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PATIENT- RELATED ASPECTS ON WAD

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In memory of my mother and father

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ABSTRACT

Forces acting on the neck at a motor vehicle MVA accident can result in soft tissue injuries (commonly considered as "whiplash injuries"), with different clinical manifestations, (Whiplash-associated Disorders (WAD)). The pathogenesis of WAD is obscure and the diagnosis is mainly based on history and symptoms. There is no known effective treatment and the human suffering and the socio-economic burden due to WAD are obvious.

The Quebec Task Force proposed a WAD-classification of injury severity and a follow up schedule in 1995. We investigated the predictive value of the classification proposed by the Quebec Task Force. The results indicate that female gender, neck or shoulder pain before the accident and self reported emotional distress at the time of the accident were significant risk factors for chronic neck pain. The WAD class and the follow-up regimen had no predictive value.

Coping can be defined as making purposeful efforts to manage or counteract the negative impact of stress. The different coping strategies in the acute phase after the injury were recorded using the Coping Strategies Questionnaire (CSQ). However the CSQ did not appear to be appropriate for predicting chronic symptoms.

Psychological factors have been reported to be a consequence of chronic pain rather than a causative factor. We investigated psychiatric morbidity by comparing a group of patients with chronic symptoms after a whiplash injury to an age and gender matched control group of fully recovered persons. We used the Structured Clinical Interview (SCID), which is a rigorous psychiatric tool that has not been used in WAD-studies before. The results indicate that persons developing chronic symptoms after this type of injury more often had a history of psychiatric illness, especially depression, than those without persisting symptoms.

The immune system is known to be affected by trauma but the possible involvement of the immune system during the disease process in WAD is not known. Effector molecules including chemokines and their receptors could play a role in WAD.
We studied the immune response in blood mononuclear cells (MNC) from patients in the acute phase after a whiplash injury (WAD) and, for reference, patients with ankle sprain, patients with multiple sclerosis (MS) and healthy subjects. Enzyme-linked immunospot (ELISPOT) assays were used to examine numbers of MNC secreting certain pro- and anti-inflammatory cytokines. The acute WAD patients showed a systemic increase of the proinflammatory TNFα and IL-6 and of anti-inflammatory IL-10; these cytokine alterations became normalized after 14 days. Control patients with ankle sprain showed cytokine profile changes similar to those observed in the WAD group, when examined within 3 days after trauma, implicating that measurements of the cytokines under study (IL-6, IL-10, TNFα and INFγ) do not discriminate between these two types of minor trauma. In contrast, there were no differences for cytokine profiles between patients with WAD examined 14 days after the whiplash injury and healthy subjects. A further study of the systemic immune response was done in patients who had an acute whiplash injury (measured within three days after the trauma and again after 14 days) and for reference, in healthy controls. Flow cytometry was used to study percentages of mono-nuclear- (MNC) and CD3+T cells expressing certain chemokines and the chemokine receptor CCR-5. In conclusion we found a systemic dysregulation in percentages of RANTES and CCR-5 expressing MNC and T cells. However the changes were transient which was considered to be in accordance with a posttraumatic reaction from a minor trauma.

Keywords: Whiplash injury, SCID, psychiatric morbidity, neck pain, depression, coping, cytokines, chemokines, prognosis.
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LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals.

I. **Predicting Chronic Pain in WAD**
Jouko Kivioja, Irene Jensen, and Urban Lindgren
Manuscript.
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II. **Coping after Whiplash Injury: A Prospective Study**
Jouko Kivioja, Irene Jensen, and Urban Lindgren
Injury, Submitted.

III. **Psychiatric Morbidity Among Patients with Chronic WAD**
Jouko Kivioja, Mikael Själin and Urban Lindgren
Spine, 2004, In Print.

IV. **Systemic Immune Response in Whiplash Injury and Ankle Sprain: Elevated IL-6 and IL-10**
Jouko Kivioja, Volkan Özenci, Luciano Rinaldi, Mathilde Kouwenhoven, Urban Lindgren, and Hans Link
Clinical Immunology Vol. 101, No. 1, October, pp. 106–112, 2001.

V. **Chemokines and Their Receptors in Whiplash Injury: Elevated RANTES and CCR-5**
Jouko Kivioja, Luciano Rinaldi, Volkan Özenci, Mathilde Kouwenhoven, Nikolas Kostulas, Urban Lindgren, and Hans Link
Journal of Clinical Immunology, Vol. 21, No. 4, 2001.

LIST OF ABBREVIATIONS

WAD	**W**hiplash **A**ssociated **D**isorder
ROM	**R**ange of **M**otion
VAS	**V**isual **A**nalogue **S**cale
SCID	**S**tructured **C**linical **I**nterview
PTSS	**P**ost **T**raumatic **S**tress **S**yndrome
MVA	**M**otor **V**ehicle **A**ccident
QTF	**Q**uebec **T**ask **F**orce
MS	**M**ultiple **S**clerosis
FA	**F**atal **A**ccident
CT	**C**omputed **T**omography
IASP	**I**nternational **A**ssociation for the **S**tudy of **P**ain
CEH	**C**ervicogenic **H**eadache

CONTENTS

1 INTRODUCTION

History and definition

Hyperextension/ flexion neck injury was first recognized in the late 19th century when railway traveling became common practice [1]. At that time it was called "railway spine". Crowe used the term whiplash at a symposium in 1928, reporting on eight neck injuries after rear end motor vehicle accidents (MVA) [2]. In the medical literature the term whiplash seems not to have been used until 1946 when it was mentioned in a report of neck injuries associated with motor vehicle-, diving- and falling accidents [3]. Whiplash is a descriptive term for an injury mechanism but regrettably it is also often used synonymously with a soft tissue injury in the neck.
In 1995 the Quebec Task Force (QTF) [4] proposed a new classification for whiplash injuries, Since earlier research reports were often difficult to compare they felt that proper diagnostic criteria were needed. Furthermore it had became obvious that symptoms involving even other areas than the neck should be included [4]. The proposed criteria were intended to serve as an allocation tool in future research.

According to the QTF a whiplash trauma generates acceleration-deceleration forces acting on the neck that can result in soft tissue or bony injuries, with different clinical manifestations, Whiplash-Associated Disorders (WAD)[4].Patients´ complaints and/or so called objective clinical signs are the cornerstones for the Quebec classification. The clinical signs can be either of a musculoskeletal or a neurological type. The WAD classification has five grades (WAD 0-4) for the "injury severity and prognosis" (table 1). Most reports on WAD (including this thesis) exclude grades 0 (i.e. no symptoms no signs) and grade 4 (i.e. bony injury or subluxation).

The symptoms that are considered to be a part of the WAD include; neck pain, neck stiffness, headache, numbness, paraesthesia, dizziness, vertigo,visual symptoms, auditory symptoms and cognitive impairment. According to QTF criteria, the WAD is considered as chronic if symptoms persist more than six months.

Two other classification for WAD have been proposed lately by Swedish and Swiss workers but their usability remains to be established [5,6].

The most common cause of whiplash trauma is a motor vehicle accident (MVA) especially involving rear-end impact but it can result from frontal, side, and single impact collisions and the term is even used for injuries from diving or sports like ice hockey, football, alpine skiing and other mishaps [4].

