoms seen.

It can be clearly seen that the motor, sensory and autonomic theories postulated for pathogenesis for CRPS demonstrate a constant overlap in. If these theories were to be scrutinized outside their symptomatology domain as categorized above, two clear patterns evolve; a central pattern and a peripheral pattern of postulated theories.

Central patterns include:

- cortico-thalmic reorganisation
- central sensitisation
- central autonomic dysregulation

Peripheral patterns include:

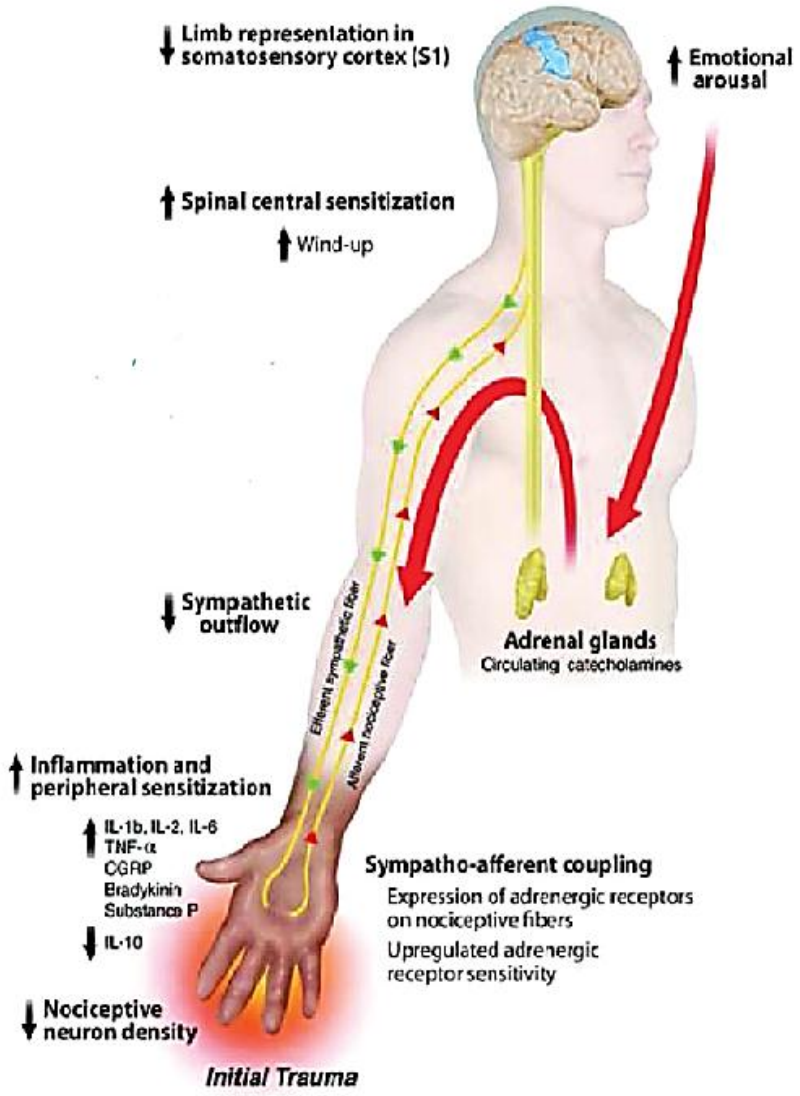
- sympathetically mediated pain
- sympathetic denevation super-sensitivity
- neurogenic inflammation

The postulated pathophysiological mechanisms are summarized in table 10.1 and figure 10.2.

MECHANISM	SUPPORT
Altered cutaneous innervation	Reduced density of C- and Aδ-fibers in CRPS-affected region (53) Altered innervation of hair follicles and sweat glands in CRPS-affected limb (53)
Central sensitization	Increased windup in CRPS patients (51)
Peripheral sensitization	Local hyperalgesia in CRPS affected vs unaffected extremity (77) Increased mediators of peripheral sensitization (see inflammatory factors later)
Altered SNS function	Bilateral reductions in SNS vaso-constrictive function predict CRPS occurrence (78) Vaso-constriction to cold challenge is absent in acute CRPS but exaggerated in chronic CRPS (58, 79, 80) Sympatho-afferent coupling (55)
Circulating catecholamines	Lower norepinephrine levels in CRPS - affected vs unaffected limb (58) Exaggerated catecholamine responsiveness because of receptor up-regulation related to reduced SNS outflow (81)
Inflammatory factors	Increased local, systemic, and cerebrospinal fluid levels of pro- inflammatory cytokines, including TNF-α, interleukin-1 & 2 (82) Decreased systemic levels of anti-inflammatory cytokines (interleukin-10) (83) Increased systemic levels of pro-inflammatory neuropeptides, including CGRP, bradykinin, and substance P (62, 64)
Brain plasticity	Reduced representation of the CRPS-affected limb in somatosensory cortex (15, 48, 49) These alterations are associated with greater pain intensity and hyperalgesia, impaired tactile discrimination, and perception of sensations outside of the nerve distribution stimulated (48, 84) Altered somatosensory representations may normalize with successful treatment, although other brain changes may persist (49)

CGRP: calcitonin gene-related peptide; CRPS: complex regional pain syndrome; SNS: sympathetic nervous system; TNF: tumor necrosis factor

Table 10.1: Summary of postulated pathophysiological mechanisms(81)



CGRP = calcitonin gene-related peptide; IL = interleukin; TNF = tumour necrosis factor.

Figure 10.2: Summary of postulated pathogenesis mechanisms (81)

CHAPTER ELEVEN

MANAGEMENT

OF

CRPS

MANAGEMENT OF CRPS

Despite intense research into CRPS the pathophysiology of this pain syndrome is poorly understood and it is therefore not surprising that there is no uniform approach to its management. There are very few controlled trials on CRPS therapy and management options are usually based on the proposed pathophysiological mechanisms. Therapy is often based on a multi-disciplinary team approach with use of non-pharmacological therapy (*eg* physiotherapy, psychotherapy), pharmacological therapy (*eg* analgesics, neuroleptics), and interventional therapy (*eg* stellate ganglion blocks, sympathectomy) (see figure 11.4). The main objective in management is to alleviate the pain and restore functionality.

11.1 NON PHARMACOLOGICAL THERAPY

11.1.1 Physiotherapy and Occupational therapy

This form of therapy is aimed at restoring function of the affected part by desensitization. Physical and, to a lesser extent, occupational therapy has shown to reduce pain and improve active mobility in CRPS (85). Furthermore active physiotherapy is not only shown to be effective, but cost effective. Physiotherapy should be first attempted under light anaesthesia to initiate movement as patients are overwhelmed by severe pain and should be cautiously performed to avoid damage to atrophied tissue and bones which have become osteo-dystrophic. Since prevention is better than cure, early institution of physiotherapy will prevent secondary complications such as decreased joint and tendon movement and subsequent atrophy. The intensity of treatment should be modified to the severity of the disease. A consensus conference for the management approach for CRPS, formulated the guidelines which included a combination of physiotherapy and occupational therapy and the addition of other therapies

(as indicated in Figure 11.1) only if patients failed to progress to next level in a period of 4 weeks (86).

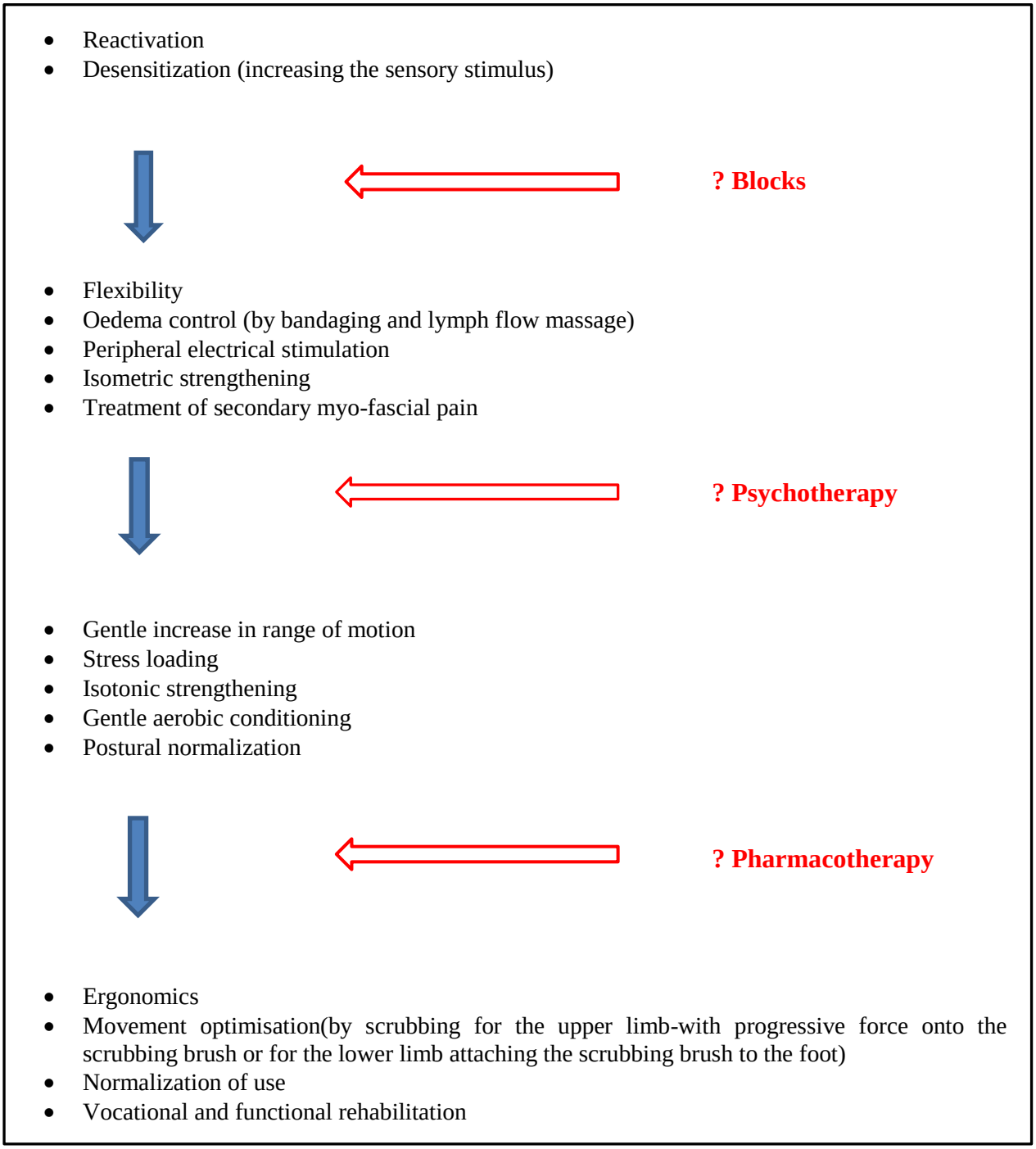


Figure 11.1 : Steps in rehabilitation of CRPS patients (86)

Although standardized physiotherapy has shown long-term relief in pain and physical dysfunction recent developments of mirror and limb recognition techniques have advanced this field. Mirror therapy (figure 11.2) has been shown to significantly reduce pain levels in CRPS patients; the affected limb is placed within a mirror box, such that the unaffected limb is reflected in such a way as to make the patient think they are looking at the affected limb. Movement of this reflected normal limb is then performed such that it appears to the patient as though they are performing movement with the affected limb. Concepts of neural plasticity within the brain have been hypothesized as to why this effect occurs, and similar mirror therapy has been used successfully to treat phantom limb pain. Results are good in early stages of CRPS but not in chronic cases (74). A graded motor learning concept is required in chronic cases, which contains a limb recognition task, then imagination of movements and in the last step, use of the aforementioned mirror therapy (75).

