Headache in systemic lupus erythematosus and primary Sjögren's syndrome

Anne Bolette Tjensvoll

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Author: Anne Bolette Tjensvoll

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Scientific environment

This PhD work originates from the research programme "Rheumatologic diseases and the nervous system" and was performed in the Research group of Clinical Immunology, at Stavanger University Hospital. This group is led by Professor Roald Omdal and focuses mainly on the neurological aspects of chronic inflammatory autoimmune diseases. The group includes members from several medical- and laboratory professions, and collaborates with a number of local-, regional- and international research groups.

The studies in this thesis have been carried out at Stavanger University Hospital, in cooperation with the Departments of Neurology, -Internal Medicine, -Radiology, -Neurophysiology, -Pathology and -Biochemistry. Professor Jan Terje Kvaløy, Department of Mathematics and Natural Sciencies, University of Stavanger, has been an important collaborator regarding statistical analyses. Also, the group`s collaboration with Professor Shunsei Hirohata, Tokyo, Japan, has been highly appreciated.

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Abbreviations

ACR	American College of Rheumatology
AECG	American-European Consensus Group
ANA	Anti-nuclear antibody
Anti-P	Anti-ribosomal P-protein
aPL	Anti-phospholipid antibody
APS	Antiphospholipid syndrome
BBB	Blood-brain barrier
BDI	Beck Depression Inventory
CD	Cluster of differentiation
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
CSD	Cortical spreading depression
CSF	Cerebrospinal fluid
DAMPs	Danger-associated molecular patterns
DNA	Deoxyribonucleic acid
EEG	Electroencephalography
ELISA	Enzyme-linked immunosorbent assay
FLAIR	Fluid Attenuated Inversion Recovery
FSS	Fatigue Severity Scale

GM	Gray matter
GWAS	Genome-wide association study
HIT-6	Headache Impact Test-6
HLA	Human leukocyte antigen
ICHD-II	The International Classification of Headache Disorders, 2nd edition
i.e.	Id est
IFN	Interferon
Ig	Immunoglobulin
IHS	International Headache Society
IL	Interleukin
MIDAS	Migraine Disability Assessment
MOH	Medication overuse headache
MRI	Magnetic resonance imaging
NK	Natural killer
NMDA	N-methyl-D-aspartate
NP	Neuropsychiatric
NPSLE	Neuropsychiatric systemic lupus erythematosus
OR	Odds ratio
PAMPs	Pathogen-associated molecular patterns
pSS	Primary Sjögren's syndrome

SD	Standard deviation
SSA	Sjögren's syndrome A antigen
SSB	Sjögren's syndrome B antigen
SLE	Systemic lupus erythematosus
SLEDAI	SLE disease activity index
SLICC-DI	Systemic Lupus International Collaborating Clinics/ACR damage index
SUS	Stavanger University Hospital
TE	Echo time
Th	T helper
TIV	Total intracranial volume
TR	Repetition time
T-reg	Regulatory T cells
TTH	Tension type headache
UiB	University of Bergen
UV	Ultraviolet
VBM	Voxel-based morphometry
WM	White matter
WMH	White matter hyperintensity

Abstract

Background

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease which can affect multiple organs. The central nervous system (CNS) is frequently affected, and headache, especially migraine, is among the most frequent manifestations. The existence of a strong and specific "lupus headache" has been debated for decades, and it is still controversial whether this type of headache is a reality or a myth, and whether headache in SLE is caused by the disease`s brain involvement, something that may have implications for the treatment of SLE in the individual patient. Moreover, even less is known about headaches in other autoimmune diseases, such as primary Sjögren`s syndrome (pSS), and there is therefore a need to obtain more knowledge on these issues.

Main objectives

- Investigate prevalence and characteristics of headaches in the autoimmune disease SLE.
- Investigate whether headaches occur with the same pattern in another autoimmune disease, namely pSS.
- Investigate whether headache-related disability is different in these diseases compared with the general population.
- Investigate whether clinical-, biochemical-, immunological- or structural brain abnormalities influence the prevalence of headache in patients with SLE.

Subjects and methods

Nearly all patients with autoimmune diseases in Rogaland County, Norway, are allocated to Stavanger University Hospital (SUS), which served about 310 000 people at the time of the study. We aimed at identifying all known cases with SLE and pSS in this area, and the studies in this thesis are therefore near population based. Cross-sectional- and case-control designs were used. Sixty-seven SLE patients and 71 pSS

patients, as well as their age- and gender matched healthy control subjects, gave written informed consent to participate.

All participants were examined by an experienced internist and neurologist. Biochemical- and immunological analyses, and cerebral magnetic resonance imaging (MRI) were performed, in the patients also analyses of the cerebrospinal fluid (CSF). International criteria for SLE and pSS, for neuropsychiatric syndromes in SLE, and for headache classification were used. Reliable and validated instruments were used for assessing depression, fatigue, and headache-related disability. Biochemical- and immunological analyses were performed at the hospital`s routine laboratories and in the research laboratory at SUS. Antibodies against ribosomal P-protein (anti-P) were analyzed in professor Hirohata`s research laboratory in Tokyo, Japan. MRI analyses were performed with the SPM8 software.

Results

Twenty-four out of 67 SLE patients and 13 out of 67 matched healthy subjects had migraine (36 % vs 19 %, P = 0.03). Out of these, nine SLE patients and 4 healthy subjects had migraine with aura (13 % vs 6 %, P = 0.14). Prevalence of tension type headache (TTH) was equal in SLE patients (60 %) and healthy subjects (58 %). SLE patients had more depression and fatigue than the healthy subjects, and depression was associated with migraine in the patients. Headaches were, with the exception of SLE photosensitivity, not associated with any SLE disease specific factors such as disease activity, accumulated organ damage, biochemical- or immunological markers in blood, impairment of the blood-brain barrier, intrathecal immunoglobulin production or white matter hyperintensities (WMHs) on cerebral MRI.

Eight pSS patients (11 %) had chronic TTH, while only one of the healthy subjects had chronic TTH last year, P = 0.05. This subtype of TTH was not associated with pSS-related antibodies, depression, fatigue, abnormalities on MRI, or any other clinical or laboratory variables. Migraines and migraines with aura were equally prevalent in patients (26.8 % and 11.3 %, respectively) and control subjects (28.2 % and 15.5 %, respectively, P = 0.61).

On cerebral MRI, increasing gray matter (GM) volumes in the SLE patients reduced the odds for migraine (OR 0.95, P = 0.004). No *localized* loss of GM was observed. Increasing global white matter volumes in the patients increased the odds for migraine (OR 1.04, P = 0.007). These findings could not be replicated in the healthy subjects. No associations with headaches in SLE patients were revealed regarding anti-NR2-, anti-P antibodies, nor protein S100B.

Conclusions

SLE patients have more migraine than healthy subjects. It is associated with mental depression, but not with disease activity, abnormalities detected on cerebral MRI, abnormalities in CSF, or any SLE characteristics except from SLE photosensitivity. The distribution of headache types in pSS patients differ from that observed in the SLE patients, and migraine is not more prevalent than in the healthy control subjects. However, pSS patients have more chronic TTH than the healthy subjects.

Headache-related disability is considerably higher in patients with SLE and pSS than in otherwise healthy headache-sufferers. Depressive mood significantly influenced headache severity in the patients. The high headache-related disability in patients with SLE and pSS may reflect the burden of chronic disease.

SLE patients with migraine have a global diffuse reduction in GM compared to patients without migraine. This GM volume reduction was not observed in the healthy subjects with migraine. Analyses of the selected biomarkers did not indicate specific pathophysiological processes in the brain. These findings indicate that unknown pathogenic and pathophysiological processes are responsible for - or influence - the increased frequency of migraine in SLE patients.

List of publications

Tjensvoll AB, Harboe E, Gøransson LG, Beyer MK, Greve OJ, Herigstad A, Kvaløy JT, Omdal R. Migraine is frequent in patients with systemic lupus erythematosus: a case-control study. Cephalalgia 2011; 31: 401-8.

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Contents

1. Background

Headache is the most frequently reported neurological phenomenon in patients with systemic lupus erythematosus (SLE) and has traditionally been regarded as part of the disease spectrum. Through decades it has been claimed by some investigators that sometimes a unique type of headache evolves in the patients. This *lupus headache* has been defined by the American College of Rheumatology (ACR) as a severe and persistent headache that "may be migrainous, but must be non-responsive to narcotic analgesia" (1). In the British Isles Lupus Assessment Group 2004 index, which was developed to assess disease activity in SLE, lupus headache is defined as a "disabling headache that is unresponsive to narcotic analgesia and lasts ≥ 3 days" (2). The significance of this type of headache is further reflected by its placement in the SLE disease activity index (SLEDAI), in which this item has a heavy weighting (1).

Whether a specific lupus headache really exists, and whether primary headache disorders are different in SLE patients compared with subjects in the general population, has now been debated in scientific fora for nearly 50 years. The matter is still not settled, an issue with potential diagnostic and therapeutic relevance for patients with SLE. Moreover, even less is known about headaches in other autoimmune diseases, such as primary Sjögren`s syndrome (pSS).

1.1 Headache classification

The phenomenon of headache has been known since antiquity, and today many specific types of headaches are described and categorized. In the first century, Aretaeus of Cappodocia classified headaches according to their phenotypes into three main categories; *cephalalgia, cephalea and heterocrania* (3). Two-thousand years later, classification is still mainly based on phenotypes, as there is limited knowledge about the pathogenesis and etiology for most of the primary headaches. In 1988 the Headache Classification Committee of the International Headache Society (IHS) published *Classifications and diagnostic criteria of headache disorders, cranial*

neuralgias, and facial pain, 1st edition (4), for the purpose of strengthening research and clinical work. In 2004 a second edition was published – *the International Classification of Headache Disorders, 2nd edition* (ICHD-II) (5). ICHD-II provided the latest criteria at the time of examination of patients, interviews and data sampling for this thesis. ICHD, 3rd edition (beta version), was published in 2013 (6).

Headache disorders are divided into *primary* and *secondary* headaches, constituting part 1-2 of ICHD-II, while *cranial neuralgias and facial pain* constitute part 3. Primary headaches are classified according to the phenomenology of the headache, and are *not* attributed to a causative condition or disease. Secondary headaches are attributed to disorders considered to be the cause of headache, thus being classified according to etiology. Phenotypes of the secondary headaches are not further specified. They may mimic primary headaches, and thereby make the differentiation between primary or secondary headache a challenge. If a headache occurs for the first time in close temporal relation to another disorder that is a known cause of headache, this headache should be coded as a secondary headache according to the causative disorder. However, a pre-existing primary headache that becomes significantly more severe in close temporal relation to such a disorder should be coded with a secondary headache diagnosis in addition to the primary headache diagnosis (6).

The three main categories of primary headaches are tension type headache (TTH), migraine and the trigeminal autonomic cephalalgias. TTH and migraine are by far the most common, and are further divided into subtypes, such as migraine with or without aura, episodic or chronic migraine, and episodic or chronic TTH. Cluster headache is probably the best known of the trigeminal autonomic cephalalgias, characterized by distinct autonomic features.

The reported prevalences of headaches vary. Methodological issues, such as bias from patient cohorts, the different use of questionnaires versus interviews in data sampling, and varying classification criteria, are considered responsible for the differences. The 1-year prevalence is frequently used as criterion for an active headache disorder. The term “headache” is not defined in the ICHD classification, but is used in

epidemiological studies, often named “headache in general” or “all headaches”, to distinguish from the specific types of headache. Epidemiological studies of headache in large populations most often use questionnaires, and often with somewhat modified criteria. Variations in the reported prevalences and patterns of headache across countries are substantial, and methodological differences probably accounts for some part of this (7). In a large population based Norwegian study, the 1-year prevalence of all headaches was 77.2 %; 84.0 % in women and 69.6 % in men (8). In a review of European headache studies, mean prevalence of migraine was 14.7 %; 8 % in men and 17.6 % in women. TTH had a mean prevalence of 62.6 % and chronic TTH mean prevalence of 3.3 % (9). Age influences headache prevalence, and women have more headaches than men, both migraine and TTH (10).

1.2 Migraine

Migraine is a complex and multifaceted neurovascular disorder of the brain and can be regarded as a prototypic functional brain disorder (11). It is a chronic, recurrent and sometimes progressive headache, and is the second most common of the primary headaches (12). The 1-year prevalence of migraine reported in a Norwegian study was 11.6 %; 15.6 % in women and 7.5 % in men (10). A large Danish population based study found migraine prevalence to be 15.5 %; 23.5 % in women and 5.4 % in men (13). Migraine prevalence varies with age, and peaks in the fourth decade of life. Women are affected 2-3 times more often than men. In Asia migraine seems to be less prevalent, and a study from USA reported less migraine in Asian Americans than in Caucasians (14).