Table 1. The Quebec WAD classification

WAD	Symtoms and/or sign/s
0	no symptoms no signs
1	neck pain and /or neck stiffness but no signs
2	neck pain and /or neck stiffness and musculoskeletal signs*
3	neck pain and /or neck stiffness and neurological signs**
4	neck pain and /or neck stiffness and fracture or luxation

* *musculoskeletal signs include; trigger points, pain on palpation and decreased range of motion*

* * *neurological signs include; objective neurological signs*

Magnitude of the problem

WAD is a substantial public health problem in the industrialized world. The annual economic cost has been estimated to be 29 billion US dollars in USA [4]. It is the most common injury in motor vehicle accidents and an important cause of chronic disability [7]. Epidemiological data available for WAD is however limited [8]. Most commonly the sources mentioned in the epidemiological literature are; ***1.*** *The police,* ***2.*** *Hospital emergency departments and* ***3.*** *Insurance companies.* Pooled data from all these three sources, is so far not available.

WAD makes up almost one third of all compensation claims after MVA with medical disability >10%, reported to all insurance companies in Sweden. In addition the study reported a significant proportional increase (from 16% to 28%) in compensation claims between 1989 and 1994 [9]. Therefore WAD also constitutes a major medicolegal issue, given the sparse scientific evidence for the pathogenesis of WAD. Injury claim settlements in court proposes a challenge to the legal system in terms of judgements based on solid evidence.

In the industrialized western world the use of the road transport system is increasing. The increase in car traffic is expected to continue in the European countries during the period until 2020 [10]. An increase of WAD from MVA between years 1982 to 1992 from 7 to 40 % has been reported [11]. Another study found that 1/3 of the personal injuries after MVA were WAD[12]. In Scandinavian countries the number of fatally injured in MVA: s declined by nearly 50% (i.e. from 19,3 to 8,1 killed / 100 000 population) between 1970 and 1995 in spite of increasing traffic[13]. At the same time data from Statistics Norway[14] show a two-fold increase of police reported whiplash injuries in connection with rear end collisions.

According to Swedish casualty registry data, men dominated the numbers of fatal traffic accidents (FTA) in Sweden 1999, the peak gender difference being found in younger age groups. FTA was more than three times more common in the age group 15-44 years in men compared to women (9.3 vs. 2.5 /100 000 population) [15]. Moreover men were more commonly involved in rear end MVA collisions (64% vs. 36%) according to data from Norway[16]. In contrast, there is a female dominance in reports on whiplash injuries after rear end collisions [17,18,19].

In the context of WAD it is important to mention that non-specific neck pain is common in our population. The point prevalence of non-specific neck pain in general population has been estimated to be from 11,5 to 22,2 % in a Finnish and a Canadian study [20,21]. One month prevalence of neck pain was 41,1 in an other Finnish study [22]. Data from a Swedish population survey in 2000 [23] showed that point prevalence of self reported pain in either shoulder or neck in the age group 16-84 was 34.4% for men and 51,2% for women, with a peak in the female age group 45-64; 59 % of the women reporting on neck or shoulder pain. In comparison the data from the same study reported self reported hand, elbow, leg or knee pain point prevalence of 30% for men and 37.2% for women in the age groups 16-84.

Reports on whiplash incidence

A population based study from northern Sweden studied all cases of soft tissue injuries of the neck, that study included also other injury mechanisms than WAD. They estimated the annual incidence of soft tissue injury of the neck to be 100 / 100.000 population [24]. In another Swedish study [25] reported an annual whiplash injury incidence of 190 / 100000 population, they included minor head and neck injuries from emergency room casualty registers in two cities in northern Sweden. Yet another study in northern Sweden [26] studied 356 cases of whiplash trauma to the cervical spine, they found the annual incidence of acute whiplash trauma to be 420 per 100.000 inhabitants and 320 per 100.000 for whiplash-associated disorder grades 1-3. Studies from Canada and USA have reported annual incidence rates varying from 100 to 700 /100.000 population [4,27].

Etiology

Both the injury mechanism and the resulting tissue injury are debated. Some authors claim that the insurance and healthcare systems generate an opportunity for economic gains and therefore cause the so-called WAD epidemic [28,29]. Organic lesions and psychological disturbances are other causative factors reported in the WAD literature [30,31]. Some authors has suggested a bio psychosocial model in WAD[32,33]. This model seems applicable in chronic WAD, because of its similarity to other chronic pain populations. A recent literature review from Norway concluded that scientific evidence is uncertain whether there exists a causality between WAD grade I-II and chronic neck pain[34].

Etiological aspects on neck pain

There are several theories about the etiology of the neck pain in WAD. Injuries in ligaments, muscles, facet joints, occipital nerves, neural ganglions, has been proposed but the overall level of evidence is low [4,34].

Recently, a hypothesis about disturbances in central pain processing in WAD gained some support in a study where hypersensitive pain responses within one month after a whiplash trauma was found in a group, who reported persistinng symptoms six months later [35].

One of the problems for generalizing the results of studies on whiplash injuries is the wide range of possible injury mechanism, since the collision forces can have virtually any direction and amplitude and still fit within the context of the criteria for WAD. The most studied injury mechanism is the rear-end collision[36,37]. " In the early phase after the rear end impact, the cervical spine compresses and forms a S-shaped curve, with flexion in upper segments and extension in lower segments[36] ".

Laboratory studies on the injury mechanism using dummies in low impact rear end MVA collisions have discovered acceleration forces up to 4.5 times higher acting on neck as compared to car itself [38,39]. These findings have generated a hypothesis about low speed rear end collision causing neck injury.

In contrast, only 7% (2 of 30) of severily injured cases after MVA had persistenst neck pain in one study [40]. The force of the impact has been shown to have no correlation to severity of the WAD [41].

Several experimental studies on animal models have found evidence for a soft tissue injury after simulated whiplash trauma[42]. Svensson et. al [43] discovered increased permeability in spinal ganglia in pigs, they believed that the increased pressure in the spinal canal caused the injury.

Etiological aspects on epidemiological studies

Scientific evidence for causality between the exposure to a whiplash trauma and persisting symptoms is twofold. Recently in an epidemiological study based on an insurance company data, it was concluded that the cases who reported initial neck pain after a whiplash trauma had a three fold increased risk for chronic neck pain seven years after the exposure to trauma as compared to those who did not report initial neck pain after whiplash trauma [44].
In contrast Schrader et al [45] found no risk of chronic neck pain after a rear end MVA in a study based on 202 cases reporting to a police in Lithauania. However their retrospective study has been critizised because the lack of power given the small sample size.
A further study conducted in Greece [46] confirmed these findings with few patients claiming persistent neck pain after whiplash trauma. The authors claimed the diverging results to be caused by cultural differencies in insurance coverage systems and thereby victims awareness of economic gain.