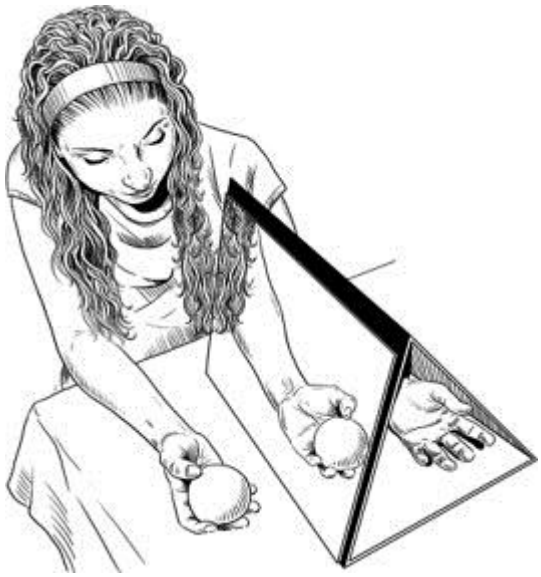


Figure 11.2: Mirror box therapy (87)

11.1.2 Psychotherapy

There is a high incidence of anxiety and depression that is related to CRPS. There is also findings of a post-traumatic like stress disorder called kinesophobia (the fear of movement), that is prevalent among these patients (86). This kinesophobia prevents mobilisation of the affected limb due to fear of pain, and this is a compounding negative re-enforcer to the commencement of physiotherapy. This can be successfully managed with graded exposure therapy. This form of therapy decreases pain-related fear, pain intensity and consequent disability (88). Depression and or anxiety should be treated with anti-depressants and anxiolytics respectively. Many physicians recommend the use of amitriptyline because of its supposed specific action on pain, but there is no hard evidence to support this view. Although adequate randomized controlled studies of psychological interventions in adult CRPS patients are not available to guide this aspect of CRPS management, the following protocol for psychological treatment has been proposed by Bruehl & Chung (89):

1. Education regarding the nature of the disease for all patients and their families.
2. If disease duration exceeds 6–8 weeks, patients should be evaluated psychologically and treated with cognitive behavioural techniques (CBT).
3. In case of psychiatric co-morbidities or major on-going life stressors, these issues should be addressed additionally with general CBT.

11.2 PHARMACOLOGICAL THERAPY

The use of drug therapy in the treatment of CRPS is by no means a sole therapy approach. The rationale for drug therapy is to alleviate symptoms of CRPS to facilitate rehabilitation. It follows that drug therapy alone is never enough and is often used in conjunction with non-

pharmacological rehabilitative therapy, as detailed above. The selection of drug therapy to combat this condition is based on identifying the most prominent mechanism producing the symptoms. However it can be seen by the array of pathophysiological mechanisms that identifying the offending mechanism may prove unsuccessful and thus a combination of drugs is often utilised in an attempt to stop the CRPS pathway at various stages.

11.2.1 Anti-inflammatory therapy

Non Steroid Anti-Inflammatory Drugs (NSAIDs)

The use of NSAIDS in chronic pain has not been extensively researched even though neurogenic inflammation has been implicated in its pathogenesis. In a small underpowered study, no improvement was demonstrated in bone scintigraphy after 3 months of use NSAIDs. Pain was not assessed properly (8).

Steroids (Prednisone)

Oral prednisone, 10mg administered three times a day showed clinical improvement in up to 75% of patients with CRPS within an average time of 13 weeks (8).

11.2.2 Immune modulators

Immunoglobulin

A double blinded controlled trial has concluded that the treatment of long-standing complex regional pain syndrome (CRPS) is empirical and often of limited efficacy. Preliminary data suggest that the immune system is involved in sustaining this condition and that treatment with

low-dose intravenous immunoglobulin (IVIG) may substantially reduce pain in some patients (90).

Monoclonal Antibodies

Two case reports (91, 92), report favourable effects of local administration of tumour necrosis alpha (TNF-α), infliximab in all symptoms of acute CRPS over 8 weeks treatment.

11.2.3 Analgesics working on sensitisation of pain

N-methyl-Daspartate blocker

The release of the magnesium block at the N-methyl-Daspartate (NMDA) receptor with consequent influx of calcium and consequent initiation of intercellular cascades appears to be a critical factor in initiation of central sensitization. Experimental and clinical literature supports the effectiveness of a NMDA (ketamine) in blocking central sensitization by its effects on the NMDA receptor. However, trial results are inconsistent. There are only results of small trials available and accordingly these compounds are only third-line recommendations in neuropathic pain (93).

Calcium channel blocker

Calcium channel blockers such as nifedipine have a very limited role in early stages of CRPS.

Sodium channel blocker

Intravenous sodium channel blocker (Lidocaine) used in a randomised double blinded control trail (94), revealed statistically significant reduction of spontaneous pain intensity, decrease of cold and mechanical hyperalgesia and mechanical allodynia.

Opioids

Although opioids have shown to be beneficial in other neurogenic pain syndromes, its use in CRPS is yet to be determined, and its use is solely by associated success in other neurogenic pain syndromes.

Anti-depressants

The use of antidepressants in CRPS has not been researched (95). Like opioids, the use of anti-depressants such as tricyclic antidepressants (TCA's) in CRPS is due to its associated success in other neurogenic pain syndromes. Selective serotonin reuptake inhibitors (SSRI's) have not shown to be beneficial in any neurogenic pain syndrome.

GABA agonist

GABA (γ-aminobutyric acid) agonist inhibits sensory input to the neurons of the spinal cord. In a double blinded randomised control study by van Hilten (96), 7 patients with reflex sympathetic dystrophy in whom the chief clinical manifestation of the disorder was multifocal or generalized fixed dystonia, intrathecal baclofen, a GABA agonist was administered. All women showed remarkable improvement and in some cases resolution of their dystonia (arms > legs) with high dose bolus (50-75µg) or continuous infusion of intrathecal baclofen, (see figure 11.3.) There were also some minor improvements to other CRPS symptoms.

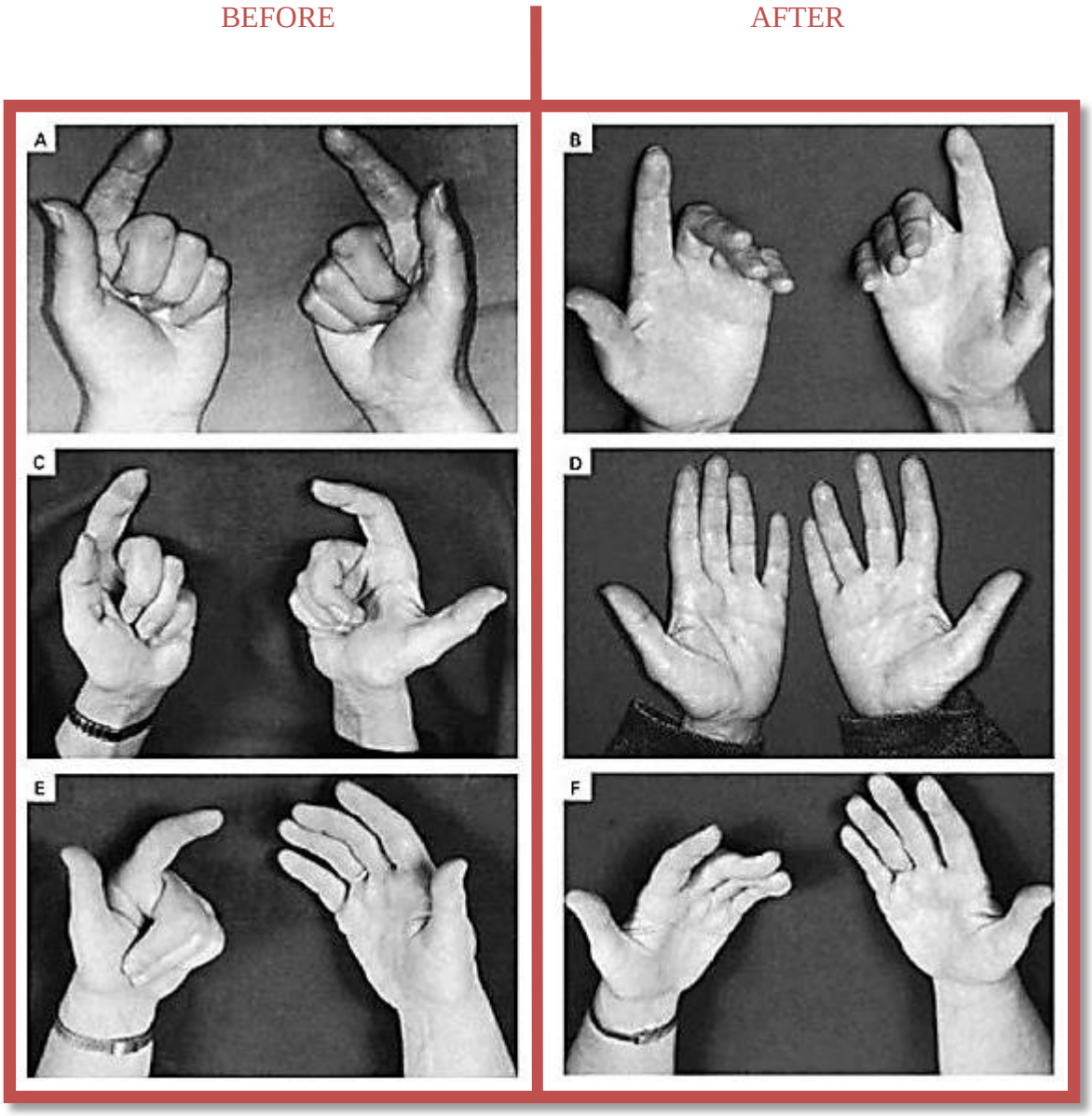


Figure 11.3: Dystonia before and after intrathecal baclofen (96)

11.2.4 Neuroleptics

Carbamazepine

Carbamazepine showed better pain relief in patients with peripheral neuropathic pain compared to morphine (97).

Phenytoin

Phenytoin has limited use due to its side-affect profile (4).

Gabapentin

In a double blinded randomised control trial by van de visse (98), gabapentin showed mild improvement in pain intensity compared to placebo which was not statistically significant, and no improvement in motor and autonomic symptoms.

11.2.5 Free radical scavengers

DMSO (dimethylsulfoxide)

Topical application in a randomised control trial showed to have some affect in warm CRPS (99).

NAC (N-acetyl-cysteine)

Oral therapy shown in a randomised control trial to have some affect in cold CRPS (98).

Vitamin C

Vitamin C has not been studied as a treatment option but rather as a prophylactic drug. Two reliable randomized placebo- controlled prevention studies have been conducted to date (100) to determine its efficacy in prevention of CRPS in patients with Colle's fractures. Both studies showed that 500mg of Vitamin C for 50 days from day of fracture can reduce the incidence by up to 5 times (99).