Migraine headache is typically unilateral, throbbing, moderate to severe in intensity, and accompanied by nausea and hypersensitivity to light and sounds. During a migraine attack, activity is avoided and premonitory and postdromal phases may involve cognitive disturbances, emotional symptoms, yawning, and gastro-intestinal disturbance. Migraine is classified as episodic (< 15 headache days per month) or chronic (≥ 15 headache days per month). The chronic subtype usually begins as episodic before transforming into the chronic form.

Approximately one third of migraine patients have aura, a condition with transient neurological phenomena, most often visual-, sensory- and/or speech disturbances. Aura is usually, but not always followed by headache. When diagnosing migraine aura, other conditions such as transient ischemic attack or focal epileptic seizure must be excluded. Moreover, headaches with clinical features similar to the characteristics of migraine, can be symptomatic to another disorder, and should then be classified as a secondary type of headache. This distinction can be challenging to make, because migraine typically can be triggered by other conditions, such as infections and metabolic and homeostatic alterations.

1.2.1 Pathophysiology of migraine

The pathophysiology of migraine is not fully understood, but involves disturbances of neuronal networks that are widely distributed throughout the brain, and also peripheral components such as nociceptors in the meninges. The initiating event or events are not known. Once started, disturbances propagate in parallel in many brain regions (15). Subcortical regions that are involved in modulation of sensory input, i.e. the brainstem and diencephalic nuclei, are activated during an attack and leads to release of neuropeptides, such as calcitonin gene related peptide (CGRP) and substance P via serotonergic pathways in the trigeminovascular system. CGRP is a strong vasodilator and substance P induces pain. Dysfunctional processing of sensory input, including lack of habituation, leads to central sensitization and hypersensitivity to sensory stimuli.

Involvement of the cerebral cortex is evident in the aura phase. A putative mechanism is a dysfunctional regulation of cortical excitability (16). This involves both neurons and glia cells, and may lead to imbalance between excitatory and inhibitory mechanisms. Increased glutamatergic neurotransmission is proposed to lower the threshold for cortical spreading depression (CSD). CSD is an electrophysiological phenomenon arising in the brain spontaneously or as a reaction to noxious stimuli, such as trauma and stroke (17). Neurons and glia cells undergo a transient activation followed by a wave of depolarization. Involvement of ion channels results in

imbalance in ion gradients and alters the normal membrane potential and excitability. CSD is accompanied by disturbances in regional blood flow, resulting in a phase with transient ischemia. The vascular changes are considered secondary to the cerebral processes. CSD is regarded as a neurophysiological correlate to aura, while activation of the trigeminovascular system is linked to migraine pain (18). Whether CSD is operative in migraine without aura, is unclear. A link between CSD and activation of the trigeminovascular system has been suggested (19).

Migraine attacks can be triggered by a variety of environmental and internal factors. Ninety-five percent of migraine patients recruited from a headache clinic, reported to have triggers for migraine attacks (20). Typical triggers are stress, hunger, menstrual cycle, changes in weather conditions, sleep disturbance, perfume or odour, neck pain and lights. However, more exact details of the trigger mechanisms are not known.

Further, migraine is comorbid with several other conditions such as cerebrovascular disease, epilepsy and mood disorders. Comorbidity refers to the greater than coincidental association of two conditions in the same individual (21). A possible explanation for the increased associations may be shared genetic and/or pathophysiologic factors.

Migraine has been suggested to be comorbid with the antiphospholipid syndrome (APS). Cavestro et al. found that migraineurs more often had anti-phospholipid (aPL) antibodies than healthy controls (22). However, this could not be confirmed by others, and a recent task force concluded that migraine should not be included in the APS criteria (23, 24). The glutamatergic N-methyl-D-aspartate (NMDA) receptor is suggested to be involved in migraine pathophysiology (17, 25).

Migraine has a strong genetic basis, with increased prevalence among first-degree relatives. Specific gene variants associated with migraine have been revealed in sporadic- and familial hemiplegic migraine (26). However, in the vast majority of migraine patients the specific genetic cause is not known. Genome-wide association (GWAS) studies have indicated gene clusters with involvement of glutamatergic transmission, synaptic- and sensory functions (18).

1.3 Tension-type headache (TTH)

TTH is the most prevalent type of primary headaches. It is typically a bilateral, pressing or tightening headache, considered to be mild or moderate in intensity, and does not worsen with routine activities. TTH does not encompass nausea, with the exception of chronic TTH (≥15 days per month) that may have mild nausea. Phono- *or* photophobia can be present, but not simultaneously as is seen in migraine. Other autonomic features, as in the trigeminal autonomic cephalalgias, are not present. Thus, TTH lacks accompanying features, and this phenotype is also common in secondary headaches. The episodic type is divided into infrequent (< 1 per month) and frequent (≥ 1 per month) episodic TTH. A diagnosis of TTH requires ≥ 10 typical headache attacks fulfilling the classification criteria.

A Danish study found the 1-year prevalence of TTH to be 86.5 %, as assessed by personal interview (13). In that study *chronic* TTH was reported by 4.8 % of the subjects, while a Norwegian study, revealed a prevalence of 2.8 % for the chronic subtype (27). TTH is slightly more prevalent in women - 5:4 - and like migraine the prevalence peaks in the fourth decade of life (28). Debut of TTH is somewhat later in life than migraine, and the occurrence of this type of headache do not decline with increasing age as much as migraine. Higher prevalences are reported in Europe compared to Asia and the Americas. Differences in research design seem to have even stronger influence on prevalence figures in TTH than in migraine. This could be due to less specific case definitions, and patients missing to report the infrequent episodic TTH that usually have little impact on the individual, especially when using questionnaires or omitting the use a neutral screening question.

1.3.1 Pathophysiology of TTH

The pathophysiology of TTH is not well understood. It has been suggested that peripheral pain mechanisms and central dysregulation of pain processing structures are involved; peripheral mechanisms in episodic TTH and central mechanisms more likely in the chronic form of TTH (29). Psychogenic and myogenic phenomena are the most frequently reported associated features, and emphasize the common view of TTH as a

psychogenic or stress-related headache. Pericranial tenderness is observed, but is not specific for TTH. One large Norwegian study found an association between chronic TTH and chronic pain from muscles and joints (30). Results from pain perception studies and pharmacological studies in patients with chronic TTH indicate that central sensitization with altered threshold for pain is operative in chronic TTH. It is suggested that central sensitization may be due to continuous nociceptive input from pericranial tissue to the trigeminal system (29).

1.4 Medication overuse headache (MOH)

MOH is a secondary chronic type of headache, associated with overuse of analgesics. It is a frequent cause of chronic headache, most often due to commonly used analgesics such as NSAIDs or paracetamol, and considered to be a complication to primary headaches, usually migraine and TTH. It is therefore important to diagnose this type of secondary headache in the setting of intractable headache.

1.5 MRI studies in headache

Cerebral magnetic resonance imaging (MRI) has revealed several abnormalities in migraine patients (31). White matter hyperintensities (WMHs) on T2-weighted images are more common in patients with migraine than in non-migraineurs. Also, WMH load increase with increasing age, is associated with hypertension, and is seen in a number of different conditions, such as cerebrovascular-, inflammatory-, and degenerative diseases of the brain. Palm-Meinders et al. reported higher WMH load in migraine patients compared with control subjects, but this association was restricted to women. No differences could be found in men (32). The association of migraine with WMH load was confirmed in a French population-based study (33). Migraine with aura has been shown to increase the risk of cerebral infarcts as revealed by MRI, especially in women (33, 34).

In voxel-based morphometry (VBM) analyses, both regions with higher and regions with lesser density in gray matter (GM) can be seen in migraine patients compared

with non-migraine control subjects (35). Localized reduced GM volumes are shown in regions of cerebral pain networks (36). However, one VBM study that compared migraine patients with healthy control subjects could not confirm such localized brain changes; nor were global GM and white matter (WM) volumes different between the groups (37).

Functional MRI shows disturbances in neural networks, especially networks involving pain modulation, but also in somatosensory- and affective pathways (38). Abnormalities in neural networks are also demonstrated during interictal periods. This complies with electrophysiological studies, in which hypersensitivity to sensory stimuli can be observed (39).

MRI studies in non-migraine headaches are few, but one study reported association of non-migraine headache with increased WMH load (33). Using VBM, another study demonstrated decreased GM volume in pain processing regions in patients with chronic TTH compared with healthy subjects (40).

1.6 Headache, depression and fatigue

Migraine and depression are comorbid (41). In a population-based study in Canada, more depression in migraineurs was not related to socio-economic variables (42). Migraine and depression may therefore interact through some unknown pathophysiological mechanisms. This was also evident for non-migrainous headache in a Norwegian study (43).

Fatigue can be defined as “an overwhelming sense of tiredness, lack of energy, and feeling of exhaustion” (44). It is a common phenomenon within a broad range of diseases, including cancer, infections, neurological-, psychiatric- and autoimmune diseases. The pathogenesis of fatigue is largely unknown, but biologic-, psychosocial- and behavioral factors are involved (45). Also, fatigue and depression are strongly associated phenomena.

1.7 Impact of headache; headache-related disability

Headache disorders impose a significant impact on individuals, their families and the society. The World Health Organization has ranked headache among the top ten disabling disorders for both sexes, and the fifth for women. Among the neurological disorders, migraine is the leading cause of disability, and is rated as the sixth highest among specific causes of disability according to the *Global burden of Disease Study 2013* (46).

The magnitude or severity of headache impact, or headache-related disability, reflects the intensity and frequency of headache, and in that sense also impose some characteristic of the headache. Two validated and widely used questionnaires for assessing impact, are the *Migraine Disability Assessment (MIDAS) Questionnaire* and the *Headache Impact Test-6 (HIT-6)* (47, 48).

A tertiary multi-center study from Canada, compared the two questionnaires, and concluded that they assessed impact in a similar fashion. There were, however, differences; HIT-6 tended to rate headache impact as more severe than MIDAS, and demonstrated a higher correlation between headache intensity and the total HIT-6 scores (49). Moreover, the total scores of both disability instruments were positively associated with depression. The MIDAS questionnaire reflects employment status, which HIT-6 does not.

1.8 The immune system – defending life

The immune system is a complex defence system, protecting the individual against pathogenic microorganisms, cancer and other dangers from the environment and internal cellular milieus. This system is highly developed in humans, and a field of extensive research. The understanding of immune signalling and processes is increasing fast, resulting in novel therapeutic options, especially in autoimmune diseases and in cancer.

The immune system can be divided into the *innate* system and the *adaptive* system. The innate immune system is phylogenetically old and represents the body`s first line of defence. It acts immediately against pathogens by recognizing evolutionary conserved molecular structures on their surfaces, known as pathogen-associated molecular patterns (PAMPs), and also to endogenous molecules associated with danger (danger-associated molecular patterns – DAMPs). Innate immunity is based on physical-, biochemical- and biological barriers, innate immune cells and the complement system, amongst others.

Innate immune cells comprise several leukocyte subtypes such as neutrophils, macrophages, dendritic cells, and natural killer (NK) cells. Macrophages and dendritic cells are distributed throughout the body, recognizing and thereafter presenting antigens to T-lymphocytes, thereby activating the second line of defence, the adaptive immune system. Especially dendritic cells connect and coordinate the innate and the adaptive immune responses. NK cells destroy damaged, dysfunctional or invaded host cells, such as tumor cells or virus-infected cells.

The adaptive immune system developed in vertebrates, and introduced an important new concept of defence; immunological memory. Memory cells in the adaptive system "remember" antigens from former exposure, and are therefore capable to react earlier and more strongly on repeated exposure to that specific antigen. The adaptive cellular defence comprises T-cells and antibody producing B- and plasma cells. Three important subtypes of T-cells are cytotoxic T-cells (CD8), T-helper (Th) cells (CD4), of which Th1, Th2 and Th17 today are considered the most important; and suppressor or T-regulatory (T-reg) cells, respectively. While CD4+ and CD8+ T-cells propagate the immune response, T-reg cells downregulate the process, and keep the immune system in balance. An ongoing adaptive immune response is constantly refined by both T-cells and B-cells developing into more specific clones with stronger avidity to antigens. Long-lived T- and B memory cells are also produced. The innate and the adaptive systems are closely integrated and in constant interaction with each other.

Immune cells produce cytokines. These are low molecular weight proteins, functioning as signal molecules between cells, or in the cell itself. Several cytokine classes are known, such as chemokines, interleukins (ILs), and interferons (IFNs). Cytokines are important players in immunity and inflammation. Some cytokines are pro-inflammatory while others are inhibitory and downregulate the immune responses. IFNs have important anti-viral functions both in innate and adaptive immunity. They are produced in large amounts in activated dendritic cells, but also in other cells as response to viral infections. IFNs comprise three main types (type I-III) and several subtypes (IFNα, -β, -γ etc.). They stimulate transcription of genes (interferon regulated genes) involved in defence of pathogens, typically viral pathogens.