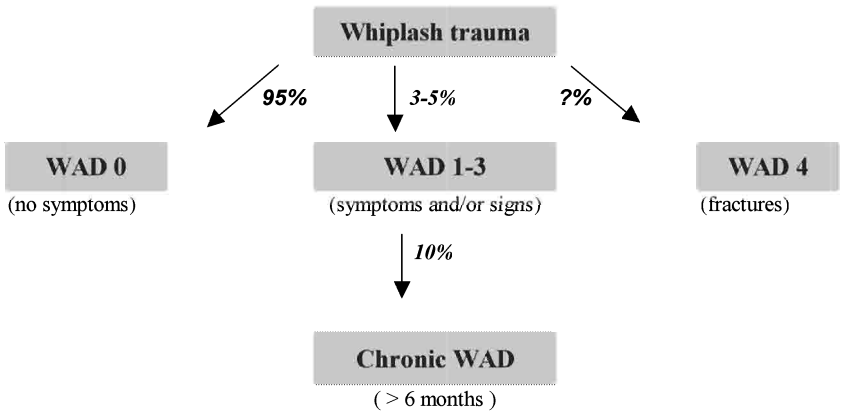
Symptoms

The common symptoms in WAD, like neck pain, and headache are also common in the general population [13,20,21,22]. There is considerable scientific uncertainty about the natural course of WAD [47,48,49,50]. Few studies are addressing the timetable for the occurrence and delay of initial symptoms [51]. According to the QTF -classification symptoms should arise within 24 hours after the accident, whereas in the whiplash debate it is often claimed that symptoms related to the accident can occur even after a non symptomatic period but there are no scientific studies issuing this matter [4]. Most studies on WAD have adopted the 24 hour symptom debut .

In a recent meta analysis from Norway [34] it was estimated that 3-5 % of persons exposed to whiplash trauma in motor vehicle collisions will develop acute symptoms within three days. Furthermore the most common symptoms after such a trauma mechanism (80% of those 3-5% developing acute symptoms) are neck pain, neck stiffness and headache. Finally a minor part of the patients (10% of those 3-5% that develop symptoms) will have persisting chronic symptoms that causes significant functional impairment.

Figure 2. Distribution of acute WAD grade and chronic WAD

(adapted from QTF and SMM 5/2000)



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Neck pain

Pain is defined by the "International Association for the Study of Pain" (IASP)[52], as;

> "*An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*.

They continue ": Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience. Experiences which resemble pain but are not unpleasant, e.g., pricking, should not be called pain. Unpleasant abnormal experiences (dysesthesias) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain ".

"Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish their experience from that due to tissue damage if we take the subjective report. If they regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause".

Chronic pain is defined by the IASP as ;

> " *Pain that persist beyond the normal time of healing*".

Since the patophysiology and healing time are not known for WAD, the "chronicity" of the pain in WAD is based on duration of the symptoms. QTF defined chronic pain as lasting more than six months, this thesis has adopted that definition [4]. Neck pain is by far the most common symptom in acute WAD and present in nearly 100% of cases[18,53].

Headache

Headache is a common complaint in WAD. It is also common in the general population and it is found to be a risk factor when reported prior to the accident [54,54,56]. It is most often of the cervicogenic type. However, the type of headache is not defined in most studies on WAD. Migraine type of headache in WAD has been postulated to be caused as a trauma induced vascular headache[57].

Cervicogenic headache (CEH) is by definition a pain radiating from the neck to the forehead[58]. According to a recent review, CEH associated with WAD is a moderate headache with a benign, but often prolonged course [56]. In a study on 222 whiplash cases, 3 % was diagnosed with CEH one year after the accident, they also found pre-existing headache to be more common in the group with persisting symptoms [59]. However there are few controlled studies about chronic headache after whiplash trauma.

CEH Diagnostic criteria according to the Cervicogenic Headache International Study Group[58]:

I. *Symptoms and signs of neck involvement:*
The presence of point A by itself signifies neck involvement, but points B and C alone do not. However, B and C together provisionally signify neck involvement.

A. Precipitation of head pain similar to the patient's usual pain:
1. by neck movement and/or sustained awkward head positioning, and/or:
2. by external pressure over the upper cervical or occipital region on the symptomatic side.

B. Restriction of the range of motion in the neck.

C. Ipsilateral neck, shoulder, or arm pain of a rather vague non-radicular natur or, occasionally, arm pain of a radicular nature.

II. *Confirmatory evidence by diagnostic anesthetic blocks.*

III. *Unilaterality of head pain without sideshift.*

A hypotesis about an injury of the occipital nerve, has been suggested but it has not been confirmed in clinical studies, morover the proposed surgical intervention has not been a success story [60].

No specific form of headache could be found in a study on 202 WAD cases. Furthermore, no difference in headache incidence was found between the WAD group and controls. Moreover the study concluded that headache prior to the MVA is a risk for future headache [54]. An other study found headache prior to the Whiplash trauma to influence later symptoms[55].

Neck stiffness

The term "neck stiffness" in the whiplash literature is used both as a self reported symptom as well as decreased ROM measured by different devices [61,62]. QTF uses neck stiffness as one their "objective" signs in their classification [4]. WAD classification does not, however define how the neck stiffness should be measured. Self reported neckstiffness is to be considered as subjective data, given the lacking validity and reliability data for the correlation between self reported neck stiffness and ROM. Using ROM data for the purpose of stiffness after a whiplash trauma is hazardously given the lack of normative data, mostly based on healthy volunteers [63]. Therefore it is diffucult to jugde whteter a certain degree of cervical ROM is "within normal limits".

Other symptoms

Numbness and paresthesia have been reported to occur in WAD by several authors [53,62,64]. Disc damage and injury to nerve plexa as in thoracic outlet syndrome has been proposed by some authors [65,66] but this seems to be a rare event in WAD. Petterson et al. [67] found no correlation between neurological signs and MR findings.
Dizziness and vertigo have reported in acute and chronic WAD and there is some evidence that proprioceptive dysfunction in cervical mucsles may be involved [68].
There are some studies with small sample sizes, indicating that cognitive impairment may occur as a result of the whiplash injury . In a Swedish study on 30 chronic WAD cases, impaired cognitive performance was found in the chronic WAD group as compared to healthy controls. Cognitive performance was also found to correlate with neck pain. They concluded that pain may be associated with cognitive impairment in chronic WAD [69]. However it may not be possible to make conclusions about causality between WAD and cognitive function, given the crosssectional study design.

Pathogenesis

Imaging studies

Imaging methods available include plain film radiography, computed tomography (CT), 2D and 3D magnetic resonance (MR), CT myelography, positron emission tomography (PET), single photon emission computed tomography (SPECT), ultrasound and bone scan. In spite of extensive studies there is a remarkable paucity of tissue lesions found when using available imaging techniques. For example, MRI, SPECT, PET, Bone-scan, CT-scan or X-ray studies have not shown injuries to muscle, discs, ligaments, spinal cord or brain stem as a result of whiplash-injuries, except for a case of rupture of the longissimus muscle of the neck [70-83]. Most imaging studies of whiplash injuries have focused on patients with late symptoms but some studies have been done in the acute phase [67,70].
It has beeen postulated that a hidden facet joint damage exists, i.e.it can not be dicovered with today´s imaging studies [84]. The "hidden damage hypothesis" has some support in post mortem case studies using cryosection techniques [85,86,87], but they seem to represent high energy, direct head impact trauma after MVA and therefore it may be difficult to generalize these results to WAD. Several neck injuries, non detectable on CT-scanning, were discovered utilizing cryosection techniques on 22 fatal traffic injury cases in an autopsy study by Jonsson et al [87]. The study pointed out some limitations of the routine imaging techniques commonly used for detecting certain injuries after whiplash trauma.
Narrow width of the spinal canal as measured from plain cervical x-ray soon after whiplash trauma was predictive for neck pain one year later in a study by Petterson et al.[88].