11.2.6 Bone metabolism drugs

Calcitonin

Two large reviews have shown contradictory results for the use of nasal spray calcitonin in the management of CRPS pain. The one study (101) demonstrated a significant analgesic effect; in contrast, the other review (102) could not show a definite efficacy of calcitonin.

Bisphosphonates

Bisphosphonates have the potential to reduce pain associated with bone loss in patients with CRPS. However, this evidence is not sufficient enough at present to recommend its use in practice (103).

11.3 INTERVENTIONAL THERAPY

Interventional treatments for CRPS patients are usually reserved for patients who have failed functional restoration (either in starting or progression) with interdisciplinary management comprising of non-pharmacological and pharmacological treatment. A stepwise progression from the less invasive blocks, to infusions or catheter infusion therapies, and ultimately to invasive therapies should be recommended in order to facilitate the patient's functional improvement and pain control, should they not progress. Although evidence for these types of therapies is sparse, interventions at the sympathetic efferent system are part of therapy algorithms in CRPS and are based mainly on enormous reported successful clinical experience and on the limited evidence of controlled trials.

A recommended Interventional Pain Treatment Algorithm for CRPS is as follows (4):

Step 1: *Minimally Invasive Therapies*

- Sympathetic Ganglion Blocks
- Intravenous Regional Nerve Blocks

Step 2: *More Invasive Therapies*

- Neuro-stimulation : Motor Cortex Stimulation (MCS), Spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS)
- Continuous Intrathecal Pump Implantation (e.g. Intrathecal Baclofen)

Step 3: *Surgical Therapies*

- Open Sympathectomy / Endoscopic Thoracic Sympathectomy (ETS)

11.3.1 Minimally invasive therapies

Sympathetic ganglion blocks (SGB)

SGB involves injections of local anaesthetic around sympathetic paravertebral ganglia that project to the affected body part. The efficacy of these blocks has not been thoroughly researched and randomised trials are lacking. The non- randomised trials however show up to 70% complete response (104). Response may be permanent or temporary. These blocks, besides being therapeutic, can also help differentiate between SMP and SIP.

Intravenous Regional Nerve Blocks

Involves the administration of regional intravenous anaesthetic such as reserpine to an isolated extremity occluded with a tourniquet. This anaesthetic depletes nor-adrenaline in the postganglionic axon. A meta-analysis of studies assessing the effect of intravenous regional sympathetic blockade for CRPS failed to draw conclusions concerning the effectiveness of this procedure, mainly due to small sample sizes (8).

11.3.2 More invasive therapies

1 Neurostimulation

Neurostimulation involves the placement of electrodes either centrally (Motor Cortex Stimulation - MCS), at level of spinal cord (Spinal cord stimulation - SCS), or peripherally on peripheral nerves (peripheral nerve stimulation - PNS). Stimulation of nerves at these levels aims to reduce pain in CRPS. Sensory and sympathetic changes accompanying CRPS may be decreased by MCS regardless of its eitology (105). A meta-analysis (106) showed that in selected patients SCS can relieve pain and allodynia and improve quality of life; however more studies are needed to determine long term efficacy and furthermore they are not without its own problems. Data regarding PNS is lacking.

*2 Intrathecal Pump Implantation (s*ee Pharamacotherapy 11.2, above)

11.3.3 Surgical therapies

See Chapter 12: The role of sympathectomy

Modality of pain relief	Analgesics	Administration route	Evidence level
Pharmacologic treatment			
Steroids	Prednisolone	po	B
Calcium-regulating drugs	Calcitonin	IN	B
	Clodronate	IV	B
	Alendronate	IV/po	B
	Pamidronate	IV	B
Free radical scavengers	DMSO	Topical	B
	NAC	po	B
Calcium channel-blocking anticonvulsants	Gabapentin	po	C
Spinal drug application			
GABA agonists	Baclofen	IT (in dystonia)	C
α2-receptor agonist	Clonidine	Epidural	C
Stimulation techniques			
Spinal cord stimulation		Epidural	B
Physical and occupational therapy Physical or occupational therapy, mirror visual feedback treatment, hand laterality recognition training, movement imagination			B
Psychologic therapy Cognitive behavioral treatment, graded exposure, disease education			B

DMSO, dimethylsulfoxide; GABA, gamma aminobutyric acid; IN, intranasal; IV, intravenous; IT, intrathecal; NAC, N-acetylcysteine; po, oral.

Table 11.1: Summary of interventions supported by evidence(8)

Modality of pain relief	Analgesics	Administration route
Pharmacologic treatment		
NSAIDs	e.g. naproxen, ibuprofen, diclofenac	po
Opioids	e.g. tramadol, morphine, oxycodone	po
Antidepressants	e.g. amitryptiline, desipramine, duloxetine	po
Calcium channel-blocking anticonvulsants	Pregabalin	po
Sodium channel-blocking agents/anticonvulsants	Lidocaine	IV
	Carbamazepine	po
NMDA receptor blockers	Ketamine	po/IV
	Dextrometorphan	po
Immune-modulating drugs	Intravenous immunoglobulin	IV
α2-receptor agonist	Clonidine	Topical
Interventional treatment		
Electrical nerve stimulation	TENS	Local
Intervention at the sympathetic nervous system level	Sympathetic ganglion blocks	Local
	Intravenous regional sympatholysis	IV
	Surgical sympathectomy	

IV, intravenous; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs; po, oral; TENS, transcutaneous electrical nerve stimulation.

Table 11.2: Summary of commonly used interventions currently unproven(8)

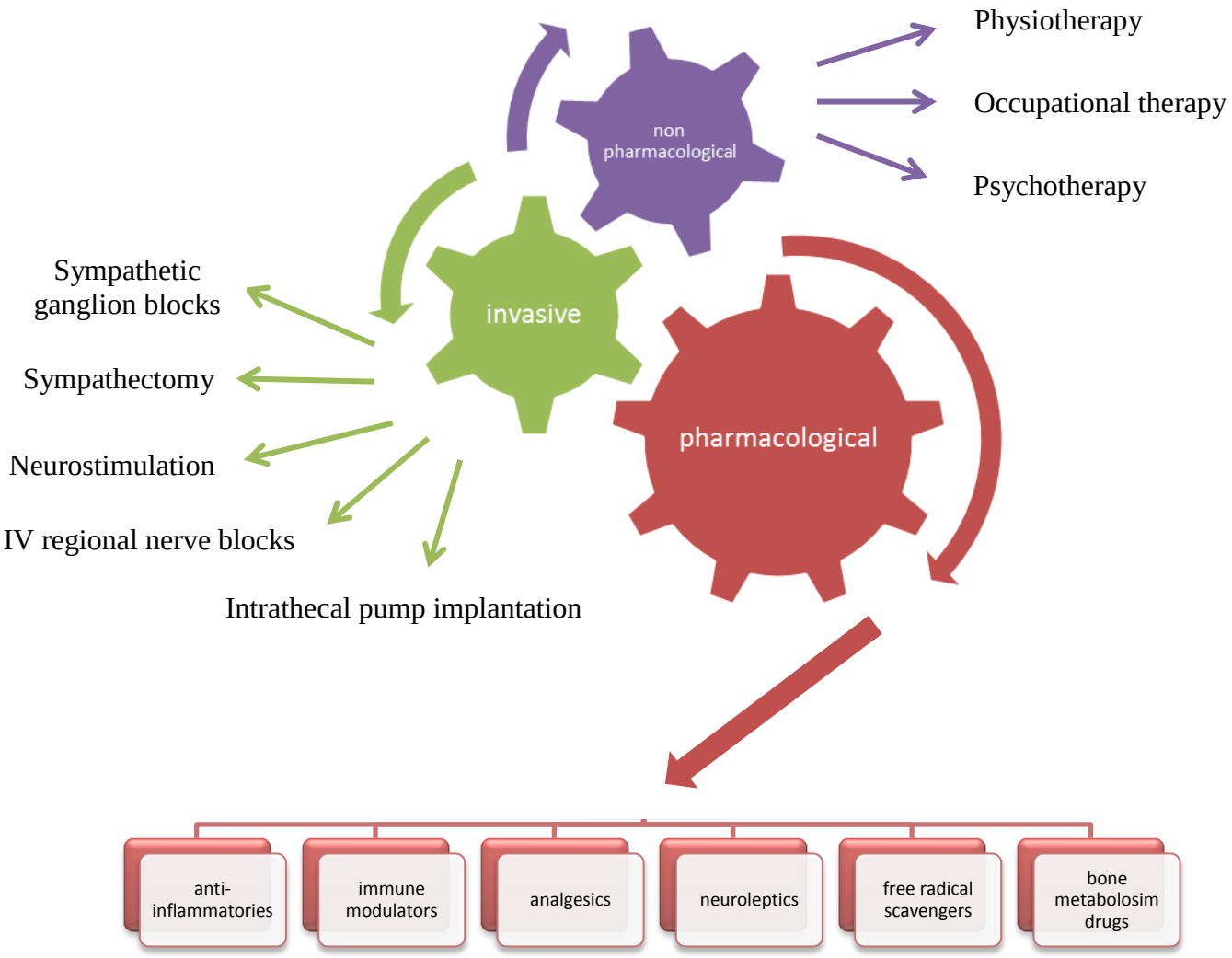


Figure 11.4: Diagramatic representation of management options

"Because time is of the essence, failure to progress should be seen as a trigger to introduce regional anaesthesia or neuro-modulatory methods to support the progressive rehabilitation."

Dr Michael Stanton-Hicks. Cleveland Clinic Foundation(4)

CHAPTER TWELVE

THE ROLE

OF

SYMPATHECTOMY

THE ROLE OF SYMPATHECTOMY

"The history of the sympathetic nervous system has been a long and colourful one. Its understanding and application in surgical practice like many other facets of surgical development has suffered from misrepresentation and denial, but benefited from serendipity and dogged perseverance. Indeed, the history of surgery in general is littered by acts of sheer inspiration and foresight that have transformed standard surgical procedures. Equally and sadly so, enterprising endeavours have been under-appreciated and cast aside, only to be belatedly appreciated decades later. The history of the sympathetic nervous system illustrates this with respect to its anatomical and surgical status".