Normally the immune system has the capability to distinguish between threatening pathogens and the body`s own tissues, or molecules of "self". This tolerance to "self" is an extremely important feature of the immune system. Immune attacks directed against "self" are avoided by central and peripheral regulatory mechanisms, such as elimination and inactivation of lymphocytes that show autoreactivity. The immune system initiates an adequate immunological response to pathogens, but just as important is the ability to turn off the response when mission is completed.

1.8.1 Defending the brain

The brain is protected by the blood-brain barrier (BBB) and blood-cerebrospinal fluid (CSF) barrier. The BBB consists of neurovascular units that include specialized endothelial cells, astrocytes, neurons and microglia. It functions as a dynamic and selective barrier between capillaries and the brain tissue, allowing homeostasis to be maintained through passive and active transport mechanisms. Small molecules and steroid hormones diffuse freely, while glucose and amino acids reach the brain by selective transporter systems. Activated CD4 T-cells are allowed to pass through the intact BBB. Antibodies on the other hand, are restricted in passing over the intact BBB and into the brain tissue. Dysfunction of the BBB is therefore a prerequisite for antibodies produced in the periphery to enter the CNS (50).

Some other regions of the brain regulating blood composition through osmoreceptors and chemoreceptors do not have an intact BBB (the circumventricular organs).

The blood-CSF barrier is located in the choroid plexus in the ventricles of the brain. This barrier is more permeable than the BBB, but selective, and allows some plasma proteins to enter the CSF. The blood-CSF barrier therefore regulates the concentration of proteins in the CSF, and keeps the protein content in CSF lower than in the blood. Thus, high concentrations of proteins in CSF indicate a dysfunctional barrier.

Physiologically, innate immunity is active in the brain, with microglia representing the brain's "macrophages". Microglia constantly survey the brain for pathogens, and also communicate with the immune system outside CNS through cytokine signalling. Activated microglia produce pro-inflammatory cytokines that in turn activate both microglia and astrocytes.

Astroglial cells (astrocytes) comprise several subtypes of cells. They envelop neuronal synapses, and astrocytic end-feet support, and maintain the tight junctions between brain endothelial cells and provide a link to nearby neurons. They support neuronal cells, modulate synaptic transmission, regulate ion concentration (especially potassium) in extracellular space, and have a number of other important functions in the brain (51). Thus, astrocytes control and regulate neuronal synaptic transmission and neuronal electrophysiological excitability. The subtype of astroglial cells in intimate contact with cerebral blood vessels secretes protein S100B when activated as a response to damage or homeostatic distortion. This protein has been suggested to behave as a general biomarker of brain dysfunction, brain damage and dysfunction of the BBB (52).

1.8.2 Neuroinflammation and headache

"Neuroinflammation" is a concept describing an immune response within the CNS, in which pro-inflammatory cytokines are upregulated. Transient neurogenic inflammation is considered part of migraine pathophysiology. Neuropeptides, especially substance P and CGRP, are central players in neurogenic inflammatory

processes and in migraine pathophysiology. Substance P is the most abundant neuropeptide in CNS, and promotes inflammation. Interestingly, substance P and substance P receptors on neurons are especially dense in amygdala which has projections to hypothalamus and periaqueductal gray matter, regions that are considered to be involved in migraine (53). CGRP is synthesized in dorsal root ganglion neurons and has effect on the trigeminovascular system. CGRP and substance P promote release of pro-inflammatory cytokines via receptors on T-cells. In murine studies, TNF-α and IL-1β, were reported to increase sensitivity and activate meningeal nociceptors, while IL-6 had only a minimal effect (54, 55). Moreover, levels of TNF-α, IL-1β and IL-6 are increased in the internal jugular vein during migraine attacks (56). One controlled study found increased levels of the pro-inflammatory cytokines TNF-α and IL-1β, and the anti-inflammatory IL-10 in plasma during migraine attacks compared with levels in headache-free periods (57).

1.9 Autoimmune diseases

Autoimmune diseases are diseases in which the immune tolerance to "self" is lost or decreased and autoreactive T- and B-cells are allowed to develop. Lymphocytes that have escaped regulation may perceive "self" as foreign and become activated. Depending on which structures in the body that the immune system recognize as foreign, different diseases develop.

IFN regulated genes are activated in a considerable proportion of patients with autoimmune diseases. Why this occurs is unclear, but dysregulation of immune pathways in genetically predisposed individuals is possible (58). When IFN regulated genes are activated, a typical constellation of genes is activated - the "interferon signature".

Another prominent hallmark of autoimmune diseases are production of antibodies against "self", i.e. auto-antibodies. Some of these, such as anti-DNA antibodies, aPL antibodies and antibodies against ribosomal P proteins (anti-P), are considered to have

pathogenetic potential, while the role of others are unknown or unclear, and may represent “innocent bystanders”.

Diseases such as SLE and pSS, typically affect *more than one organ system*, while other autoimmune diseases are *organ specific* (multiple sclerosis, diabetes mellitus type 1, autoimmune thyroiditis).

Involvement of the central and peripheral nervous system occurs in many systemic autoimmune diseases and may give rise to neurological and psychiatric phenomena. SLE and pSS share some genetic-, immunological- and clinical features, but are also by themselves separate and distinct disease entities and therefore represent interesting models to investigate the processes responsible for CNS involvement.

1.10 Systemic lupus erythematosus (SLE)

SLE is a chronic inflammatory autoimmune disease with multiorgan involvement, and is often regarded as the prototype of autoimmune disease. The reported prevalences of SLE range from 20 to 150 per 100.000, in different populations (59). The prevalence in Northern Norway was found to be 64.1 per 100.000 (60), and more women than men develop SLE (9:1). This disease can affect all ages, although most develop the disease in 50-60 years of age. Juvenile SLE is rare, and per definition starts before 16 years of age.

Almost any organ in the body can be affected, and cause glomerulonephritis, arthritis, dermatitis, hematological disturbances and involvement of the nervous system. It has a fluctuating course with alternating periods of active and quiescent disease. Disease severity varies in different ethnic populations, and tends to have a milder course in Scandinavians. Mortality rate is increased, despite earlier diagnosis and more effective treatment. In the Tromsø Lupus cohort, five-year survival was estimated to be 95 % (60).

A special feature of SLE is that ultraviolet (UV) light can trigger flares of the disease. Exposure to UV light may lead to apoptosis in exposed keratinocytes, the nuclear

material is not efficiently removed, thus activating the immune system. In the ACR classification criteria for SLE, photosensitivity is defined as “skin rash as a result of unusual reaction to sunlight”. In this thesis, photosensitivity should not be confused with migraine photosensitivity that is clinically expressed as photophobia.

SLE is characterized immunologically by autoreactive and cytotoxic T-cells and the production of a multitude of auto-antibodies. Also, T-reg cells, which downregulate the immunological processes, are dysfunctional. Autoantibodies react with nuclear antigens and form immune complexes that contribute to tissue injury. Cytokines, such as IFNs, IL-6, IL-10 and IL-17 play important roles in SLE. Activated plasmacytoid dendritic cells produce increased amounts of IFNα in many patients, resulting in activation of IFN-regulated genes, the interferon signature. Type I IFNs, together with IL-6, promotes differentiation of B-cells into plasma cells. Mature dendritic cells activate cytotoxic CD8 T-cells, and dendritic cells may have pivotal roles in the pathogenesis of SLE. Antibodies against double-stranded DNA are considered an immunological marker of the disease.

The genetic basis of SLE has for a long time been evident due to observations of heritability and familiar clustering of cases. In recent years genetic studies have begun to reveal susceptibility loci with relevance to regulation of immune responses and inflammation. It is important to understand that there are not specific “SLE-genes”, but rather it is the interplay between gene variants (polymorphic genes) that in the individual subject leads to immune dysregulation and development of the clinical SLE phenotype. *ITGAM*, *STAT4*, *BLK*, and *IRF5* are only a few of the genes that now have been identified as important for SLE (61). Also, in addition to the genomic background, epigenetic regulation, hormonal influence and infections, are important players in SLE.

The classification criteria for SLE comprise clinical, immunological and biochemical items, where at least 4 out of the 11 items have to be present (62).

1.10.1 Neuropsychiatric SLE (NPSLE)

SLE frequently involves the nervous system. ACR has defined 19 neuropsychiatric (NP) syndromes thought to represent specific manifestations of SLE (NPSLE) (63). Twelve of these are CNS related, and are categorized into *focal* and *diffuse* NP syndromes. The criteria offer a framework that helps to decide whether a phenomenon or a condition is attributed to SLE, to non-SLE conditions, or a combination of these. Clinical-, laboratory- and neuroimaging data are used for fulfilment or exclusion in the case definitions. No gold standard for diagnosing NPSLE exists, and clinical judgement still decides whether a neuropsychiatric condition in an SLE patient should be attributed to SLE or not.

A recent meta-analysis found NPSLE syndromes to occur in 56 % of SLE patients (64), while Ainiala et al. reported 91 % in a Finnish SLE cohort (65). In comparison our own research group found 63 % (headaches excluded) prevalence of NPSLE (66). The differences in NPSLE prevalences can at least partly be explained by the high occurrence of headaches reported in the Scandinavian studies, but also ethnic differences and selection criteria may contribute to the large variation across studies. A validation study concluded that the specificity of NPSLE criteria was low (46 %) (67). However, if diffuse and minor NP manifestations such as anxiety, mild depression, mild cognitive impairment and headache were excluded, the specificity increased to 93 %.

The pathogenesis of NPSLE is not fully understood, but immunological-, genetic- and environmental factors are considered important. The large heterogeneity of the NP syndromes may reflect various pathogenetic mechanisms operative in the specific syndromes. The main pathophysiological mechanisms behind NPSLE are thought to be thromboembolism, microangiopathy with disturbed microcirculation, pathogenetic autoantibodies and cytokines. Autoantibodies, such as aPL, cause thrombosis and microangiopathy, while anti-P- and anti-NR2 antibodies are more brain specific, leading to psychosis or cognitive dysfunctions.

The NPSLE case definitions are based on clinical experience and expert opinions. These case definitions have been extensively debated over years as knowledge about pathophysiology and disease mechanisms have increased. NPSLE syndromes, such as mild cognitive impairment, mild mood disorders and headaches, have recently been suggested by several authors to be excluded from the NP case definitions, because they also are frequent encountered in the general population (68, 69).

1.10.2 Headache in SLE

Clinical observations decades ago acknowledged a migrainous, intense and intractable headache in patients with SLE (70). This led to an appreciation of headache as part of the disease spectrum in SLE, although disease mechanisms were unknown. The last fifty years, a number of studies have focused on SLE and primary headaches with inconclusive and apparently divergent conclusions. However, headache still has a place in measures for SLE disease activity, and is defined as one of the NPSLE manifestations as well. The central placement of headache has therefore been questioned by many authors, and is still subject to an ongoing debate.

Headache is the most common of the reported NPSLE syndromes, both in juvenile and adult SLE. A meta-analysis concluded that there were no difference in headache prevalence between lupus patients and healthy subjects, while others report more often *all headaches*, and/or more migraine in patients with SLE (67, 71-73). In an uncontrolled Norwegian study, using the IHS criteria, migraine was reported in 38 % of SLE patients (74). This prevalence is in accordance with a controlled study reporting migraine in 34 % of patients (75).

Does the clinical observation of headaches as an extremely common phenomenon in SLE represent the truth or a myth? A mistaken association could easily occur because headache is so common in the general population. Notably, both SLE and migraine are more frequent in women, with age-related peak prevalence being almost identical. Conflicting results could therefore be due to methodological issues such as studies performed in tertiary centers, selection of patients, lack of control groups, lack of adequate headache classification criteria, and small study samples. Some authors have

reported headaches to be dependent on disease activity or accumulated organ damage (72, 75, 76). This could indicate that headache is a manifestation of general disease mechanisms in SLE. However, others have not confirmed such associations (68, 74, 77).

1.11 Primary Sjögren`s syndrome (pSS)

PSS is an autoimmune, chronic inflammatory disease, directed against exocrine glands such as salivary and lacrimal glands (78). Chronic inflammation in the glands results in dryness phenomena of eyes and mouth. Fatigue, migrating muscle- and joint pain and neuropsychiatric phenomena are also frequently encountered. Arthritis, serositis, renal disease, skin vasculitis and lung fibrosis are less common manifestations, but point to the systemic nature of pSS. The prevalence of pSS varies considerably between studies probably reflecting different populations and ethnicities and different classification and diagnostic criteria applied. The point-prevalence in western part of Norway (Rogaland and Hordaland counties) using the The American-European Consensus Group (AECG) criteria for pSS, was 0.05% (79). Peak incidence is in the fourth and fifth decade of life, and like in SLE, women are affected 9 times more often than men.