Muscles/Ligaments

The imaging methods available today have not been able to show ligamentous or muscle injuries in WAD other than in short series and case reports like a Swedish study that demonstrated a case of rupture of the longissimus muscle of the neck [78]. Recently Volle [89] demonstrated instability of the craniocervical junction (15 % of the cases) by using fMRI-video technique. Since no control group was used we do not know to what extend their findings represent biological variation.

Neural tissue

Although the major symptoms reported after whiplash injuries relate to the neck, some patients develop symptoms that are suspected to originate in the brain stem or the brain [90]. Recently a Swedish study reported that 3 of 17 cases after a whiplash trauma had increased levels of nervous tissue markers in cerebrospinal fluid [91].
A term "thoracic outlet syndrome" (TOS) was proposed by Peet et al in 1956 to describe arm symptoms after whiplash and other work-related trauma [66]. However, it seems to be a rare event after whiplash trauma and since that time little evidence on its pathogenesis have presented.

Intervertebral disc

The hypothesis of disc damage in WAD has not been confirmed in clinical studies.other than some studies with few highly selected cases included. Abnormal discs are frequently seen in asymptomatic cases, probably representing the normal ageing process [92]. A number of well conducted studies have failed to show disc damage after whiplash trauma [70-72,78,81].
Preoperative findings indicating disc damage was found in 8 patients with chronic WAD treated by surgical fusion of vertebral bodies [65]. In conclusion, according to the current literature a disc damage after whiplash trauma seems to be a rare event.
New insights about the pathomechanisms in the lumbar disc hernia have evolved lately. In past it was thought that mechanical nerve root compression was the major cause of pain associated with lumbar disc hernia, but later research has discovered nerve root inflammation to be more important [98]. There are no studies in relation to WAD, however.

Facet joints

Some evidence that chronic neck pain in WAD originates from the facet joints has emerged, using diagnostic facet joint injections of local anesthetic in a blinded and randomised study [93]. Pain relief was found in 50% of the cases. Apparently about half of the cases had other pain origin than the facet joint. So far these results have not been confirmed by others.

Immune system reaction to trauma

The immune system is a complex entity composed of numerous cell types and regulated by a multitude of autocrine, paracrine, and hormonal mechanisms. Immune system responses were once considered to be a host's reaction against pathogens, but are now known to be induced by many different factors including trauma. Numerous changes within the immune system upon severe trauma may even be deleterious and lead to complications such as systemic inflammatory response syndrome (SIRS) and contribute to multiple system organ failure[94, 95]. Cytokines are the main orchestrators of the immune response.
Analysis of cytokine profiles is becoming increasingly important for understanding physiological responses and pathological mechanisms associated with immune stimulation[96]. Despite the growing awareness that cytokines play an important role in a wide variety of clinical disorders, their complex biology can put limitations on the clinical usefulness of the findings. Determination of the nature of the immune response may however be helpful in developing treatment strategies [97, 98].

Psychological aspects

Association between psychological factors and disability in WAD has been widely debated in the WAD literature. Several studies have focused on personality, coping mechanisms and psychiatric morbidity, but little evidence has been gained from these efforts [100-102].
Berry [103] points out the lack of studies about the role of illness as an adjustment to trauma and that "marginal, tentative, or hypothesized physical changes are taken to be convincing, and obvious emotional and behavioural evidence is ignored."
In an attempt to go beyond the scope of organic findings as a sole explanation for chronic pain syndromes, some of the latest report have focused on bio psychosocial models adapted from studies on other chronic pain states, such as low back pain [103,104,105].
A Swedish study[104] on traffic accident victims including WAD(13%) concluded that "inadequate medical information about the injury and the prognosis, as well as a lack of psychosocial support is associated with a higher risk of complications. A "holistic' approach in the care of victims of traffic accidents is important. Early intervention as a routine practice in medical care might enable the injured better to cope with the trauma of a traffic injury and to recover from the injury itself."

Coping

Coping can be defined as purposeful efforts to manage or counteract the negative impact of stress [106,107]. Since neck pain is the dominant feature of WAD and pain is by definition always an emotional experience, coping has major implications in the study of neck pain in WAD. Models of stress and coping can be used to explain adjustment differences in chronic pain conditions[108]. A significant relationship between the experience of stress and painful conditions has been demonstrated [109-111]. Craig et a1.[112] pointed out that family's reactions to an injured individual may lead to changes in family roles. Depending on the coping skills of the family, inappropriate 'coping' patterns may pose a threat.
Most studies on coping in relation to whiplash have focused on patients who already had developed a "late whiplash syndrome"[4,110,114]. Especially the catastrophising item has gained interest in that context. Recently a Swedish study on 275 cases on chronic WAD, reported explanatory value for pain, depression and coping especially catastrophising for health-related quality of life[115]. The initial response might be of importance for the outcome. However, no prospective study has been published where the effect of different pain coping strategies in the acute phase is described. Recently a study based on an insurance company population found that several coping mechanism in the acute phase predicted outcome. They suggested that, the attitude to "act as usual" in the acute phase after a whiplash injury may help to prevent chronic complaints as proposed in other reports [116,117,118].

Personality

The mechanisms involved in the development of the chronic whiplash syndrome are poorly understood. It has been suggested that many cases of chronic WAD had a certain preexisting personality [119]. The term whiplash neurosis was used but no data supporting this assumption were presented. Illness behaviour after a whiplash injury does not appear to be related to the patients' perception of the severity of the accident or their concern about illness or disability [120]. Neither Radanov et al.[121] nor Mayou & Bryant [122] found that initial measures of psychological vulnerability or neuroticism predicted the symptomatic outcome. They suggested a somatic basis for the noted changes in psychological functioning. In a study based on 88 acute WAD cases attending an emergency clinic in Norway, no predictive power of the premorbid personality traits was found using the MCMI-1 questionnaire[100].

Psychiatric morbidity

The prevalence of mental or behavioural disorders is relatively high in the general population. It has been estimeted that about one fourth of the general population develop one or more such disorders during their life time [123-125]. Psychiatric morbidity is known to have an impact on the recovery of somatic diseases [126]. Several studies have indicated that recovery from a somatic disease may not be solely dependent on the treatment given. For example psychosocial, compensation claim issues and work related factors have been shown to better predict recovery than clinical and imaging findings in the treatment of low back pain [127-129].

During the latest decades reports on the on the raising role of illness behavior as an adjustment to life, stresses, and expectations has started to emerge[130]. This has necessitated a definition for it; according to DSM IV [131] criteria, somatoform disorder consists of multiple somatic complaints, frequent visits to physicians, and disability disproportionate to physical findings, often with a lack of emotional insight. There is however no study on WAD fulfilling the DSM IV criteria on illness behavior. Somatisation has been shown to have important influence on the outcome in different somatic diseases like rheumatoid arthritis, asthma and in low back pain [131-133].

Post traumatic stress syndrome (PTSS) is a DSM IV diagnosis that has been widely recognized after MVA [134.135]. Only few reports on its occurrence in WAD has been published[136,137]. Mayou et.al [137] found 5% PTSS diagnoses in their study using semi-structured interviews at 3 months and one year after a whiplash injury.