B Singh 2002 (107)

12.1 STELATE GANGLION BLOCK (SGB)

In the absence of a universally accepted role for sympathectomy in the management of CRPS, the advocacy for sympathectomy has largely reflected institutional bias vindicated by the demonstration of SMP following SGB. It follows that sympathectomy following the demonstration of SMP would prompt permanence to the pain relief. Tradationally, the SGB is performed by a specialist anaesthetist under local anaesthesia undertaken via the supraclavicular paratracheal approach. With the patient supine and the neck extended to the contralateral side, the stellate ganglion is localized along the medial aspect of the sternocleidomastoid muscle at the level of the cricoid cartilage. The needle is advanced posteriorly between the carotid and internal jugular sheaths, aiming for the lateral bony mass of the C7 and T1 vertebrae. Ten millilitres of local anaesthetic (0.25% Bupivacaine solution) is then injected. Classically, development of a Horner's Syndrome with warming and drying of the hand and relief of pain indicates a successful SGB. The accuracy of the SGB may be

enhanced with the use of ultrasound to localise the sympathetic outflow to the limb (see figure 12.1)

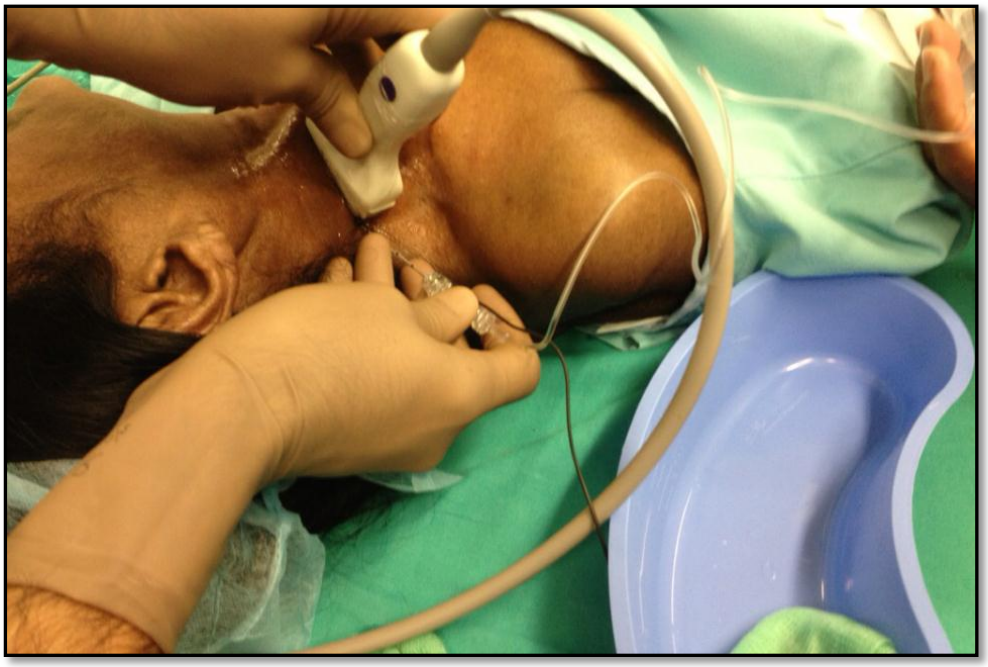


Figure 12.1: SGB undertaken with ultrasound guidance

Notwithstanding the use of a localising technique to SGB it is imperative to emphasize that present day technique for upper limb sympathectomy entails the excision of the 2nd thoracic ganglion. It follows that the accurate demonstration of SMP in the upper limb must follow the "block" of the 2nd thoracic ganglion. The 2nd thoracic ganglion is located retro-pleurally and is not readily "blocked" using percutaneous techniques (108). The accuracy of the SGB is pivotal, since a false negative SGB may deny the patient an effective and enduring therapy in the form of a sympathectomy.

12.2 SYMPATHECTOMY FOR CRPS: A BRIEF HISTORY

Historically in the absence of ethical restraint sympathectomies were undertaken for a variety of conditions, often unsuccessfully. The unsuccessful outcome to sympathectomy often relegated the role of this technique in surgical practice. Notwithstanding this, the first successful sympathectomioes were performed in the 1920's for the management of hyperhidrosis and vasospastic disorders. The first documented sympathectomy for CRPS (then known as causalgia) was by performed by Leriche in 1917 (107).

However, its use for the management of CRPS quickly faded with the experimentation of pharmacology, and other non-operative options for its management, rightfully so at the time due to the morbidity from open sympathectomies.

Sympathectomies however came back to the fore with the advent of minimal access surgery, with a large decline in morbidity compared to that that was experienced in the open surgery era. This method was first described by Kux in 1954 (107). However this too became unpopular due to its invariable sporadic success. Genuine indications for sympathectomy were thereby relegated.

Despite this unpopularity of the procedure it is a known fact that sympathectomy has freed many patients from the agonizing pain of "causalgia". Sympathectomy has also been reported as being successful in the management of disabling hyperhidrosis and effective in the management of vasculopathies, thereby preventing the development of digital ulceration or complete gangrene and avoiding amputation (107).

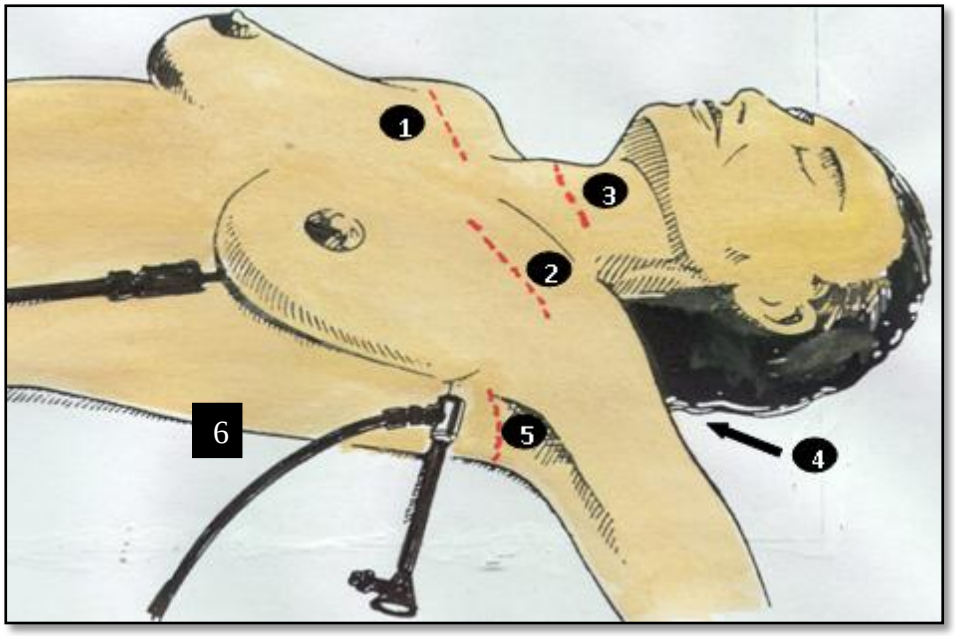
12.3 SURGICAL APPROACH TO SYMPATHECTOMY

The surgical approach (in particular to the upper limb) has long been a vexed issue, despite a greater understanding of the anatomy sympathetic nervous system. Historically, several surgical techniques have been described (see figure 12.2). This reflects the historical failure to establish a technique that is universally safe and reproducible.

These techniques not only employed different approaches (anterior cervical, anterior thoracic or posterior extra-pleural), but also different forms of handling of the sympathetic chain ranging from resection of the stellate ganglion with or without segments of the upper thoracic sympathetic chain. Consistently, these approaches are invariably demanding, prone to complications and much debility.

The supraclavicular approach is arguably the most widely used of the available “open” surgical approach, thereby establishing “cervical sympathectomy” as primarily a vascular procedure vascular surgeons are most facile with this approach.

In current practice sympathectomy may be readily, safely and effectively undertaken by the minimally invasive techniques (thoracoscopic and lumbar sympathectomy). Indeed the minimal access approach is today acknowledged as the approach of choice to effect sympathectomy.



1. Anterior supraclavicular - Garry (1949)
2. Anterior transthoracic - Palumbo (1956)
3. Anterior neck - Lougheed (1965)
4. Posterior Midline - Cloward (1969)
5. Axillary transthoracic with 1st rib resection - Roos (1971)
6. Minimally invasive thorascopic sympathectomy - Byrne (1990)

Figure 12.2: Surgical options for sympathectomy (107)

12.4 TECHNIQUE OF THORACOSCOPIC SYMPATHECTOMY(107)

The wide popularity and effectiveness of thoracoscopic sympathectomy merits a brief description of this technique.

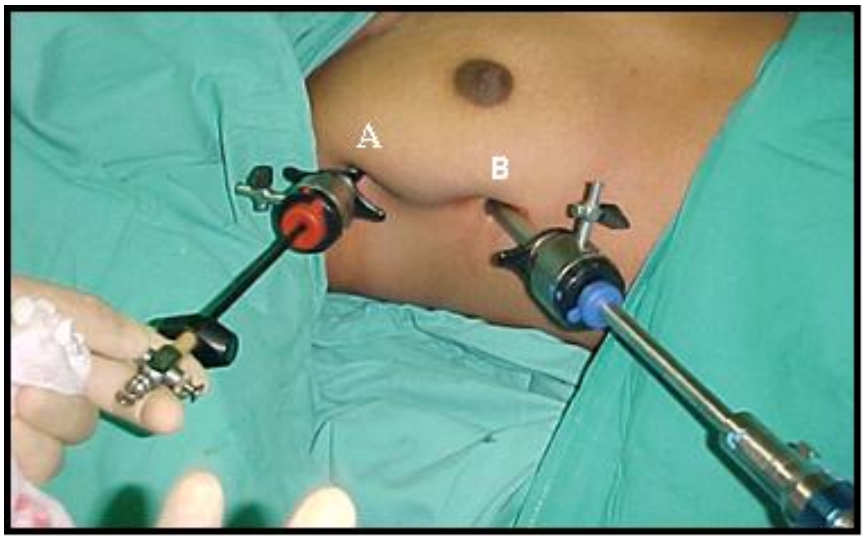
The operation is undertaken under a general anaesthetic employing a single lumen endotracheal tube. The arms are abducted to about 90 degrees. A small pillow is located between the scapulae to throw the chest into profile and 30 degree reverse Trendelenberg position effected.

The procedure begins (if bilateral) on the right side. The pleural space is insufflated with carbon dioxide delivered via a Veress needle is inserted posterior to the lateral aspect of the

pectoralis major muscle at the level of the sternal angle; mechanical ventilation is stopped, simultaneously facilitating partial collapse of the lung. The carbon dioxide insufflation is continued to no more than an intra-pleural pressure of 7cms water. The patient's ventilation is thereafter maintained by intermittent shallow manual ventilation.

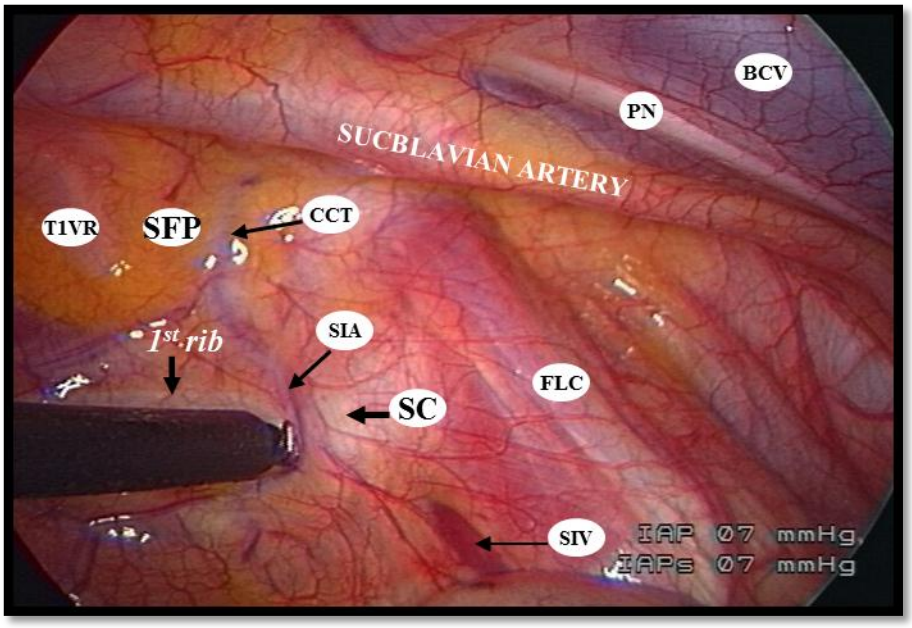
The telescope port is then introduced along the 5th intercostal space in the anterior axillary line, (see figure 12.3); a 5mm telescope (either 0 degrees or 30 degrees) connected to a video monitor is passed into the pleural space. At the site of the Veress needle a second 5mm point is placed. This point serves as the access for the dissecting instrument.