Similar to other autoimmune diseases, the etiology of pSS is not completely understood, but is considered to involve environmental factors in a genetic susceptible individual. In addition to the known association between autoimmune diseases and genes in the HLA region, several other genes with importance for regulation of innate and adaptive immune responses have been discovered in recent large GWAS studies. Examples of such genes are *IRF5-TNPO3, STAT4, IL12A, FAM167A-BLK, DDX6-CXCR5,* and *TNIP1*, but this list is steadily increasing (80).

Autoantibodies directed against Ro (SSA) and LA (SSB) proteins, are present in up to 70-80 % of the patients (79). These proteins have important functions in immune regulation, but exactly how they participate in the pathogenesis of pSS is incompletely understood. Many patients with pSS exhibit the “interferon signature”. This implies an

increased expression of type I interferon regulated genes in minor salivary glands as well as in monocytes in peripheral blood in the patients.

Classification and diagnostic criteria for pSS have varied over time. AECG criteria are widely accepted both for diagnosing and for classification of pSS (81). These criteria include symptoms, signs and laboratory items, such as symptoms of dryness, signs of decreased exocrine function, presence of anti- SSA and/or anti-SSB antibodies and/or typical histopathological finding in biopsies of minor salivary glands with focal infiltration of mononuclear lymphoid cells. A provisional revision, approved by ACR, was published in 2012 aiming to represent a more objective set of criteria (82).

1.11.1 Neuropsychiatric pSS

PSS frequently involves the nervous system. Cranial- and peripheral neuropathies were the most frequently documented neurological conditions in a large study of pSS patients with neurological disease (83). In this study, CNS involvement was mostly focal or multifocal, including myelopathy and demyelinating disease. However, also diffuse neuropsychiatric manifestations, such as cognitive impairment, headaches and mood disorders occur in pSS. The prevalence of neurological conditions in pSS have varied in different studies, reflecting the shifting diagnostic criteria in use for the disease, selection bias of subjects, studies performed in tertiary neurological centers, and definitions of NP events. Applying the NPSLE criteria defined by ACR, we found that NPSLE were as frequent in pSS patients as in SLE patients, although with a different pattern. Peripheral nerve involvement was more common in pSS patients, while cerebrovascular disease was more prevalent in SLE (66).

1.11.2 Headache in pSS

Although pSS shares several clinical and immunological features with SLE, headaches have not been regarded as a manifestation of pSS and have thus not been a focus for research as in SLE. Few studies have investigated the epidemiology and headache characteristics in pSS. One study in 1989 and one in 2008 reported more migraine in pSS patients compared with control subjects (84, 85). These studies had

methodological limitations such as lack of diagnostic criteria for both pSS and headaches in the first study, and lack of matched control subjects in the other study. No systematic studies of headaches have previously been conducted in Scandinavian pSS populations.

1.12 Auto-antibodies in SLE and pSS

Autoantibodies are a laboratory hallmark of systemic autoimmune diseases, and there is often a characteristic pattern of autoantibodies in the specific diseases. Among the antinuclear antibody (ANA) subtypes, anti-DNA antibodies are highly prevalent in SLE, while anti-SSA- and anti-SSB antibodies are more common in pSS. However, no specific type of autoantibody is pathognomonic for SLE or pSS.

A number of autoantibodies have been studied in search of mechanisms and biomarkers for NPSLE (86). Some of them seem to have pathogenetic potential, such as aPL, anti-NR2-, and anti-P antibodies (87-89): Antibodies targeting neurons, may disturb neuronal function, and even lead to neuronal death by apoptosis.

aPL antibodies are associated with thrombosis and cerebrovascular disease such as strokes (90, 91). They interfere with coagulation factors and endothelial cells. They have also been implicated as a pathogenic factor for non-thrombotic conditions, such as cognitive impairment, possibly through binding to neuronal or endothelial cells (92). Conflicting results have been reported regarding an association between headaches and aPL in SLE patients (72, 74, 75, 90).

The NMDA receptor plays an important role in the main excitatory signal system of the brain. NMDA receptors are present on neurons throughout the brain, consist of 4 subunits, and regulate synaptic strength and neuronal plasticity. Dysfunction of NMDA receptors is involved in several brain disorders, such as autoimmune encephalitis, schizophrenia, stroke and epilepsy. Antibodies against the subunit NR2 of the NMDA receptor can cause prolonged opening of the ion channel followed by excessive and damaging influx of Ca^{2+}. These effects are dose-dependent. Small concentrations lead to dysfunction while strong concentrations may lead to apoptosis

and death (93). Anti-NR2 antibodies are found in patients with NPSLE, both in the blood and the CSF. Murine studies indicate that anti-NR2 antibodies in systemic circulation gain access to the CNS through a dysfunctional BBB (50). A recent study in SLE patients supports this hypothesis, but also suggests intrathecal production of antibodies to occur as well (94). In that study, acute confusional state in SLE patients was clearly associated with presence of anti-NR2 antibodies in CSF. In general, anti-NR2 antibodies in SLE patients have mostly been associated with non-focal neuropsychiatric phenomena, such as cognitive impairment and depression (95).

Anti-P antibodies bind to neurons and lead to Ca^{2+} influx and neuronal dysfunction, or even apoptosis (96). They are demonstrated to be pathogenetic in murine SLE models, and have been implicated in NPSLE, such as psychosis and depression (97, 98).

1.13 Cerebral MRI in SLE and pSS

MRI of the brain is the gold standard for imaging of cerebral structural abnormalities. Several brain abnormalities such as WMHs, infarcts and cerebral atrophy are evident in SLE patients, WMHs being the most frequent (99-103). WMHs in SLE may be reversible or non-reversible like in other inflammatory diseases of the brain, such as multiple sclerosis, and may also progress more over time compared to matched control subjects (104, 105). Both number and volume of WMHs have been reported to be increased in NPSLE, although WMHs also occur in SLE patients with no history of CNS involvement (103, 105). Two studies investigating WMHs in SLE patients with headache, revealed no associations (77, 106). Thus, their clinical relevance in NPSLE is unclear, and reports of associations between WMHs and NPSLE are disputable.

Cerebral infarcts are more frequent in SLE patients compared with pSS patients, and reflect the increased cerebrovascular risk in SLE, partly associated with increased thrombophilic tendency caused by aPL antibodies, and accelerated atherosclerosis (66).

Cerebral atrophy has been observed early in the SLE disease course, and both global atrophy and localized atrophy are reported (107). Appenzeller et al. reported reduction

of GM and WM volumes in SLE patients compared with control subjects, and reduced GM and WM volumes were in the patients associated with cognitive impairment, aPL antibodies, and disease duration (99). In a controlled study of childhood-onset SLE, cognitive dysfunction was associated with decreases in both global and regional GM volumes (108).

Also in patients with pSS, the most frequent finding is WMHs. They seem to be unspecific, and like in SLE most often lack a clinical correlate (109, 110). Also, cortical and subcortical GM atrophy is reported in pSS (111). We found that WMHs were not increased in patients with pSS compared to healthy subjects (112). Recently we observed that pSS patients had diffuse reduction of cerebral WM volumes compared with healthy subjects, but no difference in global GM volumes and no localized loss of GM or WM volumes (113).

None of the MRI abnormalities demonstrated in patients with SLE and pSS are disease specific, and may thus be seen in a number of different brain diseases and conditions.

1.14 Depression and fatigue in SLE and pSS

Both depression and fatigue are common in SLE- and pSS patients (114-116). In a Norwegian SLE cohort, 22 % had clinical depression as defined by Beck Depression Inventory (BDI) scores >13, while in a Finnish study (BDI cut-off scores ≥10), depression was reported in 44 % of the patients (65, 74).

Although frequently encountered, fatigue is not part of the NPSLE criteria defined by ACR. Nevertheless, it is a common phenomenon of many inflammatory, neurodegenerative and other diseases, and is strongly associated with depressive mood and pain. In a study of 94 pSS patients, Segal et al. reported depression in 32 % and fatigue in 67 % of the patients respectively (116). Hence, even though there is a clear association between depression and fatigue, fatigue also occurs in patients without depression.

An association between depression and all types of headache and/or migraine has been described in some studies in SLE (73, 74). Also, depression has been reported to be associated with cognitive dysfunction, but not with disease related variables such as disease duration, organ damage or measures of disease activity (114, 117).

The exact mechanisms that generate depression and fatigue are only partly known. Immune mediated brain dysfunction, or psychosocial factors such as stress in the context of chronic disease, are possible causes. The innate immune system and cellular stress defence mechanisms seem to have a pivotal role, at least for generation of fatigue (118). Both depression and fatigue have been postulated to be signalled through IL-1 pathways, and may explain why these conditions are so common. Interestingly, Omdal et al. found depression associated with the presence of anti-NR2 antibodies and anti-P antibodies, indicating an autoimmune mechanism for this phenomenon (119).

1.15 Impact of headache in SLE and pSS

While headache in SLE and pSS has been the subject of several studies, less is known about the impact of headache in these patients. In a large inception cohort of SLE patients, Hanly et al. found that patients with headache reported lower quality of life as assessed by Short Form-36 than the patients without headache (68). The consequence of headache on work, studies, and daily life, has not been systematically investigated in these populations. It is therefore unclear whether headache in lupus patients is more bothersome, intense and disabling, than headache in the general population. Thus, we do not know for sure whether headaches in autoimmune diseases cause more disability than headaches experienced in people without these diseases, or whether headaches in patients with SLE are more disabling than headaches in pSS patients. The impact of headache can be regarded as an indirect measure of headache severity. Investigating headache impact in this perspective might therefore provide indirect evidence for the existence of a “lupus headache”.

2. Aims of the study

- Investigate prevalence and characteristics of headaches in the autoimmune disease systemic lupus erythematosus (SLE) (Paper I).
- Investigate whether headaches occur with the same pattern in another autoimmune disease, namely primary Sjögren's syndrome (Paper II).
- Investigate whether headache-related disability is different in these diseases compared with the general population (Paper III).
- Investigate whether clinical-, biochemical-, immunological- or structural brain abnormalities influence the prevalence of headache in patients with SLE (Paper I and IV).

3. Subjects and methods

3.1 Subjects

Nearly all patients with autoimmune diseases in Rogaland County, Norway, are allocated to Stavanger University Hospital, where clinical investigative examinations were performed. At the time of study Stavanger University Hospital served about 310 000 people, and all study participants were examined between 2003 and 2006.

3.1.1 Patients with SLE

Medical records of all in- and outpatients with a diagnosis of SLE between 1980 and 2004 were reviewed. Re-examinations were done when in doubt about the diagnosis. Eighty-six patients, all Caucasians, fulfilled the 1982 revised ACR criteria for SLE (62), and 70 patients (81 %) consented to participate in the study. Three patients were excluded; two patients withdrew their consent, and one was excluded because of a brain tumor. Thus, 67 patients - 58 women (87 %) and 9 (13 %) men - were included. Mean age was 43.4 ± SD 13.3 years (median 42.4 years, range 19.6-75.9 years). Mean disease duration was 12.3 ± SD 8.6 years (median 11 years, range 0.5-32.0 years), mean disease activity (SLEDAI) (1) 3.7 ± SD 3.9 (median 2.0, range 0-26) and mean cumulative organ damage index (SLICC-DI) (120) was 2.2 ± SD 2.1 (median 2.0, range 0-11). At the time of the investigation, 55 patients (82 %) were on medication for SLE; 44 patients (66 %) used corticosteroids, 34 (51 %) antimalarials and 35 (52 %) received immunosuppressants (mostly azathioprine or cyclophosphamide).

3.1.2 Patients with pSS

Medical records of all patients with the diagnosis of pSS between 1980 and 2005 were reviewed. When in doubt about the diagnosis, patients were re-examined. We also obtained results of all minor salivary gland biopsies analyzed in the hospital`s department of pathology from 1990 to 2004 (N = 410). In cases of biopsies with a focus score ≥ 1, patients were re-examined for pSS. Seventy-two (73 %) out of the 99 patients that fulfilled the AECG criteria (81) provided informed consent to participate

in the study. One patient was excluded due to a brain tumour revealed by MRI. Thus, 71 patients - 61 women (86 %) and 10 men (14 %) - were included.