Recently, depression was found to be an important factor predicting neck pain in a general population; "Depression is a strong and independent predictor for the onset of an episode of intense and/or disabling neck and low back pain"[138].

Outcome and Prognosis

A large number of studies have shown a residual disability in WAD[4,139]. The cause of the disability is not known, however. Reports on prognostic factors on WAD have employed different outcome measurements, making it difficult to compare the results. Perhaps suprisingly, only a few studies have employed the most common complaint (neck pain) in chronic WAD as an outcome measurement. Further the studies with more than one year follow-up are few. In many reports in the WAD literature, the statistical methods used for prediction analysis are questionable regarding sample sizes, power of the studies and the prognostic modelling employed. Most studies employ weaker, univariate analyses to find prognostic variables. Therefore large prognostic studies based on emergency department populations with well defined, valid outcome measurements, analysed by statistically robust multivariate techniques are still needed [140].

Majority of studies on chronic WAD have found generally good prognosis, the proportion of chronic disability being about 6 to 18% [18,24,121,141-143]. Some other studies have reported higher figures, however[144,145]. Several studies indicate, that female gender, older age, high initial neck pain intensity and previous neck pain and previous head ache are risk factors for chronic WAD[139].

Crush- related prediction

Swedish research reports focusing on crush related factors have pointed out peak acceleration force and existence of a tow bar in rear end collisions as predictors [146,147]. Rotated head position at the time of the trauma and non awareness of the accident has been found to a risk factor for whiplash injury [62]. Car manufactures have taken the consequence of the increasing numbers of whiplash injuries and designed new seats and head rests made to absorb some of the collision forces before they can be transferred to the neck. A scientific report on such a design in a Volvo® car lend some evidence, that construction of the car seat and head rest can reduce the risk for WAD [148].

2 AIMS

Study I

To identify predictors for chronic WAD, especially the WAD classification suggested by the Quebec task force and to compare two follow-up regimens after WAD.

Study II

To determine the predictive value of pain-coping strategies after whiplash injury.

Study III

To compare psychiatric morbidity in patients having chronic symptoms after whiplash injury to a control group of fully recovered individuals.

Study IV

To study the systemic immune response after whiplash injury and after ankle sprain i.e. a minor trauma.

Study V

To study the systemic immune response in the acute phase of WAD and longitudinally over the 14 days.

3 MATERIAL AND METHODS

Study I

A series of 186 consecutive cases seen in the emergency room during the acute phase after a whiplash injury was prospectively studied for one year after the injury.
At the first visit all subjects filled out questionnaires about symptoms including neck pain intensity (VAS), details about the accident, employment and education. Physical examination was done by one of the authors (J.K) and findings were recorded using a standardized protocol. Cases involving fractures or dislocations of the cervical spine, head trauma or pre-existing neurological disorders were not included. Follow-up visits to the same doctor were done at 1 week, 3 weeks, 6 weeks, 12 weeks and 1 year after the accident. Due to limited resources for follow-up 79 of 186 subjects were seen only in the acute phase. These cases were encouraged to continue with normal activities and advised to return only as needed. After one year all subjects (n=186) were called to a follow-up visit to the same doctor (J.K). The outcome parameter was self-reported neck pain at one year after the accident.

Study II

A consecutive series of 96 patients who were seen in the emergency room in the acute phase after the injury were followed prospectively for one year. Age and whether or not pain in the neck preceded the accident was recorded. Cases involving fractures or dislocations of the cervical spine, head trauma or pre-existing neurological disorders were not included. The mean interval between the accident and the initial examination was 3±2(SD) days. Coping was measured using the Coping Strategies Questionnaire (CSQ). The outcome parameter was self-reported neck pain at one year after the motor vehicle accident.

Study III

We studied a consecutive sample of 278 patients with a whiplash injury. Eighty-five had persisting neck pain after one year and 38 of these participated in this study. For each patient with chronic neck pain at the one year follow up a gender- and age-matched fully recovered patient was selected from the study cohort of 278 cases. Psychiatric morbidity was determined using the Structured Clinical Interview for DSM-IV (SCID). The interview was conducted at one year after the accident (360days, SD ± 2).

Study IV

A consecutive series of 27 cases (9 females) with WAD, examined by J.K. not later than 3 days after the accident, were studied. They were examined according to a standardized protocol focusing on information regarding previous history, injury-related factors, and physical findings. None of the patients received nonsteroid anti-inflammatory drugs or steroids during the study period. Any occurrence of infections in the past 3 months was also registered.
In parallel, three control groups were examined:

(i) Fourteen patients (5 females) with acute ankle sprain were included as trauma controls. Their mean age was 35 ± 13 years. The patients with ankle sprain had visible haematoma at the ankle but no fracture or other injury. They were examined within 3 days after the ankle sprain. The mean interval between the accident and the initial examination was 2 ± 1 days.
(ii) Twenty-seven patients (18 females) with a diagnosis of multiple sclerosis (MS). Their mean age was 43 ± 12 years.
(iii) Twenty-three healthy subjects (16 females; hospital staff and blood donors) with a mean age of 32± 12 years.

Study V

Patients with whiplash injuries being examined at emergency departments of the hospitals serving the southern region of Stockholm were routinely referred to one of the authors (J.K.) for a prospective study on WAD. A subgroup of 29 patients (10 females; mean age, 36 6 11) with WAD, examined by J.K. not later than 3 days after the accident, was included in this study. The mean interval between the accident and the initial examination in these 29 patients was 2 ±1 days. Inclusion criteria were (a) car accident within the last 3 days and (b) age range between 18 and 65. Exclusion criteria were (a) previous neck injury, (b) abnormal signs at a standardized neurological examination, and (c) cervical fracture or dislocation. According to the Quebec classification 25 patients had WAD grade II and 4 patients had WAD grade III injury. Twenty-seven of these patients (10 females; mean age, 37 6 10) with WAD were examined by J.K. at 14 days after the accident. Nineteen of the patients with WAD were examined at both time points and thus included in both groups. In examining the changes in chemokine- and chemokine receptor-expressing cell levels over the course of WAD; data obtained from paired samples from these 19 patients were used. All patients with WAD were examined according to a standardized protocol giving information regarding history, injury-related factors, and physical findings. None of the patients received nonsteroid anti-inflammatory drugs during the study period. Any occurrence of infections in the past 3 months was also registered. In parallel, 14 healthy controls (7 females; blood donors with mean age of 39 ± 10 years) were examined.

4 RESULTS

Study I

At one year, 18 % of the total material had significant neck pain (>30 visual analog scale (VAS) 0-100). Logistic regression analysis showed that female gender, pain in the neck or shoulder before the accident and self reported emotional distress at the time of the accident were the only statistically significant predictors of chronic symptoms (neck pain). The Quebec classification (WAD 1-3) was not useful for the prediction of chronic pain. The QTF follow-up regimen was not associated with a better outcome.

Study II

At one year, 34% of the patients had neck pain. Women developed chronic neck pain more often than men (71% vs. 29%); they also had significantly higher coping activity, such as diverting attention, praying or hoping ($p<0.05$), catastrophising and increasing behavioral activities ($p<0.0001$). Women reported pain in the neck or shoulder more often before the accident and this was the only statistically significant predictor of chronic symptoms (Odds ratio 4.5).