The highest rib noted is the 2nd rib; the neck of the 1st rib is obscured by the stellate ganglion. The pleura below the neck of the 2nd rib is stripped, (see figure 12.4) to demonstrate the 2nd thoracic ganglion and associated interganglionic segment of the sympathectic chain. The 2nd thoracic ganglion is mobilised and excised. Following thorough haemostasis PEEP is applied with suction of the pneumothorax. A routine post-operative chest X-ray is not routinely undertaken. The patient is usually discharged within 24 hours.



Dissection port (5mm) – [A] along the 3rd intercostal space posterior to pectoral fold Camera port (5mm) – [B] along the anterior axillary line, 5th intercostal space

Figure 12.3: Port placement for thoracoscopic sympathectomy (107)



BCV -	Brachiocephalic vein	**SIA** -	Superior intercostal artery
PN -	Phrenic nerve	**SC** -	Sympathetic chain
T1VR-	T1 ventral ramus	**SIV** -	Supreme intercostal vein
SFP -	Stellate fat pad	**FLC** -	Fascia over longus colli muscle
CCT -	Costocervical trunk		

Figure 12.4: Intrathoracic view of sympathetic chain & structures (107)

12.5 EFFICACY OF SYMPATHECTOMY- DOES IT HAVE A ROLE IN CRPS?

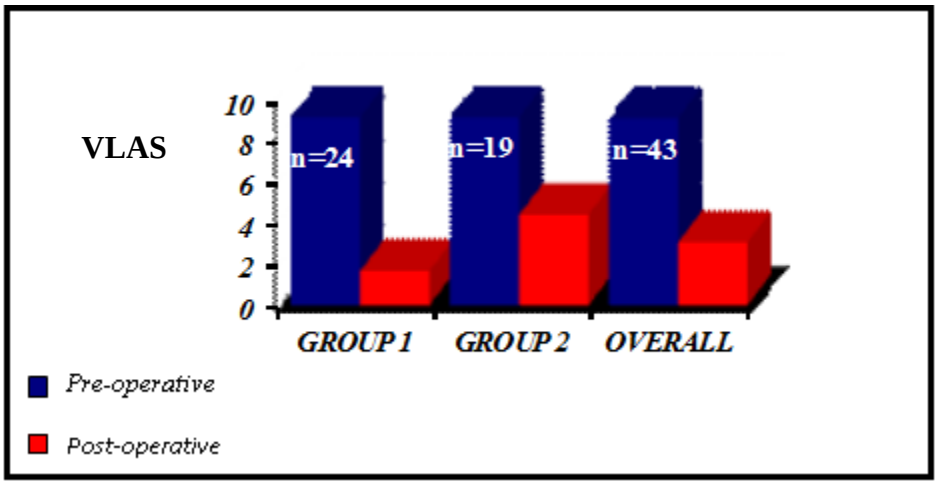
The traditional therapeutic approach to CRPS is a conservative with the use of pharmacological agents, physiotherapy and occupational therapy. Stellate ganglion blocks (SGB) are performed if there is no clinical improvement to conservative treatment. SGB may even prove to be curative when the pain relief extends beyond the durations of the block. The guidelines for repeated SGB when pain is not adequately controlled are unclear. It has been recommended that if relief from repeated SGB becomes less effective or static, and if the initial response is dramatic but of a short duration, surgical sympathectomy should be undertaken (107).

The SGB has long been considered pivotal in defining those patients who may benefit from a sympathectomy, the so called sympathetically maintained pain (SMP) CRPS patients; thus, an inaccurate SGB will mislead the clinician and may deny a patient a potentially beneficial procedure. A successful (or positive) SGB in the context of CRPS is defined as the development of a transient Horner's Syndrome (with even minor, evanescent eye signs) with the alleviation of the upper limb pain of CRPS. This latter effect is described as being reflective of SMP; in such a situation a sympathectomy would be invaluable in the management of CRPS.

In the era of evidence based medicine it is unsurprising that the advocacy for sympathectomy has been criticised. Reports attesting to the value of sympathectomy in the management of CRPS are largely based on descriptive studies with no controlled randomized studies supporting the use of sympathetic block or sympathectomy over placebo controls or pharmacological measures. However sympathetic denervation in the management of CRPS has been reported to be an effective management option, as described by Singh et al (109). In this study (conducted over a 9-year period) 42 patients with CRPS type II of the upper extremity were referred for sympathectomy. Patients were categorized according to the duration of the symptoms (group I, <3 months; group II, >3 months). The median duration of symptoms in patients in Group1 (n = 24; symptoms < 3 months) was 6.5 weeks. The median duration of symptoms in patients in Group 2 (n = 18; symptoms > 3 months) was 26.5 weeks. All patients underwent initial medical treatment; stellate ganglion blocks were performed when symptoms persisted beyond 6 weeks. Patients were referred for thoracoscopic sympathectomy on persistence of the pain syndrome. A visual linear analogue scale was used to evaluate outcome of sympathectomy. All 42 patients underwent upper limb sympathectomy.

Thoracoscopic sympathectomy was successfully undertaken in 32 patients. In the remaining 10 patients, thoracoscopy was not technically feasible and open sympathectomy was performed.

The pain response to sympathectomy showed an overall improvement in all 42 patients from a median preoperative score of 9.0 to a median postoperative score of 2.0 which was noted to be significant (Figure 12.5.)



VLAS: Visual Linear Analogue Scale (0 least pain, 10 most pain)

Figure 12.5: Mean outcome to sympathectomy (109)

The outcome in group I was significantly better than in group II. The diagnosis SMP with stellate blockade did not correlate with clinical outcome. Possible reasons for this maybe:

1. That the procedure is operator dependant and its universal accuracy unknown.
2. Furthermore, the stellate ganglion is distant from the 2nd thoracic ganglion that is now considered pivotal in effecting upper limb sympathetic denervation.
3. Also, alternate neural pathways to the brachial plexus bypass the stellate ganglion and may not be blocked by a standard SGB.

SBG may thus under-estimate the true incidence of SMP and thereby deny patients a potentially beneficial outcome from sympathectomy. Patients undergoing thoracoscopic

sympathectomy had a better outcome than those undergoing open sympathectomy. There were no complications, and the hospital stay was shorter in the thoracoscopic group.

Singh et al (109) concluded that:

1. Early recognition of CRPS and prompt recourse to surgical sympathectomy is a useful option in the management of CRPS and demonstrated that all patients referred timeously (within 3 months) for sympathectomy had an excellent or good result.
2. When sympathectomy is undertaken beyond this stage, a favourable outcome is not guaranteed. However up to 44.4% had a good or excellent outcome, (see figure 12.6).
3. Overall, sympathectomy was noted to have a good or excellent outcome in 76.2% of their patients.
4. The results in this series and the range of available therapies suggest that a placebo-controlled trial may not be feasible or indeed ethical.
5. The role of sympathectomy in current practice is enhanced by the ease and safety of the thoracoscopic approach.

Several other studies within the confines of this review period have showed similar results and are summarized in the table 12.1.

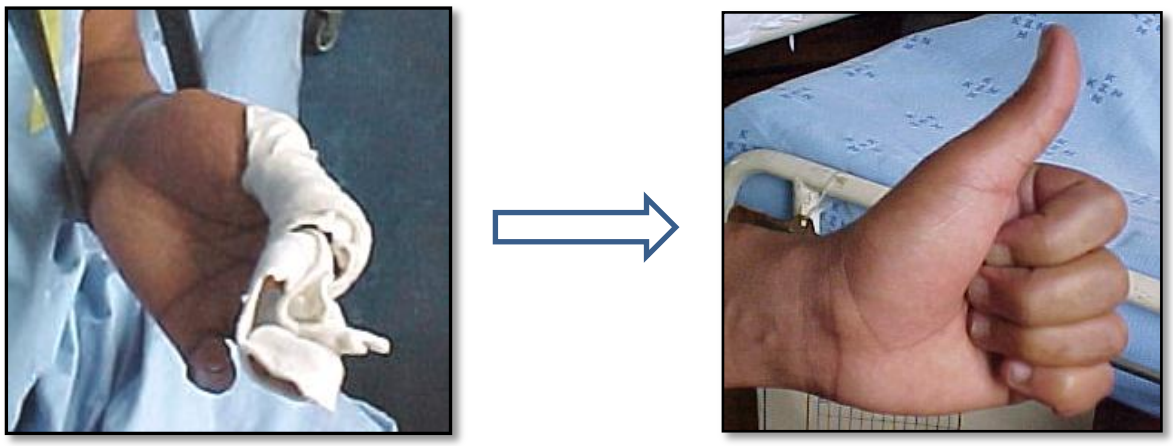


Figure 12.6: Pre and post thoracoscopic sympathectomy

AUTHOR (year)	STUDY PERIOD	N*	SYMPTOM DURATION	RESULTS	CONCLUSIONS
Bandyk (110) 2000	1992-2000	73	26 mths	90% success VAS mean 8,7 to 3,4	SMP can benefit long term with SS
Singh (109) 2003	9 year period	42	<3 mth group >3 mth group	100% success VAS mean 9,0 to 2,0	Early recognition and prompt recourse to SS is a useful option
Duarte (111) 2003	-	7	-	100% success VAS mean 8,46 to 2,62	SS efficient for the relief of pain and improvement of the quality of life
Hassantash (112) 2003	1966-2000 review of literature	791	only 101/791 reported mean < 1year	94% success	Immediate SS should be offered; safe with no long term complications
Rizzo (113) 2004	-	12	-	100% success 50% excellent & 50% varying degrees of improvement	SS offers promise in the treatment
Golubev (114) 2008	-	26	2 mths	100% success	SS effective and mostly successful at the early stage CRPS
Demey (115) 2011	5 year period	12	3,8 mths	100% success	SS effective at decreasing pain and improving quality of life; should be considered
Kassem (116) 2011	2006-2009	13	-	100% success	SS effective and the treatment of choice, particularly for patients responding to SGB

N* - number of patients; SS – surgical sympathectomy; SYMPTOM DURATION – mean duration of symptoms in months (mths)

Table 12.1: Summary of studies looking at efficacy of sympathectomies

CHAPTER THIRTEEN

CONCLUSION

CONCLUSION

"Those who have such a severe degree of pain that they cannot work, and claim that 'nobody really understands' what is happening to them, are going to be depressed. The affective component of this pain may be worse than in many other conditions……"

RJ Schwatzman (117)

"…they described as burning or mustard red-hot or as red-hot fire rasping the skin… Exposure to the air is avoided with a care which seems almost absurd…"

Silas Weir Mitchell

The above are some of the gruesome descriptions by medical personal dating as far back as 1864 when trying to describe the level of discomfort and pain that patients experience in CRPS. It is so painful that it has been ranked 42 out of 50 on the McGill pain index making it one of the most painful conditions that exist to mankind to date. The incidence of this condition has been reported as high as 26.2 per 100 000 making this condition not uncommon. It is therefore not surprising that this condition has been studied extensively with much research dedicated to better understanding its pathology and treatment success.