The mean age of the patients was 57.5 ± SD 12.9 years (median 58.1, range 27.1-86.6). The mean disease duration was 6.9 ± SD 4.9 years (median 6.1, range 0.4-24.1). At the time of the investigation, 35 patients (49.3 %) were taking medication for pSS; two patients (2.8 %) were on corticosteroids only, 18 on antimalarials (25.4 %), one received intravenous cyclophosphamide infusions, and 13 patients (18.3 %) used combinations of drugs for pSS. Thirteen patients (18.3 %) used thyroxin, four (5.6 %) vitamin B12 supplements, and two (2.8 %) used β-blockers. Fifty-six (79 %) patients had anti-SSA antibodies, 33 (46 %) also had anti-SSB antibodies. No patients had only anti-SSB antibodies. Fifty-seven (80 %) patients had a positive minor salivary gland biopsy (focus score ≥ 1) and 13 (18 %) patients had "normal" histopathological findings (focus score < 1). In one patient, the gland biopsy was inconclusive due to insufficient biopsy volume.

3.1.3 Healthy subjects

108 subjects without known neurological, immunological, or malignant diseases consented to participate in the study. These were recruited among members of the staff, their unrelated friends and neighbours, as well as unrelated friends and neighbours of the patients. The healthy subjects were matched by age (± 2 years) and by gender to the subjects in the SLE- and pSS cohorts, respectively.

3.2 Clinical evaluation

All patients and healthy subjects were investigated during a 2-day stay at the hospital for research purposes only. Clinical examinations were performed by a specialist in internal medicine (EH) and in neurology (ABT) respectively. Disease activity was assessed by SLEDAI, and organ damage by SLICC-DI. None of the SLE patients were into a disease flare at the time of examination. The study complied with the Helsinki

Declaration and was approved by the Regional Research Ethics Committee. Written informed consent was obtained from all participants.

3.2.1 Headache classification and prevalence

Headaches were assessed through a structured interview by one neurologist (ABT) and classified according to the ICHD-II (5). A neutral question of having had headache within the last year was used as screening question. A detailed neurological- and headache history was taken covering the criteria necessary to diagnose the headaches and exclude differential diagnosis like transient ischemic attack or focal epileptic seizure. The 1-year prevalence of headache was based on the participants reporting at least one headache attack the previous 12 months.

According to the ICHD-II criteria, primary headaches should not be due to other diseases or conditions; otherwise they are classified as secondary headaches. For the purpose of headache studies in patients with SLE or pSS, we chose to use the term "*migraine*" and not "*migrainous*" or "*migraine-like*" headache. Secondary headaches considered due to any other diseases than SLE or pSS were excluded. A definite headache diagnosis always trumped a probable one, according to ICHD-II. Probable migraine was classified as a subtype of migraine, missing only one migraine feature and not fulfilling the criteria of another definite type of headache. The same applied to probable TTH and probable MOH. We used the term "*all headaches*" when referring to having any type of primary headache, regardless of migraine or TTH. We have used "*TTH only*" and "*pure TTH*" synonymously, referring to have only TTH, not combined with migraine.

3.2.2 Impact of headache

Headache-related disability was investigated using the validated questionnaires MIDAS and HIT-6 (47, 48). All study participants answered the questionnaires during the headache interview and were asked to rate the most bothersome headache if they had more than one type. MIDAS scores > 10 and HIT-6 scores > 55 were considered moderate to severe headache impact (grades III-IV).

The MIDAS questionnaire measures the influence of headaches on daily activities, according to limitations in three domains during the previous three months (paid work or school, household work, and non-work activities).

The HIT-6 questionnaire assesses the extent of headache-related impact on various aspects of daily life during the previous four weeks, and some for an unspecific period of time. In contrast to MIDAS, HIT-6 also takes fatigue, mood and pain severity into account, and is therefore considered to provide a wider assessment of headache impact. Headache impact is categorized into four severity grades by both questionnaires; minimal (grade I), mild (grade II), moderate (grade III) and severe (grade IV). MIDAS scores > 10 and HIT-6 scores >55 encompass grades III-IV, i.e. moderate to severe grades of headache-related disability. When assessing headache impact in a subject with more than one type of headache, it is recommended to ask the individual to focus on the most bothersome headache (121).

3.2.3 Fatigue

Fatigue was evaluated with The Fatigue Severity Scale (FSS) and a fatigue visual analogue scale (fatigueVAS) (122). Both are generic and uni-dimensional fatigue measuring instruments.

3.2.4 Depressive mood

Depressive mood was evaluated with the BDI (123). BDI is a widely used and validated questionnaire for depression. A score ≥ 13 was considered as clinical depression.

3.3 Laboratory analyses

3.3.1 Blood

Routine haematological, biochemical, and immunological analyses were performed at the hospital's laboratories. ANA were detected by the HEp-2000 assay (Immunoconcepts, Sacramento, CA, USA), and presence of anti-double-stranded (ds)

DNA by Nova Lite dsDNA Crithidia luciliae 708200 indirect immunofluorescence assay (Nova Diagnostics, San Diego, CA, USA). Anti-SSA, and anti-SSB antibodies were detected by ELISA with the QUANTA Lite ENA 6 assay (Inova Diagnostics, San Diego, CA, USA), and positive results confirmed by Quanta Lite SSA and SSB Elisa (Inova Diagnostics). Anti-cardiolipin IgM and IgG antibodies were detected with the QUANTA Lite™ ACA IgM and IgG ELISA (Inova Diagnostics). Lupus anticoagulant was measured by the activated partial thromboplastin time and dilute Russell's viper venom time (Dade Behring, Marburg, Germany). aPL were considered positive if the patient had a positive anti-cardiolipin IgM- or IgG-antibody test, was lupus-anticoagulant positive, or any combination of these. Complement factors C3 and C4 were analyzed by nephelometry.

3.3.2 CSF

Fifty-two patients with SLE and 54 patients with pSS underwent lumbar puncture between 1 pm and 2 pm. CSF samples were immediately placed on ice and centrifuged at 4°C at 3000 *g* for 10 minutes. The supernatants were then immediately aliquoted and frozen at -70°C until analysis.

IL-6 was measured with the Luminex 100 (Luminex Corp., Austin, TX, USA) using IL-6 UltraSensitive™ AB Bead Kit, together with human extracellular buffer kit (BioSource™, Invitrogen Corp., Carlsbad, CA, USA). The sensitivity for IL-6 was <1.0 pg/ml (range, 0.84 – 614 pg/ml). Acquired data were analyzed using the StarStation software v2.3 (Applied Cytometri, UK).

IgG and albumin were measured in CSF and serum according to the manufacturer`s instructions with the Cobas Integra Immunoglobulin G (Turbidimetric) and Tina-quant a Albumin Gen.2, respectively (Roche Diagnostics, Mannheim, Germany). Impairment of the blood-brain barrier was defined by a CSF/serum albumin index [$albumin_{CSF}$ (mg/l)/$albumin_{ser}$ (g/l)] > 9. Intrathecal immunoglobulin production was defined as an IgG_{CSF}/$albumin_{CSF}$ ratio [IgG_{CSF} (mg/l)/$albumin_{CSF}$ (mg/l)] > 0.27 and an IgG index [IgG_{CSF} (mg/l) x $albumin_{ser}$ (g/l)/IgG_{ser} (g/l)/$albumin_{CSF}$ (mg/l)] > 0.7 (Silverman LM 1996).

Anti-NR2 antibodies were detected using electrochemiluminescence on a SECTOR Imager 2400 platform (MSD, Gaithersburg, MD, USA). A high bind plate (L15XB-3; MSD) was coated with 25 µl of the synthetic DWEYSVWLSN decapeptide at a concentration of 2 µg/ml and incubated overnight at 4 °C. The plate was blocked with 150 µl of 3% bovine serum albumin (MSD Blocker A) for 1 hour. Then, 25 µl of each sample was added in duplicate to the wells and incubated for 2 hours. 25 µl (1 µg/ml) of anti-human antibody (goat) with Sulfo-TAG (MSD) was added and incubated for 1 hour. Read Buffer T (150 µl of 2x buffer; MSD) was added and results were read on a Sector Imager 2400 (MSD). All incubation steps except coating, were conducted at room temperature on a plate shaker (300-400 rpm), and the plate was thereafter washed three times with PBS (pH 7.2-7.3) plus 0.05% Tween 20. Anti-NR2 antibody positivity was based on analysis of CSF from 24 subjects who underwent lumbar puncture as part of a neurological examination. None of the subjects had inflammatory, autoimmune, or malignant diseases. The CSF sample with the highest signal (approximately 3 SD above the mean of these samples) was chosen as the cut-off value/internal calibrator and measured together with the samples on each plate. For each sample, a ratio against the internal calibrator was calculated. Anti-NR2 antibodies were considered present with a ratio ≥ 1.0.

Protein S100B was analyzed with the Human S100B ELISA kit (Abnova, Jhongli City, Taiwan) according to the manufacturer's instructions.

Analyses of anti-P antibodies were performed in professor Hirohata's research laboratorium, as previously described (98).

3.4 EEG

Patients with SLE and the corresponding healthy subjects were examined with electroencephalography (EEG), and all EEG recordings except for one were assessed by the same electroencephalographer (AH). Digital EEG machines were used (Walter Graphtec GMBH, Lübeck, Germany and Galileo NT, Florence, Italy). The EEG electrodes were positioned according to the international 10-20 system (124). Standard

recording were performed for 20 minutes during relaxed wakefulness, with 3 minutes of hyperventilation, and with photic stimulation.

3.5 Cerebral MRI

The interval between clinical- and MRI examinations for the participants, was median 12 days, range 0-75 days.

3.5.1 MRI image acquisition and preprocessing

The MRI examinations were performed using a 1.5-Tesla Philips Gyroscan NT Intera Release 10 (Philips Medical Systems, Best, The Netherlands). An axial T2 turbo spin echo was performed with repetition time (TR) 3240 ms, echo time (TE) 19 ms/80 ms, slices 5 mm, and gap l.5 mm. Sagittal T2 fluid-attenuated inversion recovery (FLAIR) was conducted with TR 6500 ms, inversion recovery 2200 ms, TE 105 ms, slices 5 mm, and gap 1 mm. Axial T1 3-dimensional turbo field echo had TR 17 ms, TE 4 ms, slices 1.41 mm, and no gap. Field of view was 230 x 230 mm, matrix 256 x 256, nominal resolution 0.9 x 0.9 x 1.4 mm. Axial T1 spin echo was performed with TR 525 ms, TE 12 ms, slices 5 mm, and no gap, before and after intravenous gadolinium contrast. Sagittal T1 spin echo was performed with TR 525 ms, TE 12 ms, slices 5 mm, and no gap. The axial T1 3-dimensional turbo field echo with nominal resolution 0.9 x 0.9 x 1.4 mm was used for the image analyses.

Pre-processing of the MRI images was performed using the default settings in the VBM8 extension (Gaser, http: //dbm.neuro.uni-jena.de/vbm/download/) of the SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The images were bias-corrected, tissue classified (GM, WM and CSF) and registered by using linear and non-linear transformations within a unified model (125). The normalization included correction for individual brain size. The images were smoothed by using a 12-mm full-width-half-maximum Gaussian Kernel to reduce the inter-subject variability and obtain a more normal distribution of the data (126).

The segmentation of GM and WM was visually controlled. Quality of data and sample homogeneity were evaluated by inspection of one normalized, unsegmented slice for each patient and healthy control subject and by evaluating the covariance matrix of the covariance among all volumes using a VBM8 tool (Gaser, http: //dbm.neuro.uni-jena.de/vbm/download/).

3.5.2 WMHs (Paper I and II)

The MRI scans were rated independently in a blinded manner by two experienced radiologists (MKB and OJG). Consensus was reached by discussion whenever disagreements occurred. WMHs were assessed in accordance with the semi-quantitative visual rating scale of Scheltens et al. (127). Spatial location, size and numbers of WMHs were scored within the periventricular region, the subcortical and deep white matter of the frontal-, parietal-, temporal- and occipital regions, the basal ganglia, and the infratentorial region, respectively. WMH load measured as the total WMH sum score has previously demonstrated good correlation to the WMH lesion volume (128).The inter- and intra-rater reliabilities were good to excellent in a previous study performed by the same radiologists (129).

3.5.3 Volumetric analyses (Paper IV)

Global GM, WM, and CSF volumes for the SLE patients and their matched healthy control subjects were estimated using the VBM8 tool (MBL). Total intracranial volumes (TIV) were calculated as sums of GM, WM, and CSF volumes. TIV is considered to reflect premorbid brain size (130). The following ratios were calculated; GM volume/TIV, and WM volume/TIV.

Voxel-wise analyses were conducted using the SPM8 software, and the two-samples *t*-test in SPM8 was used for voxel-wise comparison of GM volumes between groups. All voxels with a < 10 % probability of being GM were excluded to avoid possible edge effects between different tissue types. Family-wise error correction was applied for correction for multiple testing, and $P < 0.05$ was used as threshold for significance.

3.6 Statistical analyses

Continuous data were reported as mean ± SD when normally distributed, otherwise as median and range. Categorical data were reported as numbers and percentages. Unpaired t-test was used to test for differences in means in two independent groups with continuous, normally distributed data. The Mann-Whitney U test was used to test for significant differences in two groups in independent, not normally distributed data. Independent categorical data were compared by using the Chi-square test. When expected frequencies were ≤ 5, Fisher's exact test was used.