Study III

In the group with chronic WAD a significantly ($p<0.05$) greater number had diagnoses according to Axis-I (acquired psychiatric disorders) (n=22; 58%) than the patients who were free of symptoms (n=11; 29%). This was also the case for Axis-I diagnoses that were reported to have occurred before the accident (n=13; 34% vs. n=3; 8%, $p<0.01$). The most common diagnosis was depression and the number of patients with a history of depression at the time of the accident was significantly higher in the group of patients who developed chronic pain than in the group who recovered (n=11; 29% vs. n=3; 8%$p<0.05$).

Study IV

An immune response reflected by elevated numbers of TNF-α and IL-10-secreting blood MNC was observed in patients with WAD examined within 3 days compared to findings at 14 days after the whiplash injury. The patients with WAD examined within 3 days after the injury had also higher numbers of IL-6 and IL-10 secreting blood MNC compared to healthy subjects. Similar alterations of cytokine profiles as were observed in WAD were also observed in patients with ankle sprain when examined within 3 days after trauma. In contrast, there were no differences for cytokine profiles between patients with WAD examined 14 days after the whiplash injury and healthy subjects. Relatively minor trauma like WAD and ankle sprain are associated with a systemic dysregulation in numbers of cells secreting pro- as well as anti-inflammatory cytokines.
A high numbers of TNF-α and IL-6 and low numbers of IL-10-secreting blood MNCs seen in our control group of MS patients.

Study V

In a prospective study using flow cytometry, we examined percentages of blood mononuclear cells (MNC) expressing the chemokines RANTES, MCP-1, MIP-1a, MIP-1b, and IL-8, the chemokine receptor CCR-5, the T cell activation marker CD25, and the T cell chemo attractant IL-16 in patients with WAD and, for reference, in healthy controls. Higher percentages of RANTES-expressing blood MNC and T cells were observed in patients with WAD examined within 3 days compared to 14 days after the whiplash injury and likewise, compared with healthy controls. The patients with WAD examined within 3 days after the accident also had higher percentages of CCR-5-expressing blood MNC, T cells, and D45RO1 T cells compared to healthy controls. In contrast, there were no differences for any of these variables between patients with WAD examined 14 days after injury and healthy controls.

5 GENERAL DISCUSSION

Study I

There are numerous prospective studies of WAD based on hospital emergency department data in the literature, however a recent review (2001) found only four studies that fulfilled their scientific criteria[140]. They also proposed a new conceptual framework for literature reviews on the prognosis of WAD. It is interesting to note that they found no prospective study on WAD based on the emergency department population that qualified as an exploratory study using multivariate models. Some other often cited prognostic studies like those by Radanov et al 1995 and 1996 were based on cases recruited by advertising in the Swiss Medical Weekly Journal and by sending letters to primary health care centers. This makes it difficult to draw general conclusions from their results. There is no consensus in Sweden about the preferred follow-up regimen after a whiplash injury. Nygren et al.[8] recommended the model suggested by the Quebec Task Force [4] but we believe that no routine follow-up is the most common practice. The current study was designed to find predictive factors during the acute phase of the WAD in an emergency department population. To minimize recall bias, self reported symptoms prior to the accident were collected soon after the MVA (3days). Inclusion criteria were based on recommendations made by the QTF. We used standardized measurement tools.

The study hypothesis was made before data collection began. Cases included were classified and follow up was done according to QTF recommendations. The cohort was a consecutive series of patients attending the emergency department at the Karolinska University Hospital, Huddinge. All cases were examined and treated by the same doctor (J.K) in a standardized fashion. To our knowledge this is the first study of WAD to employ a single examiner in the acute phase. We believe that this strengthens the validity and reliability of the data collected at the time of the accident. The procedure used to allocate cases into two groups might include a risk of sampling bias, but randomization was not possible since the patients in the no follow up group should not be aware of their being participants in a study. Furthermore the risk of a significant sampling bias was limited since the listing was done in chronological order as the patients were scheduled and allocation was done by the nurse on duty who was unaware of the details of the study. Indeed, we found no statistical difference between the follow up groups for gender and socioeconomic characteristics.

The study was planned to make multivariate statistics possible, given the fact that there was lack of exploratory studies using more robust statistical methods[140]. Earlier as well as the current study has indicated that female gender, neck pain prior to the accident and emotional distress soon after the accident are predictors [135,148].
In contrast to the current study, Hartling et.al. [149] concluded that the Quebec classification was useful for predicting chronic WAD. However they used a nonvalidated pain score - questionnaire based on telephone interviews as an outcome measurement. The score was equally based on pain from three different anatomical regions; 1) neck- and/or 2) upper back and/or 3) shoulder pain. The initial WAD classification, which was based on physical examinations made by different physicians on call, was retrospectively determined from the medical records. WAD grade 0 was included (10 % of the total study sample). However,

Berglund et al. (1) concluded in their prospective study that cases without symptoms after rear end collisions (i.e. WAD grade 0) do not have an increased risk of developing chronic symptoms. There were a high number of cases missing in the study by Hartling et al., increasing from 12% at the 6 month follow-up to 25 % at 24 months, which further weakens the statistical power of their study. Furthermore, the WAD-grade was treated as a continuous variable in the statistical analysis all of which makes their conclusions questionable.

Sterner et al.[148] found female gender, low educational level, pretraumatic neck pain and WAD grades 2-3 to be associated with persistent disability. The predictive power of female gender and pretraumatic neck pain is in accordance with our study; however we found that the educational level and WAD grade had no predictive power. Their study is not directly comparable to the present one because of different outcome measurements (our study used chronic neck pain as outcome whereas Sterner et al. studied disability). The geographical difference (i.e. a major city area in our study, vs. the rural area Umeå) may have influenced the socioeconomic status of the two populations under study. For example, blue collar workers had a higher prevalence of neck-shoulder disorders than white collar workers in Finnish study [150]. Furthermore Sterner et al. included WAD grade 0 (21 % of total) in their study whereas WAD 0 was excluded in our study, and only 1 % of their patients had WAD grade 3. The numbers in the WAD-categories found in our study are in better agreement with larger epidemiological studies than the study by Sterner et al who might have had difficulties in classifying cases from the medical records [148].

Preceding symptoms have been found to be risk factors for subsequent disorders of the low back [151,152]. Episodes of neck/shoulder pain are known to involve increased risk for new episodes of neck/shoulder pain. Neck symptoms in 1969 were risk factors of neck disorders 24 years later [153]. This is of interest in context with our findings regarding previous neck pain as a prognostic factor. Moreover their findings, where mainly psychosocial factors among women and mainly physical factors among men were associated with neck/shoulder disorders is interesting in view of our finding that emotional distress was important for the outcome.

In conclusion, the WAD-classification could not predict persistence of chronic neck pain after a whiplash injury in this hospital emergency department based population. Nor was there a statistically significant difference in the rate of chronic neck pain between the no follow-up regimen and the multiple follow up regimen proposed by the QTF.

The multiple follow up regimen is both time consuming and costly and may not be justified in a routine clinical setting. A careful history, physical examination and information about the nature of the condition at the first visit is probably the preferred treatment for patients who have been exposed to whiplash injuries. Patients with a relatively high risk of developing chronic pain should be selected for studies in prophylactic treatment programs when available. In this study cases with neck pain before the accident and a high degree of emotional discomfort at the time of the accident had a 10-fold increase in the risk of developing chronic neck pain.