CRPS has been known by many names over the years, most commonly as reflex sympathetic dystrophy and causalgia. In the past there was no standardised and idiosyncratic diagnostic system in place. The IASP has provided scientific input and direction to this important pain condition; in 1994, the IASP redefined CRPS and established diagnostic criteria to standardise this diagnosis globally. It had the potential to lead to improved clinical communication and greater uniformity across research samples. Notwithstanding this, over the years it was realized that this criteria was limited and its use in the literature was sporadic at best. This led to the development of "tighter" criteria at the Budapest conference in 2003 to improve sensitivity and

specificity of diagnosis and to improve research. The IASP has yet to accept this, revised diagnostic criteria. This may be due to influential groups resisting the change (e.g. personal injury lawyers, who may benefit by the "looser" criteria, and some ill-informed patient advocacy organizations that, fear a "tighter" criteria may cause many previously diagnosed patients to be thrown into diagnostic limbo) (22). These new criteria will therefore now, of course, need to be further validated.

A gold standard in the form of an objective test is not available despite many efforts. However the triple phase bone scintigraphy looks promising in terms of aiding in a diagnosis of CRPS. It is most accurate early on and further evaluation of this diagnostic entity may prove to be rewarding.

Although there is evidence for possible differences in clinical presentation, the clinical significance between type I and type II CRPS in terms of treatment strategies is yet to be established, as questioned at the Budapest conference. Thus the need to differentiate between type I and type II at this stage seems irrelevant and until there is clear evidence for its differentiation, the need to differentiate these 2 types is meddlesome and lacks scientific clinical significance.

Despite the pathogenesis of CRPS is still not well understood, we have come a long way and definitely closer to understanding this mind boggling condition. Yet despite this we still seem far from realising the real truth to this condition. This area thus remains open to more intense research. The role of the sympathetic nervous system - either in concert or sequential to the pathology has not been previously considered. The precise role of the immunological system via the sympathetic ganglia in the pathophysiology of CRPS has not been evaluated. In the light of foregoing information, an investigation into the nature of the inflammatory infiltrate in the ganglia of excised from patients CRPS is appropriate and may provide insight into the pathogenesis of this condition.

There is no uniform approach and clear guidelines to the management of CRPS. However what can be seen from this review is that early physiotherapy and occupational therapy are key to rehabilitation. The problem is the difficulty in achieving this due to intense pain. This may be alleviated by a host of drugs described. However, most importantly if non-surgical methods of pain management fail, surgical sympathectomy should be considered early on in the disease process as it has shown to be effective when undertaken within 3 months of onset of symptoms. There is a poorer outcome when sympathectomy is undertaken belatedly. However the rationale for sympathetic ganglionectomy, the timing of this approach and the accuracy of SGB in the management of CRPS also merits review. In current practice, thoracoscopic sympathectomy has been shown to be an attractive option for the following reasons:

- an effective, safe and accurate technique
- enduring outcome
- technically easy
- readily reproducible
- standard anaesthetic technique
- widely available
- day care procedure

The role of compensation neurosis in a patient demonstrating an unsatisfactory outcome to a seemingly logical therapeutic approach is difficult to quantify but should always be borne in mind.

REFERENCES

1. Sebastin SJ. Complex regional pain syndrome. Indian Journal of Plastic Surgery. 2011;44(2):298.
2. Schwarzer A, Maier C. Complex regional pain syndrome. In: Kopf A, Patel NB, editors. Guide to Pain Management in Low-Resource Settings. Seattle: IASP; 2010. p.249-254.
3. Maihöfner C, Seifert F, Markovic K. Complex regional pain syndromes: new pathophysiological concepts and therapies. European Journal of Neurology. 2010;17(5):649-60.
4. Saxena AK, Batra J, Dhakate G, Batra A. Evidence-Based Interventional Pain Medicine in Complex Regional Pain Syndrome: Update on this Methodological Minefield and the Challenges Ahead. Indian Society for the Study of Pain (ISSP). 2010;24:16-27.
5. Dommerholt J. Complex regional pain syndrome 1: History, diagnostic criteria and etiology. Journal of Bodywork and Movement Therapies. 2004;8:167-77.
6. Wilson J, Serpell M. Complex regional pain syndrome. Continuing Education in Anaesthesia, Critical Care & Pain. 2007;7(2):51-4.
7. Sandkühler J. Models and mechanisms of hyperalgesia and allodynia. Physiological reviews. 2009;89(2):707-58.
8. Binder A, Baron R. Complex regional pain syndrome. In: Stannard CF, Kalso E, Ballantyne J, editors. Evidence-Based Chronic Pain Management. Oxford: Wiley Blackwell; 2010.p.248-66.
9. Bruehl S, Harden RN, Galer BS, Saltz S, Backonja M, Stanton-Hicks M. Complex regional pain syndrome: are there distinct subtypes and sequential stages of the syndrome? Pain. 2002;95(1):119-24.
10. Van Hilten J, Van de Beek W, Vein A, Van Dijk J, Middelkoop H. Clinical aspects of multifocal or generalized tonic dystonia in reflex sympathetic dystrophy. Neurology. 2001;56(12):1762-5.
11. Birklein F. Complex regional pain syndrome. Journal of Neurology. 2005;252(2):131-8.
12. Lewis JS, Kersten P, McCabe CS, McPherson KM, Blake DR. Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). Pain. 2007;133(1):111-9.
13. Swart C, Stins JF, Beek PJ. Cortical changes in complex regional pain syndrome (CRPS). European Journal of Pain. 2009;13(9):902-7.
14. Forderreuther S, Sailer U, Straube A. Impaired self-perception of the hand in complex regional pain syndrome (CRPS). Pain. 2004;110(3):756-61.
15. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Patterns of cortical reorganization in complex regional pain syndrome. Neurology. 2003;61(12):1707-15.
16. Moseley GL. Why do people with complex regional pain syndrome take longer to recognize their affected hand? Neurology. 2004;62(12):2182-6.
17. Moseley GL. Is successful rehabilitation of complex regional pain syndrome due to sustained attention to the affected limb? A randomised clinical trial. Pain. 2005;114(1):54-61.
18. Birklein F, Riedl B, Sieweke N, Weber M, Neundörfer B. Neurological findings in complex regional pain syndromes-analysis of 145 cases. Acta Neurologica Scandinavica. 2000;101(4):262.
19. Raja SN, Grabow TS. Complex regional pain syndrome I (reflex sympathetic dystrophy). Anesthesiology. 2002;96(5):1254-60.
20. Harden RN, Bruehl S, Perez RSGM, Birklein F, Marinus J, Maihofner C, et al. Validation of proposed diagnostic criteria (the "Budapest Criteria") for complex regional pain syndrome. Pain. 2010;150(2):268-74.
21. Moon DE. Diagnosis and treatment of complex regional pain syndrome. Journal of the Korean Medical Association. 2006;49(8):688-700.
22. Harden RN, Bruehl S, Stanton-Hicks M, Wilson PR. Proposed new diagnostic criteria for complex regional pain syndrome. Pain Medicine. 2007;8(4):326-31.
23. Sumitani M, Shibata M, Sakaue G, Mashimo T. Development of comprehensive diagnostic criteria for complex regional pain syndrome in the Japanese population. Pain. 2010;150(2):243-9.

24. Edwards RR. Individual differences in endogenous pain modulation as a risk factor for chronic pain. Neurology. 2005;65(3):437-43.
25. Harden R. Objectification of the diagnostic criteria for CRPS. Pain Medicine. 2010;11:1212-5.
26. Pankaj A, Kotwal P, Mittal R, Deepak K, Bal C. Diagnosis of post-traumatic complex regional pain syndrome of the hand: current role of sympathetic skin response and three-phase bone scintigraphy. Journal of Orthopaedic Surgery-Hong Kong. 2006;14(3):284.
27. Wüppenhorst N, Maier C, Frettlöh J, Pennekamp W, Nicolas V. Sensitivity and specificity of 3-phase bone scintigraphy in the diagnosis of complex regional pain syndrome of the upper extremity. The Clinical Journal of Pain. 2010;26(3):182.
28. Bryant PR, Kim CT, Millan R. The rehabilitation of causalgia (complex regional pain syndrome-type II). Physical Medicine and Rehabilitation Clinics of North America. 2002;13(1):137.
29. Jänig W, Baron R. Complex regional pain syndrome is a disease of the central nervous system. Clinical Autonomic Research. 2002;12(3):150-64.
30. Rooij AM, Perez RSGM, Huygen FJ, Eijs F, Kleef M, Bauer MCR, et al. Spontaneous onset of complex regional pain syndrome. European Journal of Pain. 2010;14(5):510-3.
31. Maleki J, LeBel AA, Bennett GJ, Schwartzman RJ. Patterns of spread in complex regional pain syndrome, type I (reflex sympathetic dystrophy). Pain. 2000;88(3):259-66.
32. Van Rijn MA, Marinus J, Putter H, Bosselaar SRJ, Moseley GL, Van Hilten JJ. Spreading of complex regional pain syndrome: not a random process. Journal of Neural Transmission. 2011;118(9):1301-9.
33. Beerthuizen A, van't Spijker A, Huygen FJPM, Klein J, de Wit R. Is there an association between psychological factors and the Complex Regional Pain Syndrome type 1 (CRPS1) in adults? A systematic review. Pain. 2009;145(1):52-9.
34. De Mos M, Huygen F, Dieleman J, Koopman J, Stricker B, Sturkenboom M. Medical history and the onset of complex regional pain syndrome (CRPS). Pain. 2008;139(2):458-66.
35. Rooij AM, Mos M, Sturkenboom MCJM, Marinus J, Maagdenberg AMJM, Hilten JJ. Familial occurrence of complex regional pain syndrome. European Journal of Pain. 2009;13(2):171-7.
36. de Rooij AM, de Mos M, van Hilten JJ, Sturkenboom MCJM, Gosso MF, van den Maagdenberg AMJM, et al. Increased Risk of Complex Regional Pain Syndrome in Siblings of Patients? The Journal of Pain. 2009;10(12):1250-5.
37. Vaneker M, Van Der Laan L, Allebes W, Goris R. Genetic factors associated with complex regional pain syndrome 1: HLA DRB and TNF alpha promotor gene polymorphism. Disabil Med. 2002;2:69-74.
38. van de Beek WJT, Roep BO, van der Slik AR, Giphart MJ, van Hilten BJ. Susceptibility loci for complex regional pain syndrome. Pain. 2003;103(1):93-7.
39. Marinus J, Moseley GL, Birklein F, Baron R, Maihöfner C, Kingery WS, et al. Clinical features and pathophysiology of complex regional pain syndrome. The Lancet Neurology. 2011;10(7):637-48.
40. Terkelsen AJ, Bach FW, Jensen TS. Experimental forearm immobilization in humans induces cold and mechanical hyperalgesia. Anesthesiology. 2008;109(2):297-307.
41. Zyluk A. Complex regional pain syndrome type I. Risk factors, prevention and risk of recurrence. Journal of Hand Surgery (British and European Volume). 2004;29(4):334-7.
42. De Mos M, Huygen F, Stricker B, Dieleman J, Sturkenboom M. The association between ACE inhibitors and the complex regional pain syndrome: Suggestions for a neuro-inflammatory pathogenesis of CRPS. Pain. 2009;142(3):218-24.
43. Peterlin B, Rosso A, Nair S, Young W, Schwartzman R. Migraine may be a risk factor for the development of complex regional pain syndrome. Cephalalgia. 2010;30(2):214-23.
44. Sandroni P, Benrud-Larson LM, McClelland RL, Low PA. Complex regional pain syndrome type I: incidence and prevalence in Olmsted county, a population-based study. Pain. 2003;103(1):199-207.
45. De Mos M, De Bruijn A, Huygen F, Dieleman J, Stricker B, Sturkenboom M. The incidence of complex regional pain syndrome: a population-based study. Pain. 2007;129(1):12-20.
46. Dijkstra PU, Groothoff JW, Duis HJ, Geertzen JHB. Incidence of complex regional pain syndrome type I after fractures of the distal radius. European Journal of Pain. 2003;7(5):457-62.