The Wilcoxon paired samples test was used to test for differences in paired continuous data, and McNemar`s test for pair-wise categorical data in Paper II. McNemar`s test with mid-P value was used to compare pair-wise categorical data in Paper IV (131). Correction for multiple testing was not performed.

The ANOVA F Test was used to test for differences in means of independent continuous data between several groups when normally distributed, and the Kruskal-Wallis test when not normally distributed. Mann-Whitney U test without correction for multiple testing was used for post-hoc analyses.

Depending on whether the response variable was continuous or dichotomous, linear or logistic regression analyses were used, when testing for risk factors for headache development or headache-related disability. P values below 0.05 were considered significant.

4. Summary of results

4.1 Paper I

Headaches were classified according to ICHD-II in the 67 patients with SLE and 67 age- and gender matched healthy subjects. The 1-year prevalence of all headaches, and of the subtypes of headache, was compared. Twenty-four SLE patients (36 %) and 13 healthy subjects (19 %) had migraine, P = 0.03. Out of these, nine SLE patients and 4 healthy subjects had migraine with aura (13 % vs 6 %, P = 0.14). Prevalence of TTH was equal in SLE patients (60 %) and healthy subjects (58 %).

Possible clinical and laboratory associations with headaches in the SLE patients were explored. BDI scores were higher in the patients with SLE (median 6.0, range 0-27) vs healthy subjects (median 2.0, range 0-9; P < 0.0001), but also associated with all headache and migraine in the patients, but not in the healthy subjects. No associations between TTH and depressive mood were revealed.

Fatigue was more prevalent in the patients with SLE compared to the healthy subjects as assessed by FSS scores (median 4.3, range 1.3-7.0 vs median 2.0, range 1.0- 5.3; P < 0.0001) and fatigueVAS (median 49.0, range 1-98 vs median 12.0, range 1-72; P < 0.0001). Fatigue was in SLE patients associated with all headaches, with migraine with aura, and with a trend towards all migraine. These associations could not be confirmed in the healthy subjects. Neither SLE patients nor the healthy subjects with TTH demonstrated any associations between headache and fatigue.

Headaches in the SLE patients were, with the exception of SLE photosensitivity, not associated with any disease specific factors such as disease activity, accumulated organ damage, biochemical or immunological markers in blood, impairment of the BBB, intrathecal immunoglobulin production or WMHs on cerebral MRI.

Conclusion: Migraine is prevalent in SLE patients. It is associated with mental depression, but not with disease activity, and not with abnormalities on cerebral MRI, in CSF analyses, or any other SLE characteristics except from SLE photosensitivity.

4.2 Paper II

In this study we investigated prevalence of primary headaches in 71 patients with pSS compared with 71 age- and gender matched healthy subjects. 1-year prevalence of all headaches in the pSS patients was 72 % (N = 51) and in the healthy subjects 59 % (N = 42), P = 0.10. Eight pSS patients (11 %) had chronic TTH, while only one of the healthy subjects had chronic TTH last year, P = 0.05. BDI scores (median 9.0, range 0-38 vs median 2.0, range 0-16; P < 0.0005) and FSS scores (median 5.3, range 0-28 vs median 1.9, range 1-6; P < 0.0005) were higher in the patients than in the healthy subjects. Headaches in the patients were neither associated with depression or fatigue, nor with pSS-related autoantibodies, abnormalities in CSF or on cerebral MRI.

Conclusion: Only chronic TTH was more prevalent in patients compared to the healthy control subjects. This subtype of TTH was, however, not associated with depression, fatigue or any other clinical or laboratory variables. Migraine was not more prevalent in patients with pSS, thus the headache pattern seen in pSS patients differed from that seen in the SLE patients (Paper I).

4.3 Paper III

In this study we investigated the magnitude and severity of headaches by evaluating the impact of headaches on daily life in SLE patients, and compared with pSS patients and healthy subjects. Sixty-seven SLE patients, 71 pSS patients and 108 healthy subjects were included in this study. Out of these, 55 SLE patients, 51 pSS patients and 69 healthy subjects had headaches the previous year. The validated instruments HIT-6 and MIDAS were used for assessing headache-related disability. SLE patients had higher HIT-6 scores than healthy subjects (median 51, range 36-67 vs median 46, range 36-72; P = 0.02), as had pSS patients compared with healthy subjects (median

54, range 36-72 vs median 46, range 36-72; P = 0.0009). Also MIDAS score were higher in SLE patients vs healthy subjects (median 0, range 0-110 vs median 0, range 1-10; P = 0.04) and in pSS patients vs healthy subjects (median 1, range 0-40 vs median 0, range 0-10; P = 0.003). In regression analyses, age and BDI scores influenced headache impact significantly.

Conclusion: Headache-related disability is considerably higher in patients with SLE than otherwise healthy headache-sufferers. Notably, patients with pSS reported a similar impact from headaches as the SLE patients. Depressive mood significantly influenced headache severity. The high headache-related disability in patients with SLE and pSS may reflect the burden of chronic disease.

4.4 Paper IV

To elucidate possible causes for headache in SLE, we investigated associations between headaches and cerebral abnormalities on MRI, anti-NR2-, and anti-P antibodies, and a marker for astroglial cell activation; protein S100B. We hypothesized that structural and/or immunological factors might alter the threshold for migraine activation and thereby explain the high migraine prevalence in SLE patients. Sixty-seven SLE patients and 67 age- and gender matched healthy subjects were included in this study. Fifty-three SLE patients with eligible MRI scans and their healthy control subjects were included in volumetric analyses which were performed by applying the SPM8 software. Anti-NR2- and anti-P antibodies, and S100B were analysed in CSF from the patients. We found that increasing GM volumes in the SLE patients reduced the odds for all headaches in general (odds ratio [OR] 0.98, P = 0.048) and for migraine in particular (OR 0.95, P = 0.004). No localized loss of GM was observed. Increasing global WM volumes in the patients increased the odds for migraine (OR 1.04, P = 0.007). We could not confirm these findings in the healthy subjects. No associations with headaches in lupus patients were revealed regarding anti-NR2-, anti-P antibodies, nor protein S100B.

Conclusion: SLE patients with migraine have a global and diffuse reduction in GM compared to patients without migraine. This finding was not observed in the healthy subjects with migraine. Selected biomarkers did not indicate specific pathophysiological processes in the brain. These findings indicate that unknown pathogenic and pathophysiological processes influence the frequency of migraine in SLE patients.

5. Discussion

The central position of the headache topic in SLE is reflected by its placement in the criteria for SLE disease activity, and neuropsychiatric SLE (63, 132). This strong weighting has frequently been questioned in scientific papers and discussions, as has also the possible existence of a special "lupus headache". Whether migraine really is more frequent in SLE patients, and if headache is a true NP manifestation also remains a matter of debate. Does headache, especially migrainous headache, indicate SLE involvement of the brain, and even implicate a threat to the brain; or is headache more indirectly due to the systemic effects of SLE, such as disturbances of metabolic and homeostatic conditions, renal failure, inflammation, anemia, thyroid- or liver failure? Also, one could ask whether these topics are clinically important in pSS, another autoimmune systemic disease.

The relevant hypothesis is that disease related factors lead to a lower threshold for migraine activation in SLE patients. These factors could be genetic, biochemical and/or immunological factors, or caused by structural alterations in the brain. Thus, disease mechanisms in SLE patients interfere with migraine mechanisms in such a manner that the threshold for initiating migraine is lowered.

In this PhD project we have explored these topics in SLE- and pSS patients, and compared with healthy subjects.

5.1 Main findings

We found that patients with SLE suffered from migraine more frequently than healthy subjects. We could not confirm that migraine in the SLE patients was related to specific SLE disease factors, such as disease activity, organ damage or biochemical and immunological variables. PSS patients, on the other hand, did not have more migraine than their matched control subjects. Headache in SLE patients was stronger and had a stronger impact on daily life compared with otherwise healthy subjects that suffered from headache. The stronger, or more serious headache was also evident in

pSS patients. Using cerebral MRI, we found that SLE patients with migraine had a diffuse reduction of gray matter compared to patients without migraine, indicating that some disease associated processes could be responsible for the increased tendency of migraine in SLE patients. We could not replicate this association in the healthy subjects with migraine. This supports our hypothesis of a biologically based etiology and pathogenesis for increased migraine in SLE patients.

5.1.1 Discussion of main findings

Headache prevalence

Our findings in Paper I strenghten the hypothesis that migraine is more common in patients with SLE than in the general population. Previous studies have to some degree been mutually inconsistent, probably due to different research designs and methodology of studies, especially such as the selection of patients, use of classification criteria for SLE disease and for headache classification, and whether questionnaires or interviews are used. Our prevalence figures are in line with other relevant studies: An early controlled study found migraine in 34 % of SLE patients and 17 % in the control subjects (75). A population based, uncontrolled study from northern Norway found almost exactly the same migraine prevalence (38 %) and another population based controlled study from Finland reported migraine in 39 % of patients in contrast to 20 % of control subjects (67, 74). We found that migraine with aura was twice as frequent in SLE patients as in healthy subjects. Notably, this difference did not reach statistical significance. However, the same high prevalence of aura was found in the pooled data of one meta-analysis (71). In these larger samples, analysis revealed a significant difference between the patients and the control subjects.

Compared with other SLE studies TTH was more common in both the patients and the control subjects. A reason for this could be that we used personal interviews, which is considered to be a more sensitive method than questionnaires and to provide higher prevalences than those using questionnaires (9). We also sought for infrequent TTH. This subtype may be overseen if not searching specifically after all types of headaches with neutral screening questions about “having had” headache (not “suffered” from

headache). Our findings regarding frequent TTH are in agreement with other studies of the general population (28, 133). The main finding in Paper I was therefore that of all the headaches investigated, only migraine was more frequent in SLE.

In contrast to what we observed in SLE, migraine was not more common in pSS patients than in their matched control subjects (Paper II). However, the patients had more chronic TTH. Chronic headache may be secondary to frequent use of analgesics, and according to the ICHD-II criteria, MOH had to be ruled out before a definite diagnosis of chronic TTH could be set. Hence, withdrawal of analgesics was required for definite diagnosis. This was not possible in the context of our cross-sectional design. In the ICHD-III criteria this requirement is removed, and both the diagnosis of chronic TTH and MOH is set. In reporting the prevalence of patients with chronic TTH, we included those with probable MOH, as accounted for in the methods chapter. Thus, the change in the criteria for chronic TTH did not alter our results. Medication overuse according to the criteria may have explained chronic headache in three of the pSS patients classified as having chronic TTH. Many patients with pSS use analgesics due to chronic pain such as the frequent occurring myalgias and arthralgias, and may therefore be at risk of developing MOH. Further, chronic pain and chronic headache are associated conditions, and may partly explain the high prevalence of chronic headache in pSS patients (30). Our data are new and draw the attention toward increased awareness of headaches in pSS patients; MOH is a preventable and treatable condition.

Primary or secondary headache?

Headache classification in SLE and pSS patients raises important questions concerning whether a headache should be classified as a primary headache or as secondary headache. According to ICHD-II, headaches secondary to SLE or other autoimmune diseases should be classified as *7.3. Headache attributed to non-infectious inflammatory disease*. Whether a headache should be attributed to SLE, and thus be classified as a secondary headache, requires that it occurs for the first time, or gets significantly worse, in close temporal relation to SLE. In the NPSLE criteria, however,

this time-relationship is not required. Although the ACR nomenclature from 1999 has been widely accepted and used, it has also repeatedly been debated due to its weaknesses. Hanly emphasize the importance of correctly attributing a NP event to either SLE- (primary NPSLE) or non-SLE (secondary NPSLE) causes, regarding appropriate treatment (134). Some have argued that headache ought to be removed from the NPSLE criteria because of the high prevalence that exists in the general population (67, 69). A new algorithm for attribution of NP events in SLE was recently published based on a probability score that takes into account timing and type of the NP event (135). However, how to attribute headaches in SLE patients remains a challenge. Without biomarkers or other characteristics that can attribute headaches to SLE, clinical judgement remains the only relevant choice.

Headache-related disability

To further explore headache characteristics, we investigated whether headaches experienced by patients with SLE or pSS were more bothersome and intense than headaches in the general population (Paper III). The impact of headache – or headache-related disability – had not been investigated systematically in patients with SLE and pSS before. We found that headaches were considerably stronger and had higher impact in SLE patients compared with comparable healthy subjects. These findings may at least partly, reflect why headache have had such a strong weighting in disease activity evaluation in SLE, and also its placement as a NP manifestation. A somewhat unexpected finding was that the headaches in pSS patients also had more impact than in control subjects. Moreover, more depression in the patients could be a cofactor that explained these differences.