Study II

There is no doubt that an MVA can be horrifying and even a potentially life threatening event. The response to it depends on different factors among them earlier experience and knowledge. In this context the victim's ideas about the seriousness of the injury are probably important [154]. The CSQ-questionnaire we employed to measure coping is a widely used and reliable instrument [155, 156]. Further the collection of data was done prospectively in a standardized fashion including cases attending a hospital emergency department.

There are several studies indicating a role of coping in the development of chronic neck pain in WAD [157-159]. However recently, an insurance company based population was studied in the acute phase (within 30 days after MVA) of WAD. Several coping mechanisms were associated with poor outcome [154]. This differs from our finding possibly due to the differences in study populations i.e. insurance vs. hospital emergency cohort. Furthermore, in our study coping was measured within 7 days (i.e. at the first visit), since one of the study goals was to find a prognostic tool to be useful in the acute phase in WAD. However, the post injury period may have been too short for coping mechanisms to develop. There is however no scientific consensus about the time frame for the development of pain coping strategies after the onset of acute pain. Our finding of lower mean value for catastrophising than found in other studies of chronic pain may be ascribed to the recent onset of pain. It has been also stated that coping in the acute phase is different and also an adaptive process as compared to later phase [160].

The results of the current study demonstrated that women were at greater risk of developing chronic symptoms than men. Women also reported greater use of diverting attention, praying and hoping, catastrophising and increasing behavioral activities, as also seen in a study by Jensen et al.[161]. However the same pattern was seen in both the recovered and the symptomatic groups. Previous neck pain was also more frequent in women.

We used previous neck and shoulder pain item as covariate in our model because the high prevalence in the normal population. Thereby we tried to avoid interference bias with the CSQ findings, given the longer pain exposure in the group with pre-accident neck pain. Indeed, in the group of patients with pre-accident neck pain, praying or hoping and catastrophising were significantly more frequent than in the group with previous neck pain.

We also tested another logistic regression model that included all CSQ variables, but this model was rejected because of the lack of power considering the large number of independent variables.

Although neck and shoulder pain before the accident had significant predictive power, there seems to be other factors not included in this study that predict the outcome after acute WAD, given the low (23%) overall explanation level in this study.

Our findings indicate that pain coping strategies in the early phase after the MVA may not be important for predicting chronic symptoms. Further studies on well-defined patient cohorts exploring different time points in the acute phase after WAD needs to be made in order to identify when and how the pain coping mechanisms may influence the outcome in WAD.

Study III

Scientific evidence is evolving that other factors than the whiplash injuries itself are important for recovery. The influence of psychiatric morbidity on the outcome of somatic diseases is widely recognized [131-137]. However reports focusing on psychiatric morbidity in WAD are few. Previous studies investigating psychopathology in WAD have mostly utilized self-reported questionnaires whereas our study employed a rigorous tool for measurement of psychiatric diagnoses (SCID). SCID is a widely used and found to be a reliable and valid instrument [162-165]. In the current study, the retrospective nature of questioning about previous psychiatric morbidity may have introduced a recall bias. However, we believe it to be less likely, since the SCID has been designed to permit retrospective diagnosis of the major psychiatric disorders, including those that occurred before the MVA. By doing the SCID interview at the end of the observation period a case control study design was possible and the post injury period could be included. The rigid structure of the SCID interview is likely to eliminate influence of an ongoing depressive state on the results; however such a possibility cannot be ruled out completely. It is also possible that patients might have a tendency to underreport previous psychiatric morbidity believing that this could make the relationship between the symptoms and the accident look weaker. Such a mechanism would however only strengthen the conclusions of this work.

Lifetime prevalence of psychiatric morbidity in the general Dutch population has been estimated to be 41%, this is comparable to the findings of our study [166]. The point prevalence (last month) of depression was 3% in the recovered group; similar figures were reported in a study on the Swedish general population (PART study)[167]. In our study 58% of the symptomatic patients had a lifetime history of a DSM IV axis I disorder compared to 29% of the asymptomatic patients. Even if we disregard those subjects in the symptomatic group who developed a first episode of depression after the trauma, nearly one third of the patients reported a history of depression.

We found that depression was especially common in the group with persisting neck pain. Our results also suggested that depression was not merely a consequence of chronic pain. The higher prevalence of pre-injury Axis-I morbidity and depression in the group with persisting neck pain, suggested that in fact psychiatric morbidity and in particular a history of depression might directly or indirectly have an impact on the prognosis after a whiplash injury. In the total study sample, a depressive syndrome prior to the traumatic incident was reported in fourteen patients (18%) and eleven (79%) of those developed chronic neck pain.

The overrepresentation of psychiatric symptoms in the group with chronic neck pain may be related to the mental condition itself but an indirect mechanism can not be ruled out. For example it has been shown that patients with psychiatric disorders smoke more than others and social factors such as isolation and unemployment could also be more common in this group and possibly contribute to the development of chronic symptoms [168].

The lifetime prevalence of anxiety disorders in the current study was comparable with data from NEMESIS study [166]. We found only one posttraumatic stress disorder (PTSD) whereas Mayou et.al.[137] found 5% in their study using semi-structured interviews at 3 months and one year after a whiplash injury. In their study, however, no information regarding the outcome or severity of the accident was available which makes a comparison difficult. In our study only a few patients

had experienced a motor vehicle accident serious enough to meet the A criterion for PTSD (e.g. life threatening).

The lifetime prevalence of substance abuse disorders in this study was 9% vs. 18.7% in the NEMESIS study. No new cases of anxiety disorder or substance abuse/dependence appeared after the accident. One reason for the lower frequency of substance abuse disorders may be that we studied a population with many car drivers. A selection bias with underepresention may have occurred.

The high rate of patients not willing to participate (55%) may have introduced a selection bias, but a post hoc test using the HAD data collected at one year after the accident showed no significant difference in the occurrence of clinical depression or anxiety between the participants and the nonparticipants.

In conclusion, there was a significantly higher lifetime- and pre-accident prevalence of psychiatric diagnoses in the group of patients who developed chronic neck pain after a whiplash injury than among those who recovered. The most frequent psychiatric diagnosis was depression. Previous psychiatric morbidity seems to be a patient-related risk factor for the development of chronic pain after a whiplash injury. The development of chronic symptoms after a whiplash injury seems to be associated with psychiatric vulnerability. In several cases a consultation with a psychiatrist may be warranted. In addition, given the high prevalence of depression among cases with chronic WAD, treatment studies focusing on depression could be undertaken.

Study IV

Analysis of cytokine profiles is becoming increasingly important for the understanding of mechanisms associated with the immune system. Cytokines play an important role in a wide variety of clinical disorders. Enzyme linked Immunospot assays (ELISPOT) are among the most sensitive and specific assays available for cytokine research today. They permit the ex vivo identification of cells actively secreting cytokines without any prior stimulation in vitro. The assays are 10–200 times more sensitive than Enzyme linked Immunosorbent assays (ELISA) [169], efficient, and fast. Using ELISPOT assays, we found that acute WAD is associated with a detectable systemic immune response.