47. Pleger B, Janssen F, Schwenkreis P, Völker B, Maier C, Tegenthoff M. Repetitive transcranial magnetic stimulation of the motor cortex attenuates pain perception in complex regional pain syndrome type I. Neuroscience Letters. 2004;356(2):87-90.
48. Maihöfner C, Handwerker HO, Neundörfer B, Birklein F. Cortical reorganization during recovery from complex regional pain syndrome. Neurology. 2004;63(4):693-701.
49. Pleger B, Tegenthoff M, Ragert P, Förster AF, Dinse HR, Schwenkreis P, et al. Sensorimotor returning in complex regional pain syndrome parallels pain reduction. Annals of Neurology. 2005;57(3):425-9.
50. Juottonen K, Gockel M, Silén T, Hurri H, Hari R, Forss N. Altered central sensorimotor processing in patients with complex regional pain syndrome. Pain. 2002;98(3):315.
51. Eisenberg E, Chistyakov AV, Yudashkin M, Kaplan B, Hafner H, Feinsod M. Evidence for cortical hyperexcitability of the affected limb representation area in CRPS: a psychophysical and transcranial magnetic stimulation study. Pain. 2005;113(1-2):99-105.
52. Ji RR, Woolf CJ. Neuronal plasticity and signal transduction in nociceptive neurons: implications for the initiation and maintenance of pathological pain. Neurobiology of Disease. 2001;8(1):1-10.
53. Albrecht PJ, Hines S, Eisenberg E, Pud D, Finlay DR, Connolly MK, et al. Pathologic alterations of cutaneous innervation and vasculature in affected limbs from patients with complex regional pain syndrome. Pain. 2006;120(3):244-66.
54. Ali Z, Raja SN, Wesselmann U, Fuchs PN, Meyer RA, Campbell JN. Intradermal injection of norepinephrine evokes pain in patients with sympathetically maintained pain. Pain. 2000;88(2):161-8.
55. Baron R, Schattschneider J, Binder A, Siebrecht D, Wasner G. Relation between sympathetic vasoconstrictor activity and pain and hyperalgesia in complex regional pain syndromes: a case-control study. The Lancet. 2002;359(9318):1655-60.
56. Schattschneider J, Binder A, Siebrecht D, Wasner G, Baron R. Complex regional pain syndromes: the influence of cutaneous and deep somatic sympathetic innervation on pain. The Clinical Journal of Pain. 2006;22(3):240-4.
57. Drummond P, Finch P. Persistence of pain induced by startle and forehead cooling after sympathetic blockade in patients with complex regional pain syndrome. Journal of Neurology, Neurosurgery & Psychiatry. 2004;75(1):98-102.
58. Wasner G, Schattschneider J, Heckmann K, Maier C, Baron R. Vascular abnormalities in reflex sympathetic dystrophy (CRPS I): mechanisms and diagnostic value. Brain. 2001;124(3):587-99.
59. Jänig W, Baron R. Complex regional pain syndrome: mystery explained? The Lancet Neurology. 2003;2(11):687-97.
60. Goldstein DS, Tack C, Li ST. Sympathetic innervation and function in reflex sympathetic dystrophy. Annals of Neurology. 2001;48(1):49-59.
61. Birklein F, Weber M, Neundörfer B. Increased skin lactate in complex regional pain syndrome: evidence for tissue hypoxia? Neurology. 2000;55(8):1213-5.
62. Schinkel C, Gaertner A, Zaspel J, Zedler S, Faist E, Schuermann M. Inflammatory mediators are altered in the acute phase of posttraumatic complex regional pain syndrome. The Clinical Journal of Pain. 2006;22(3):235-9.
63. Huygen FJPM, De Bruijn AGJ, De Bruin MT, Groeneweg JG, Klein J, Zijlstra FJ. Evidence for local inflammation in complex regional pain syndrome type 1. Mediators of Inflammation. 2002;11(1):47-51.
64. Birklein F, Schmelz M. Neuropeptides, neurogenic inflammation and complex regional pain syndrome (CRPS). Neuroscience Letters. 2008;437(3):199-202.
65. Tan ECTH, Oyen WJG, Goris RJA. Leukocytes in complex regional pain syndrome type I. Inflammation. 2005;29(4):182-6.
66. Groeneweg JG, Huygen FJPM, Heijmans-Antonissen C, Niehof S, Zijlstra FJ. Increased endothelin-1 and diminished nitric oxide levels in blister fluids of patients with intermediate cold type complex regional pain syndrome type 1. BMC Musculoskeletal Disorders. 2006;7(1):91.
67. Alexander GM, Van Rijn M, Van Hilten J, Perreault MJ, Schwartzman RJ. Changes in cerebrospinal fluid levels of pro-inflammatory cytokines in CRPS. Pain. 2005;116(3):213-9.

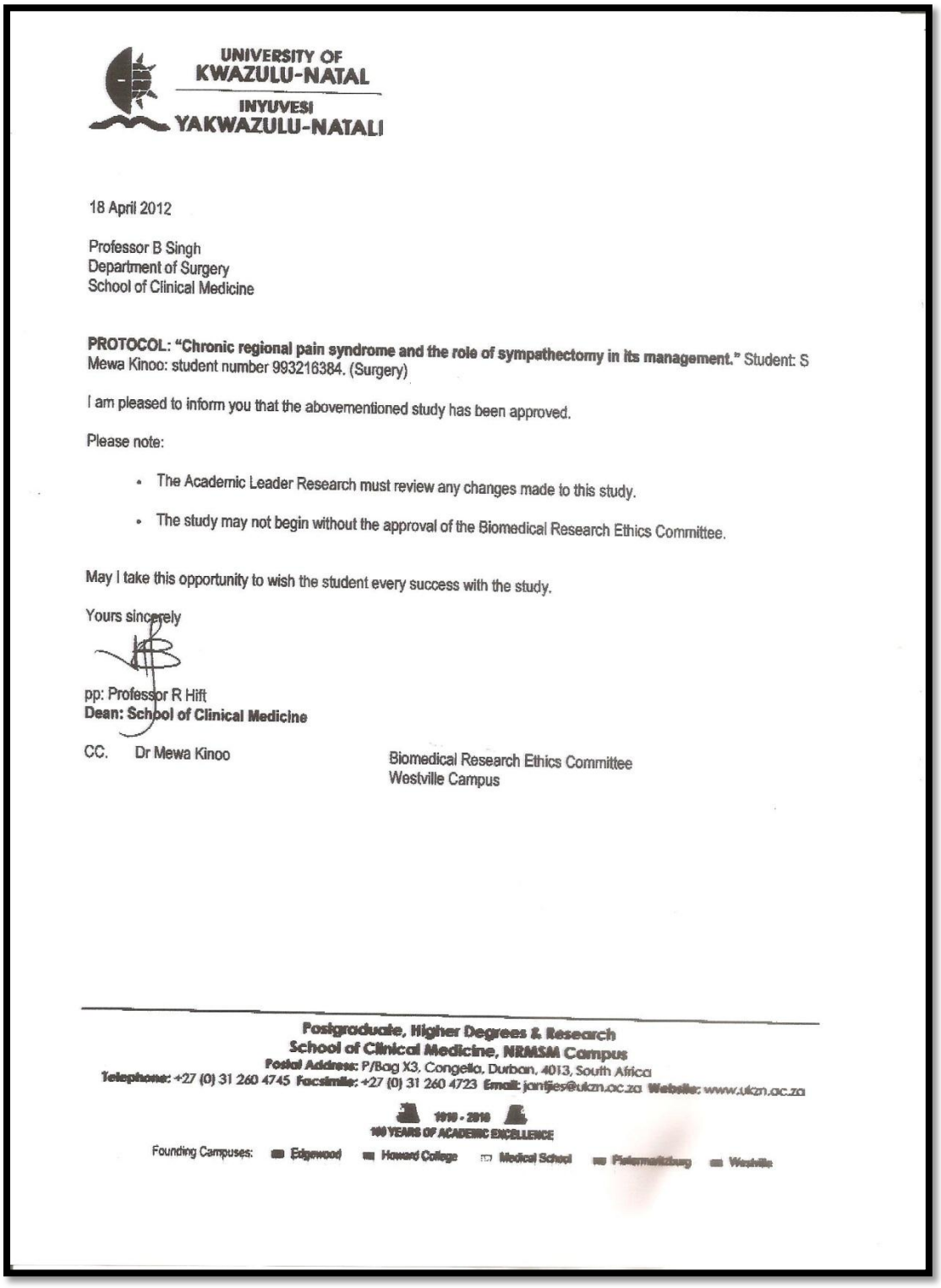
68. Goebel A, Vogel H, Caneris O, Bajwa Z, Clover L, Roewer N, et al. Immune responses to Campylobacter and serum autoantibodies in patients with complex regional pain syndrome. Journal of Neuroimmunology. 2005;162(1):184-9.
69. Blaes F, Schmitz K, Tschernatsch M, Kaps M, Krasenbrink I, Hempelmann G, et al. Autoimmune etiology of complex regional pain syndrome (M. Sudeck). Neurology. 2004;63(9):1734-6.
70. Kohr D, Tschernatsch M, Schmitz K, Singh P, Kaps M. Autoantibodies in complex regional pain syndrome bind to a differentiation-dependent neuronal surface autoantigen. Pain. 2009;143(3):246-51.
71. Kiralp M, Yildiz S, Vural D, Keskin I, Ay H, Dursun H. Effectiveness of hyperbaric oxygen therapy in the treatment of complex regional pain syndrome. The Journal of International Medical Research. 2004;32(3):258-62.
72. Turton AJ, McCabe CS, Harris N, Filipovic SR. Sensorimotor integration in Complex Regional Pain Syndrome: a transcranial magnetic stimulation study. Pain. 2007;127(3):270-5.
73. Schattschneider J. Complex regional pain syndrome—are we neglecting neglect? Nature Clinical Practice Neurology. 2007;3(1):16-7.
74. McCabe C, Haigh R, Ring E, Halligan P, Wall P, Blake D. A controlled pilot study of the utility of mirror visual feedback in the treatment of complex regional pain syndrome (type 1). Rheumatology. 2003;42(1):97-101.
75. Moseley G. Graded motor imagery is effective for long-standing complex regional pain syndrome: a randomised controlled trial. Pain. 2004;108(1):192-8.
76. Krause P, Foerderreuther S, Straube A. Effects of conditioning peripheral repetitive magnetic stimulation in patients with complex regional pain syndrome. Neurological research. 2005;27(4):412-7.
77. Vaneker M, Wilder-Smith OHG, Schrombges P, de Man-Hermsen I, Oerlemans HM. Patients initially diagnosed as 'warm'or 'cold' CRPS 1 show differences in central sensory processing some eight years after diagnosis: a quantitative sensory testing study. Pain. 2005;115(1):204-11.
78. Ackerman WE, Ahmad M. Recurrent postoperative CRPS I in patients with abnormal preoperative sympathetic function. Journal of Hand Surgery-American Volume. 2008;33(2):217-22.
79. Drummond PD, Finch PM, Skipworth S, Blockey P. Pain increases during sympathetic arousal in patients with complex regional pain syndrome. Neurology. 2001;57(7):1296-303.
80. Wasner G, Schattschneider J, Baron R. Skin temperature side differences-a diagnostic tool for CRPS? Pain. 2002;98(1-2):19-26.
81. Bruehl S. An update on the pathophysiology of complex regional pain syndrome. Anesthesiology. 2010;113(3):713.
82. Wesseldijk F, Huygen FJPM, Heijmans-Antonissen C, Niehof SP, Zijlstra FJ. Six Years Follow-up of the Levels of TNF-α. Mediators of Inflammation. 2008;2008.
83. Uçeyler N, Eberle T, Rolke R, Birklein F, Sommer C. Differential expression patterns of cytokines in complex regional pain syndrome. Pain. 2007;132(1):195-205.
84. Maihöfner C, Neundörfer B, Birklein F, Handwerker HO. Mislocalization of tactile stimulation in patients with complex regional pain syndrome. Journal of Neurology. 2006;253(6):772-9.
85. Margreet Oerlemans H, Oostendorp RAB, de Boo T, van der Laan L, Severens JL, Goris RJA. Adjuvant physical therapy versus occupational therapy in patients with reflex sympathetic dystrophy/complex regional pain syndrome type I. Archives of Physical Medicine and Rehabilitation. 2000;81(1):49-56.
86. Harden RN. Complex regional pain syndrome. British Journal of Anaesthesia. 2001;87(1):99-106.
87. Liebenson C. Musculoskeletal myths. Journal of Bodywork and Movement Therapies. 2012;16(2):165-82.
88. de Jong JR, Vlaeyen JWS, Onghena P, Cuypers C, Hollander M, Ruijgrok J. Reduction of pain-related fear in complex regional pain syndrome type I: the application of graded exposure in vivo. Pain. 2005;116(3):264-75.
89. Bruehl S, Chung OY. Psychological and behavioral aspects of complex regional pain syndrome management. The Clinical Journal of Pain. 2006;22(5):430.