Headache-related disability was higher in both patients and healthy subjects with migraine than in those with TTH, showing the same pattern as in the general population, however, with one exception: Headache impact measured with MIDAS was identical in pSS patients with migraine and in those with TTH. The MIDAS instrument assesses days lost for activity due to headache, and a possible explanation

could be that TTH has a stronger impact on daily activity in pSS patients. This aspect was not further explored in our study.

Clinical and laboratory associations with headaches in SLE and pSS

More migraine in SLE patients could not be explained by the selected disease associated variables. We investigated such as biochemical or immunological factors, disease activity, disease duration, or organ damage. This is in line with most studies conducted on headache in SLE. We assessed whether headaches in SLE patients were associated with selected autoantibodies or with measure for glial activation known to influence synaptic transmission, and thus with potential to lower the threshold for migraine by altering the cortical excitability. However, as far as the autoantibodies investigated and protein S100B are relevant measures for this, we found no associations. Other unknown processes, for example simultaneously interactions between several autoantibodies, or other pathophysiological processes, may be operative.

Both the patients with SLE and the pSS patients had more depression and fatigue than their matched healthy subjects, but only in SLE patients was an association with headaches (i.e. all headaches and migraine) demonstrated. Although pSS patients were as depressed as the SLE patients, depression did not influence headache prevalences or clinical characteristics. Thus, migraine is comorbid with depression in SLE patients as in the general population. Our findings contrast a meta-analysis arguing that there was no good evidence that headaches in SLE patients were influenced by depression (71). This comorbidity was not observed in the pSS patients as all the patients regardless of presence or not presence of headache, had the same high BDI scores. Alternatively may depression and migraine in SLE patients share some pathogenetic mechanisms that are not operative in pSS patients.

MRI

Findings in Paper IV support the hypothesis of a biological basis for more migraine in SLE patients. Presence of migraine was associated with reduced global volumes of

GM on cerebral MRI, but this could not be replicated in the healthy subjects. No localized loss of GM was demonstrated in the SLE patients with migraine. The diffuse and global reduction of GM volumes is as would be expected if due to diffuse and general disease processes.

An unexpected finding was that SLE patients with migraine had larger WM volumes than the patients without migraine. In one study, SLE patients treated with hydroxychloroquine and cyclophosphamide had larger WM volumes than SLE patients that never had been treated with such drugs (136). Another study in juvenile SLE patients reported that higher cumulative intravenous corticosteroid doses were associated with increased regional WM volumes (108). One might therefore speculate whether the increased WM volumes in SLE patients with migraine may be secondary to more severe disease activity, and that treatment with immunosuppressive drugs is an indicator for more severe disease. However, our study was not designed for exploring these matters further.

WMH load was higher in SLE patients, but did not influence headache prevalence. This contrasts another study demonstrating an association between WMH load and headaches (105). No difference in the load of WMHs was detected between pSS patients and healthy subjects.

Photosensitivity

We found that SLE patients with migraine had more *SLE photosensitivity* than non-migraine patients. Photosensitivity – a more or less pronounced skin rash - is part of the SLE disease criteria, not to be confused with *migraine photosensitivity*. Migraine is a brain disorder with cortical hyper-excitability and hypersensitivity to sensory input. Photosensitivity is often part of the individual`s migraine characteristics, and may intensify the headache and inflict ocular pain. Also, hypersensitivity to light can itself be part of the premonitory phase of migraine, or bright light can trigger an attack. In SLE patients, exposure to the UV-specter of light may trigger a disease flare in susceptible individuals, and not be restricted to skin rash. Thus, the abnormal processes caused by light are essentially different in SLE and migraine. It is therefore

interesting that the skin photosensitivity seems to be associated with migraine, possibly a coincidence although a common pathway for these phenomena cannot be outruled. Our finding is in line with another study of headache in SLE patients (76).

Headache as a NP syndrome

NP syndromes with subjective and/or mild symptoms and findings, are the most difficult to identify and confirm. The ACR NPSLE criteria were developed in an effort to describe and specify the neuropsychiatric conditions to facilitate comparative research. Because headache is a common condition with subjective symptoms and lack of biomarkers, the attribution to SLE is difficult to ascertain in the individual cases. Our data support a biological origin for migraine in SLE. Thus, the headache question in SLE deserves to be further explored. Headaches in SLE patients should be diagnosed according to the ICHD, with special attention to the possibility of attribution to SLE.

"Lupus headache" is previously described in both children and adults, especially in association with high disease activity. It is our clinical experience that this very intense and intractable headache exists, but is rare. In our study two SLE patients reported to have had an intense, migrainous and intractable headache during previous flares, also documented in the hospital files. These headaches had to be classified as secondary headaches according to the close temporal relationship with acute SLE disease activity. Also in a recent publication, headaches referred to as "lupus headache" is reported (68). This clinical experience should not be underestimated. However, our study supports that headache should be omitted from the NPSLE criteria. Headaches in the SLE patients were classifiable according to the ICHD criteria. Our data do not support the removal of the headache item in SLEDAI. One could argue that headache remains an item in the disease activity index, but requires headache to be in close temporal relation to a flare, thus fulfilling the criteria for a secondary headache according to the ICHD. Further investigations directly addressing the rare "lupus headache", are needed.

In conclusion our data indicate a biological link between headache and SLE. However, the mechanisms underlying the increased migraine frequency and the influence of headaches on GM in SLE patients remain to be elucidated.

5.2 Comments on methods; strenghts and limitations

Design

Our studies have been close to population based as nearly all patients with SLE and pSS in the catchment area are allocated to the Stavanger University Hospital. The data sampling was done with a cross-sectional approach, and a case-control design was used when comparing prevalences. Cross-sectional design is considered appropriate when investigating prevalence and burden of a disease. A case-control design is considered adequate when looking for risk factors for headache, but it would have been optimal to perform longitudinal studies.

Participants

All patients had age- and gender matched healthy subjects serving as control subjects. International diagnostic criteria were used for SLE and pSS disease and for headache disorders. The data are comprehensive as the patients were extensively investigated and clinically described. All were clinically examined by an experienced internist (EH) and neurologist (ABT). Blood and CSF samples were obtained under strict standardized conditions, and rapidly processed, analyzed or frozen.

It can be discussed whether the selection process of the healthy subjects may have led to a control group not reflecting the general population in the most optimal way. The pragmatic method for selecting a control group is however well accepted and was decided in collaboration with section of statistics and epidemiology at the University of Tromsø when studies were designed.

The prevalences for headaches in control subjects were in accordance with several others, and support that the healthy control subjects were representative (9). Notably, both pSS patients and the matched healthy subjects had high prevalence of migraine

aura. Aura is usually about one third of all migraine. In the healthy subjects matched with pSS patients, the proportion of aura was one half of all migraine. Also in the pSS patients the proportion of aura was high, not different from the control subjects. This may be due to small sample sizes.

Headaches

Diagnosing headaches through a structured interview conducted by an expert is considered the "gold standard" in headache studies. We diagnosed headaches using structured interview with a neutral screening question, conducted by the same neurologist (ABT). Validated and reliable tools were used for assessing the impact of headaches. However, headache diaries were not used, thus recall bias may have been introduced. Headaches were classified according to the ICHD criteria available at the time of data collection. We do not consider the changes introduced in the ICHD-III beta version to alter our conclusions.

Socio-economic status

The socio-economic status was not systematically assessed in our study. This may have caused a bias to the prevalence estimates, as healthy control subjects were not matched with the patients regarding socio-economic status. To what extent socio-economic status is an effect of headache or causes the headache is uncertain. Low income can be a consequence of having chronic disease. Lost educational years may affect career opportunities and income. Frequent and chronic headaches (both migrainous and non-migrainous) were associated with low socio-economic status in the Norwegian HUNT study (137). However, other authors could not confirm this association, and conflicting results exist (138, 139). This is pragmatically summed up by Lipton et al, stating that socio-economic status seems to be associated with headache prevalence in USA, but not so in Europe (12).

MRI

A strenght of the study is that validated methods for VBM analyses with a conservative correction for multiple testing were used, and that cortical infarcts were

excluded. This is important as much as one of our main findings was the association of all headaches and migraine with GM volume.

The cumulative corticosteroids doses were not assessed. Corticosteroids have been described to influence brain volumes, and this might exert a bias to the measures of GM volume. SLE patients with higher cumulative doses may have less GM volume. On the other hand, the presumptive influence of corticosteroids could well be a reflection of high disease activity that led to treatment with these drugs. Hence, the association of headaches with GM volume would still be interesting to explore further as much as high doses could reflect higher disease activity over years.

Statistics

A limitation of the study is small sample sizes. Especially regarding the analyses of autoantibodies and cytokines larger samples could have revealed effects that we were not able to detect. Also, fluctuations in the concentrations over time may have limited our ability to detect associations in this cross-sectional design. We did not perform power analyses in advance, which would have supported the interpretations of the result. However, considering the low prevalences of the diseases we investigated and the number of patients that participated based on the population in this geographical area these are relatively large studies. We consider the sample sizes as close to population based as it is possible to get.

6. Conclusion

Migraine is comorbid with SLE, and headache-related disability is higher in SLE patients than in otherwise healthy subjects with headaches. Migraine in SLE patients has the same characteristics as in the general population and is not linked to measures of disease activity, immunological abnormalities in CSF, or selected autoantibodies. However, migraine is associated with reduced GM volumes, indicating diffuse pathogenetic processes in the brain.

In pSS patients chronic TTH is frequent and headaches have high impact on daily life.

7. Future perspectives

In this thesis, all the headache types recorded could be classified according to the ICHD-II criteria. Nevertheless, it is our clinical experience that a few patients report headaches meeting the description of "lupus headache". These headaches have occurred during disease flares with fever and other characteristics of active disease, and as such could not be classified as primary headaches. However, one could hypothesize that intense immunological activity might be accompanied by intrathecal immune activation and production of autoreactive antibodies that triggers this type of headache. Because headache is so common in the general population, a specific headache in SLE would be extremely difficult to capture using a quantitative study design. Qualitative studies could therefore elucidate this issue further. In such a study, also quantitative measures should be obtained, such as biochemical and immunological data, both in blood but preferably in the CSF. Measures should be performed when headache is active and ongoing, due to dynamics of the symptoms. As these headaches are rare, a multicenter study probably would be beneficial. Functional MRI studies could shed further light on the regions and networks involved.

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9. Errata

10. Supplementary

10.1 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of Systemic Lupus Erythematosus (62)

1. Malar Rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive Arthritis	Involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or Pericarditis	1. Pleuritis – convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion or 2. Pericarditis – documented by electrocardiogram or rub or evidence of pericardial effusion
7. Renal disorder	1. Persistent proteinuria > 0.5 grams per day or > than 3+ if quantitation not performed or 2. Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed
8. Neurologic Disorder	1. Seizures – in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance or 2. Psychosis – in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance.
9. Hematologic disorder	1. Hemolytic anemia – with reticulocytosis or 2. Leukopenia – < 4,000/mm^3 on ≥ 2 occasions or 3. Lymphopenia – < 1,500/ mm^3 on ≥ 2 occasions or 4. Thrombocytopenia – < 100,000/ mm^3 in the absence of offending drugs
10. Immunologic Disorder	1. Anti-DNA: antibody to native DNA in abnormal titer or 2. Anti-Sm: presence of antibody to Sm nuclear antigen or 3. Positive finding of antiphospholipid antibodies on: - an abnormal serum level of IgG or IgM anticardiolipin antibodies, - a positive test result for lupus anticoagulant using a standard method, or - a false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11. Positive Antinuclear Antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

For the purpose of identifying patients in clinical studies, a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present serially or simultaneously, during any interval or observation

10.2 American-European Consensus Group Classification Criteria for Sjögren's Syndrome (81)

I. Ocular symptoms: A positive response to at least one of the following questions:

1. Have you had daily, persistent, and troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?

II. Oral symptoms: A positive response to at least one of the following questions:

1. Have you had a daily feeling of dry mouth for more than 3 months?
2. Have you had recurrent or persistently swollen salivary glands as an adult?
3. Do you frequently drink liquids to aid in swallowing dry food?

III. Ocular signs, that is, objective evidence of ocular involvement, defined as a positive result for at least one of the following two tests:

1. Schirmer's I test, performed without anesthesia (<5 mm in 5 minutes)
2. Rose Bengal score or other ocular dye score (>4 according to van Bijsterveld's scoring system)

IV. Histopathology: Focal lymphocytic sialoadenitis in minor salivary glands (obtained through normal-appearing mucosa) evaluated by an expert histopathologist, with a focus score >1, defined as a number of lymphocytic foci (adjacent to normal-appearing mucous acini and contain more than 50 lymphocytes) per 4 mm^2 of glandular tissue.