The numbers of TNF-α and IL-10-secreting blood MNC were higher in patients with WAD examined within 3 days compared to 14 days after the accident. The patients with WAD examined within 3 days after the accident had also higher numbers of IL-6- and IL-10-secreting blood mono nuclear cells (MNC) compared to healthy subjects.

A similar elevation in IL-6 and IL-10 compared to healthy subjects were also observed in patients with acute ankle sprain. No differences were encountered for TNF-α or INFγ-secreting MNCs when comparing patients with acute WAD or ankle sprain with healthy subjects.This contrasts to the control patients who had multiple sclerosis (MS), a neurological disease associated with inflammation within the central nervous system (CNS), who showed high levels of TNF-α secreting MNCs systemically, as reported previously [170]. The elevated levels of both pro (TNF-α and IL-6) - and anti-inflammatory (IL-10) cytokine-secreting cells observed in acute WAD and of IL-6 and IL-10 after an ankle sprain suggest that both Th1 and Th2 responses are activated in parallel in these two different types of minor trauma.

We do not know whether, e.g., the high numbers of TNF-α and IL-6 and low numbers of IL-10-secreting blood MNCs seen in our MS patients are relevant for disease pathogenesis or represent epiphenomena. The first alternative seems to be the most likely one since the involvement of cytokines in MS brain lesions is well documented. TNF-α, INFγ, IL-10, IL-12 , and IL-6 are present in active MS lesions [171-173].Moreover, higher numbers of TNF-α mRNA-expressing cells are found in active demyelinating lesions than in inactive or remyelinating lesions [174]. Similarly in acute WAD and ankle sprain, the high numbers of IL-6- and IL-10-secreting blood MNCs that we observed could reflect a trauma-related activation of the immune system that could be of importance for the development of signs and symptoms associated with WAD and ankle sprain. Elevated levels of cytokine secreting cells systemically might reflect accumulation of immune cells in the traumatized tissue in WAD as well as in ankle sprain.

We found it exciting that acute minor trauma is associated with elevated production of certain cytokines, detectable systemically. This observation could make up a basis for future studies of other immune mediators in these and related (e.g., long-lasting symptoms after WAD) clinical events. In conclusion, (i) patients with WAD when examined within 3 days after a whiplash injury display a systemic increase of pro-inflammatory TNF-a and IL-6 and of anti-inflammatory IL-10; (ii) these cytokine alterations become normalized when the patients with WAD are reexamined 14 days after the whiplash trauma; (iii) control patients with ankle sprain show cytokine profile changes in the acute stage similar to those observed in patients with WAD implicating that measurements of cytokines under study do not discriminate between acute WAD and ankle sprain; (iv) the immune response reflected by cytokine secreting cells systemically is different in patients with whiplash injury and ankle sprain compared to an affection of the CNS like MS.

Study V

Determination of the nature of the immune response may provide evidence for the pathogenesis of a disease and, therefore, be helpful in developing treatment strategies.
Analysis of chemokine profiles is becoming increasingly important to understand the nature of the immune response and the profile of immune cells involved in a variety of disease states. In an attempt to identify a possible association between the immune response and WAD, we used flow cytometry to detect and enumerate cells expressing selected chemokines and their receptors without any stimulation of cells in vitro. Flow cytometry also made it possible to analyze the phenotype of the cells expressing these molecules.
Among a number of chemokines (RANTES, MCP-1, MIP-1a, MIP-1b, and IL-8) examined, we found that acute WAD, i.e., when the patients were examined within 3 days after the accident, is associated with an elevation of both RANTES-expressing MNC and CD31 T cells in blood compared to the corresponding levels in healthy controls. RANTES is a CC chemokine and attracts mainly monocytes/macrophages and T cells [175].
Besides a clearly defined role in mediating leukocyte migration, RANTES and other chemokines may act as immunoregulatory molecules in the driving of Th1/Th2 responses, switch of cytokine profiles, and induction of tolerance[176]. Therefore, altered RANTES expression might be important in development of signs and symptoms associated with WAD. CCR-5 is one of the receptors of CC chemokines including RANTES.
Interestingly, patients with acute WAD, i.e., when examination was performed within 3 days after the whiplash injury, also had higher levels of CCR-5-expressing blood MNC, T cells, and CD31, CD45, RO1 memory/effector T cells compared to healthy controls. CCR-5 has been shown previously to mark Th1 cells, whereas CCR-3 and CCR-4 mark Th2 cells [177]. Therefore our data suggest that the elevated CCR-5-expressing levels may reflect Th1-type immune responses early in WAD. When blood samples from the same individuals with WAD were studied over the course of WAD, we also observed that percentages of both RANTES-expressing MNC and RANTES-expressing CD31 T cells and of CCR-5-expressing MNC, T cells, and CD31CD45RO1 memory/effector T cells, in blood were higher in specimen I compared to specimen II, which was obtained 14 days after the whiplash injury.

Our results thus suggest that these alterations of RANTES- and CCR-5- expressing cells are normalized within 14 days after the whiplash injury. In conclusion, we show that WAD patients examined within 3 days after the accident have a systemic increase in RANTES- and CCR-5-expressing MNC and CD31 T cells. These alterations are normalized 14 days after the whiplash trauma. The findings thus indicate that the traumatic event that precedes WAD is associated with up regulated chemokine and chemokine-receptor expression. Studies should be undertaken on patients with permanent clinical symptoms after WAD, to evaluate if long-standing changes in chemokine and chemokine receptors may take place.

6 CONCLUSIONS

A careful history, physical examination and information about the nature of the condition at the first visit is the preferred treatment for patients who have been exposed to whiplash injuries. Patients with a relatively high risk of developing chronic pain should be selected for studies in prophylactic treatment programs when available.

Two main risk factors for chronic neck pain 1 year after whiplash injury was found;
1. Neck pain before the accident and
2. A high degree of emotional distress at the time of the accident
Having both these factors caused a 10-fold increase in risk of developing chronic neck pain (odds ratio 9.7 and 11).

A history of psychiatric disease was more common in patients with chronic symptoms (chronic WAD). The dominating, psychiatric diagnosis both before and after the accident was depression. Psychiatric morbidity may be a patient-related risk factor for chronic symptoms after a whiplash injury. The development of chronic symptoms after a whiplash injury seems to be associated with psychiatric vulnerability.

We found no evidence that the prognosis was related to coping in the early phase after a whiplash injury, using the CSQ. The pain coping in the early phase does not appear to be appropriate for predicting chronic symptoms.

Minor soft tissue trauma like ankle sprain show transient cytokine profile changes in the acute stage similar to those observed in patients with WAD. MS – a disease involving neural tissue in the CNS showed no similarity in the immune response, reflected by cytokine secreting cells systemically, compared to acute WAD. This may indicate that the observed immune reaction involved tissues outside the central nervous system in WAD.

Our findings suggest that; in the time perspective of three days to two weeks after the whiplash trauma certain transient up regulated chemokine and chemokine-receptor expressions take place, indicating that even in a minor soft tissue trauma like whiplash, a transient chemokine up regulation can be detected in peripheral blood sample.
Whether patients with permanent clinical symptoms after WAD, making up 5–10% of all patients with WAD, will develop long-standing changes in chemokine and chemokine receptors remains to be established.

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