90. Goebel A, Baranowski A, Maurer K, Ghiai A, McCabe C, Ambler G. Intravenous immunoglobulin treatment of the complex regional pain syndrome. Ann Intern Med. 2010;152(3):152-8.
91. Bernateck M, Rolke R, Birklein F, Treede RD, Fink M, Karst M. Successful intravenous regional block with low-dose tumor necrosis factor-α antibody infliximab for treatment of complex regional pain syndrome 1. Anesthesia & Analgesia. 2007;105(4):1148-51.
92. Huygen FJPM, Niehof S, Zijlstra FJ, Hagen P, Daele PLA. Successful treatment of CRPS 1 with anti-TNF. Journal of Pain and Symptom Management. 2004;27(2):101-3.
93. Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain. 2007;132(3):237-51.
94. Wallace MS, Ridgeway BM, Leung AY, Gerayli A, Yaksh TL. Concentration-effect relationship of intravenous lidocaine on the allodynia of complex regional pain syndrome types I and II. Anesthesiology. 2000;92(1):75.
95. Rowbotham MC. Pharmacologic management of complex regional pain syndrome. The Clinical Journal of Pain. 2006;22(5):425-9.
96. van Hilten BJ, van de Beek WJT, Hoff JI, Voormolen JHC, Delhaas EM. Intrathecal baclofen for the treatment of dystonia in patients with reflex sympathetic dystrophy. New England Journal of Medicine. 2000;343(9):625-30.
97. Harke H, Gretenkort P, Ladleif HU, Rahman S, Harke O. The response of neuropathic pain and pain in complex regional pain syndrome I to carbamazepine and sustained-release morphine in patients pretreated with spinal cord stimulation: a double-blinded randomized study. Anesthesia & Analgesia. 2001;92(2):488-95.
98. Van De Vusse AC, Stomp-van den Berg SGM, Kessels AHF, Weber WEJ. Randomised controlled trial of gabapentin in Complex Regional Pain Syndrome type 1. BMC Neurology. 2004;4(1):13.
99. Perez R, Zuurmond W, Bezemer P, Kuik D, Van Loenen A, De Lange J, et al. The treatment of complex regional pain syndrome type I with free radical scavengers: a randomized controlled study. Pain. 2003;102(3):297-307.
100. Cazeneuve J, Leborgne J, Kermad K, Hassan Y. Vitamin C and prevention of reflex sympathetic dystrophy following surgical management of distal radius fractures. Acta Orthopaedica Belgica. 2002;68(5):481.
101. Perez RSGM, Kwakkel G, Zuurmond WWA, de Lange JJ. Treatment of reflex sympathetic dystrophy (CRPS type 1): a research synthesis of 21 randomized clinical trials. Journal of Pain and Symptom Management. 2001;21(6):511-26.
102. Albazaz R, Wong YT, Homer-Vanniasinkam S. Complex regional pain syndrome: a review. Annals of Vascular Surgery. 2008;22(2):297-306.
103. Brunner F, Schmid A, Kissling R, Held U, Bachmann LM. Biphosphonates for the therapy of complex regional pain syndrome I–systematic review. European Journal of Pain. 2009;13(1):17-21.
104. Cepeda MS, Lau J, Carr DB. Defining the therapeutic role of local anesthetic sympathetic blockade in complex regional pain syndrome: a narrative and systematic review. The Clinical Journal of Pain. 2002;18(4):216.
105. Velasco F, Carrillo-Ruiz JD, Castro G, Argüelles C, Velasco AL, Kassian A, et al. Motor cortex electrical stimulation applied to patients with complex regional pain syndrome. Pain. 2009;147(1):91-8.
106. Taylor RS, Buyten JP, Buchser E. Spinal cord stimulation for complex regional pain syndrome: A systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. European Journal of Pain. 2006;10(2):91-.
107. Singh B. Upper limb sympathectomy in current surgical practice [dissertation]. Durban, KwaZulu Natal: University of Natal; 2002.
108. Pather N, Singh B, Partab P, Ramsaroop L, Satyapal K. The anatomical rationale for an upper limb sympathetic blockade: preliminary report. Surgical and Radiologic Anatomy. 2004;26(3):178-81.
109. Singh B, Moodley J, Shaik AS, Robbs JV. Sympathectomy for complex regional pain syndrome. Journal of Vascular Surgery. 2003;37(3):508-11.

110. Bandyk DF, Johnson BL, Kirkpatrick AF, Novotney ML, Back MR, Schmacht DC. Surgical sympathectomy for reflex sympathetic dystrophy syndromes. Journal of Vascular Surgery. 2002;35(2):269-77.
111. Bosco Vieira Duarte J, Kux P, Magalhães Duarte DF. Endoscopic thoracic sympathicotomy for the treatment of complex regional pain syndrome. Clinical Autonomic Research. 2003;13.
112. Hassantash SA, Afrakhteh M, Maier RV. Causalgia: a meta-analysis of the literature. Archives of Surgery. 2003;138(11):1226.
113. Rizzo M, Balderson SS, Harpole DH, Levin LS. Thoracoscopic sympathectomy in the management of vasomotor disturbances and complex regional pain syndrome of the hand. Orthopedics. 2004;27(1):49.
114. Golubev V, Krupatkin A, Zeĭnalov V, Merkulov M, Kuz'michev V. New facilities in management of complex regional pain upper limb syndrome with thoracoscopic sympathectomy. Vestn Ross Akad Med Nauk. 2008;(8):52-5.
115. Demey K, Nijs S, Coosemans W, Decaluwé H, Decker G, De Leyn P, et al. Endoscopic thoracic sympathectomy for posttraumatic complex regional pain syndrome. European Journal of Trauma and Emergency Surgery. 2011;37(6):597-604.
116. Kassem M, Badr H, El Kosha H, Ibrahim AE. Thoracoscopic sympathectomy for causalgia: Local experience. Pan Arab Journal of Neurosurgery. 2011;15(1):1-5.
117. Schwartzman RJ, Alexander GM, Grothusen J. Pathophysiology of complex regional pain syndrome. Expert Review of Neurotherapeutics. 2006;6(5):669-81.

APPENDICES

APPENDIX 1: POST GRADUATE OFFICE STUDY APPROVAL



UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

18 April 2012

Professor B Singh
Department of Surgery
School of Clinical Medicine

PROTOCOL: "Chronic regional pain syndrome and the role of sympathectomy in its management." Student: S Mewa Kinoo: student number 993216384. (Surgery)

I am pleased to inform you that the abovementioned study has been approved.

Please note:

- The Academic Leader Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

pp: Professor R Hift
Dean: School of Clinical Medicine

CC. Dr Mewa Kinoo

Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
Postal Address: P/Bag X3, Congella, Durban, 4013, South Africa
Telephone: +27 (0) 31 260 4745 **Facsimile:** +27 (0) 31 260 4723 **Email:** jantjes@ukzn.ac.za **Website:** www.ukzn.ac.za

1910 - 2010
100 YEARS OF ACADEMIC EXCELLENCE

Founding Campuses: Edgewood Howard College Medical School Pietermaritzburg Westville

APPENDIX 2: ETHICS APPROVAL LETTER

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BiomedicalResearchEthics.aspx

17 January 2012

Dr S Mewa Kinoo
P O Box 330
Greytown
3250

Dear Dr Kinoo

Protocol: Chronic regional pain syndrome and the role of sympathectomy in its management. Ref: E242.11

Your application dated 24 November 2011 refers.

Please note that this study is exempt from ethics review on the grounds that all the data to be used is already in the public domain.

Yours sincerely

Professor D Wassenaar
Chair: Biomedical Ethics Research Committee

cc: Professor B Singh, Department of Surgery, Medical School, UKZN

APPENDIX 3: PLAGIARISM DECLERATION

Plagiarism:

DECLARATION

I DR SUMAN MEWA KINOO .....declare that

(i) The research reported in this dissertation, except where otherwise indicated, is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

(iv) This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:

a) their words have been re-written but the general information attributed to them has been referenced;

b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.

(v) Where I have reproduced a publication of which I am an author, co-author or editor, I have indicated in detail which part of the publication was actually written by myself alone and have fully referenced such publications.

(vi) This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the References sections.

Signed: _____ Date: 14/01/2013