V. Salivary gland involvement: Objective evidence of salivary gland involvement defined by a positive result for at least one of the following diagnostic tests:

1. Unstimulated whole salivary flow (<1.5 ml in 15 minutes)
2. Parotid sialography showing the presence of diffuse sialectasias (punctate, cavitary, or destructive pattern), without evidence of obstruction in the major ducts
3. Salivary scintigraphy showing delayed uptake, reduced concentration, and/or

a. delayed excretion of tracer

VI. Autoantibodies: Presence in the serum of the following autoantibodies:

1. Antibodies to Ro (SSA) or La (SSB) antigens, or both

For primary SS:

In patients without any potentially associated disease, primary SS may be defined as follows:

a. The presence of any 4 of the 6 items is indicative of primary SS, as long as either item IV (Histopathology) or VI (Serology) is positive
b. The presence of any 3 of the 4 objective criteria items (that is, items III, IV, V, or VI)
c. The classification tree procedure represents a valid alternative method for classification, although it should be more properly used in a clinical- epidemiological survey

Exclusion criteria:

1. Past head and neck radiation treatment
2. Hepatitis C infection
3. Acquired immunodeficiency syndrome (AIDS)
4. Pre-existing lymphoma
5. Sarcoidosis
6. Graft versus host disease
7. Use of anticholinergic drugs (since a time shorter than 4-fold the half life of the drug)

10.3 Neuropsychiatric syndromes in SLE (63)

Central nervous system

Aseptic meningitis
Cerebrovascular disease
Demyelinating syndrome
Headache (including migraine and benign intracranial hypertension)
Movement disorder (chorea)
Myelopathy
Seizure disorders
Acute confusional state
Anxiety disorder
Cognitive dysfunction
Mood disorder
Psychosis

Peripheral nervous system

Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome)
Autonomic disorder
Mononeuropathy, single/multiplex
Myasthenia gravis
Neuropathy, cranial
Plexopathy
Polyneuropathy

10.4 SLEDAI (SLE disease activity index) (1)

1. Seizure; recent onset, exclude metabolic, infectious or drug causes.
2. Psychosis; altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behaviour. Excluded uremia and drug causes.
3. Organic brain syndrome; altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
4. Visual disturbances; retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection or drug causes.
5. Cranial nerve disorder; new onset of sensory or motor neuropathy involving cranial nerves.
6. Lupus headache; severe persistent headache; may be migrainous, but must be non-responsive to narcotic analgesia.
7. CVA; new onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8. Vasculitis; ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
9. Arthritis; ≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling or effusion)
10. Myositis; proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
11. Urinary casts; heme-granular or red blood cell casts
12. Hematuri; > 5 red blood cells/high power field. Exclude stone, infection or other cause
13. Proteinuria; > 0.5 g/24 hours
14. Pyuria; > 5 white blood cells/high power field. Exclude infection
15. Rash; inflammatory type rash
16. Alopecia; abnormal patchy or diffuse loss of hair
17. Mucosal ulcer; nasal or oral ulcerations.
18. Pleurisy; pleuritic chest pain with pleural rub or effusion, or pleural thickening.
19. Pericarditis; pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
20. Low complement; decrease inCH50, C3, or C4 below the lower limit of normal for testing laboratory.
21. Increased DNA binding. Increased DNA binding by Farr assay above the normal range for testing laboratory.
22. Fever; > 38°C. Exclude infectious cause.
23. Thrombocytopenia; < 100 000 platelets/ x 10^9/L, exclude drug causes.
24. Leukopenia; < 3000 white blood cells/x 10^9, exclude drug causes

Descriptors have to be present at the time of visit or in the preceding 10 days.

10.5 MIDAS (Migraine disability assessment) questionnaire (48)

1. Hvor mange dager siste 3 måneder har du vært borte fra skole/arbeid på grunn av hodepine?
2. Hvor mange dager siste 3 måneder fikk du ikke gjort oppgaver i hjemmet på grunn av hodepine?
3. Hvor mange dager siste 3 måneder var din produktivitet på skole/arbeid redusert med minst 50 % på grunn av hodepine?
4. Hvor mange dager siste 3 måneder var din produktivitet i arbeid med oppgaver i hjemmet redusert med minst 50 % på grunn av hodepine?
5. Hvor mange dager siste 3 måneder måtte du avstå fra fritidsaktiviteter, sosiale- og familieaktiviteter på grunn av hodepine?

A) Hvor mange dager siste 3 måneder hadde du hodepine?

B) På en skala fra 0-10, hvor smertefulle var disse hodepinene i gjennomsnitt?
(Hvor 0 = ingen smerte, og 10 = verst tenkelig smerte)

Grade I	Minimal disability	Score 0 – 5
Grade II	Mild disability	Score 6 – 10
Grade III	Moderate disability	Score 11-20
Grade IV	Severe disability	Score ≥ 21

10.6 HIT-6 (Headache Impact Test-6) (47)

1. Når du har hodepine, hvor ofte er smertene sterke?
   Alternativer; aldri, sjelden, noen ganger, svært ofte, alltid
2. Hvor ofte begrenser hodepinen din evne til å utføre vanlige daglige gjøremål slik som husarbeid, arbeid, skolearbeid eller å ha sosial omgang?
   Alternativer; aldri, sjelden, noen ganger, svært ofte, alltid
3. Når du har hodepine, hvor ofte ønsker du at du kunne legge deg ned?
   Alternativer; aldri, sjelden, noen ganger, svært ofte, alltid
4. I de siste 4 ukene, hvor ofte har du følt deg for trett til å utføre arbeid eller daglige gjøremål på grunn av hodepine?
   Alternativer; aldri, sjelden, noen ganger, svært ofte, alltid
5. I de siste 4 ukene, hvor ofte har du følt deg lut lei og irritert på grunn av hodepine?
   Alternativer; aldri, sjelden, noen ganger, svært ofte, alltid
6. I de siste 4 ukene, hvor ofte har hodepinen begrenset din evne til å konsentrere deg om arbeid eller daglige gjøremål?
   Alternativer; aldri, sjelden, noen ganger, svært ofte, alltid

Aldri:	6 poeng hver
Sjelden:	8 poeng hver
Noen ganger:	10 poeng hver
Svært ofte:	11 poeng hver
Alltid:	13 poeng hver

Total score range 36 – 78

Grade I	Minimal impact	Score ≤ 49
Grade II	Mild impact	Score 50 - 55
Grade III	Moderate impact	Score 56 - 59
Grade IV	Severe impact	Score ≥ 60

11. Original publications

Paper I
Migraine is frequent in patients with systemic lupus erythematosus: a case-control study

I

Paper II
Headache in primary Sjøgren's syndrome: a population-based retrospective cohort study

II

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Headache in primary Sjøgren's syndrome: a population-based retrospective cohort study

A. B. Tjensvoll[a], E. Harboe[b], L. G. Gøransson[b], M. K. Beyer[c], O. J. Greve[c], J. T. Kvaløy[d,e] and R. Omdal[b]

[a]Department of Neurology; [b]Department of Internal Medicine; [c]Department of Radiology, Stavanger University Hospital, Stavanger; [d]Division of Research and Human Resources, Stavanger University Hospital, Stavanger; and [e]Department of Mathematics and Natural Sciences, University of Stavanger, Stavanger, Norway

Keywords:
autoimmune disease, headache, migraine, primary Sjögren's syndrome, tension-type headache

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Background: We investigated whether the prevalence of primary headaches was higher in patients with primary Sjøgren's syndrome (PSS) than in healthy individuals.

Methods: This retrospective cohort study included 71 patients with PSS (patients) based on the American European Consensus Classification criteria, and 71 age- and gender-matched healthy subjects (controls). Headaches were classified according to the International Classification of Headache Disorders. We measured depression with the Beck Depression Inventory, and fatigue with the Fatigue Severity Scale.

Results: Fifty-one patients and 42 controls had headaches in the previous 12 months (71.8% vs. 59.2%, $P = 0.10$). Thirty-eight patients and 28 controls had tension type headaches (TTHs) (53.5% vs. 39.4%, $P = 0.12$). Eight patients (11.3%) and one control had chronic TTHs ($P = 0.05$). Migraines and migraines with aura were equally prevalent in patients (26.8% and 11.3%, respectively) and controls (28.2% and 15.5%, respectively; $P = 0.61$).

Conclusions: In general, patients did not have more migraines or headaches than controls. However, patients had more chronic TTHs than controls. Chronic TTHs were not associated with PSS-related autoantibodies, fatigue, depression, abnormalities on magnetic resonance imaging or abnormalities in the cerebrospinal fluid. Patients with PSS did, however, have higher depression and fatigue scores than controls.

Introduction

Primary Sjøgren's syndrome (PSS) is an autoimmune, chronic, inflammatory disease characterized by inflammation of the exocrine glands, followed by dryness of the mouth and eyes, migrating muscle and joint pain, and chronic fatigue. In addition, PSS frequently involves the peripheral and central nervous system (CNS), causing peripheral neuropathy, cranial neuropathy, myelopathy, focal brain lesions and cognitive dysfunction [1–3].

Primary Sjøgren's syndrome exhibits several of the clinical and immunological features observed in systemic lupus erythematosus (SLE), which is often considered a more systemic disease than PSS. The neurological aspects of SLE are fairly well studied and characterized; in contrast, less is known about these issues in PSS. Thus, reports are highly variable concerning the prevalence and characteristics of neurological manifestations in PSS. This may be due to shifting criteria over time for PSS, a lack of strict definitions for CNS involvement, or selection biases (like tertiary care studies). For example, studies performed solely in neurological departments risk overestimation of CNS involvement.

In SLE, the criteria and case definitions proposed by the American College of Rheumatology have become widely accepted; these criteria cover 19 neuropsychiatric syndromes regarded as part of the disease spectrum [4]. Applying these criteria has facilitated comparative studies of neuropsychiatric SLE in different geographic regions of the world, and in different settings. Although it remains a matter of debate, lupus headache is one of these criteria, and it is included in the SLE disease activity index [5].

Few studies have described the epidemiology and headache characteristics of PSS. We therefore wished to investigate these issues in a controlled study with age- and gender-matched subjects. PSS was diagnosed

Correspondence: A. B. Tjensvoll, Department of Neurology, Stavanger University Hospital, PO Box 8100, N-4068 Stavanger, Norway (tel.: +47 05151; fax: +47 51519916; e-mail: tjab@sus.no).

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based on the widely accepted American European Consensus Classification (AECC) criteria [6], and headache categories were assigned according to the most recently available criteria from the International Classification of Headache Disorders (ICHD-II) [7]. We also performed cerebral magnetic resonance imaging (MRI) studies to evaluate structural abnormalities and white matter hyperintensities (WMHs). Cerebrospinal fluid (CSF) was analysed for intrathecal immunoglobulin (IgG) and interleukin-6 (IL-6) production. We then investigated associations between headaches and intrathecal immune activation.

Patients and methods

Patients

All patients with systemic autoimmune diseases in the southern part of Rogaland County (310 000 inhabitants) were allocated to Stavanger University Hospital. We reviewed the medical records of all in- and outpatients diagnosed with PSS between 1980 and 2005 at the Stavanger University Hospital. When in doubt about the diagnosis, we re-examined patients to assure they fulfilled the diagnostic criteria. Also, we identified all minor salivary gland biopsies analysed in the hospital's pathology department from 1990 to 2004 (n = 410). In cases of lip biopsies with a focus score ≥ 1, patients were screened for PSS. Seventy-two (73%) out of the 99 patients that fulfilled the AECC criteria provided informed consent to participate in the study. One patient was excluded due to a brain tumour revealed by MRI. Thus, 71 patients – 61 women (86%) and 10 men (14%) – were included and subjected to a 2-day stay in the hospital exclusively for the purpose of this investigation. The study was approved by the Regional Research Ethics Committee and complied with the Helsinki Declaration.

The mean age of the patients was 57.5 ± 12.9 years (median 58.1 years; range 27.1–86.6 years). Mean body mass index (BMI) was 25.0 ± 3.9 kg/m^2 (median 24.2 kg/m^2; range 19.4–37.6 kg/m^2). The mean disease duration was 6.9 ± 4.9 years (median 6.1 years; range 0.4–24.1 years). At the time of the investigation, 35 patients (49.3%) were taking medication for PSS; two patients (2.8%) took corticosteroids only, 18 took antimalarials (25.4%), one received intravenous cyclophosphamide infusions and 13 patients (18.3%) took combinations of drugs for PSS. Thirteen patients (18.3%) used thyroxin, four (5.6%) used vitamin B12 and two (2.8%) used β-blockers. Fifty-six (79%) patients had anti-SSA antibodies, 33 (46%) also had anti-SSB antibodies. No patients exhibited only anti-SSB antibodies. Fifty-seven patients had a positive salivary gland biopsy (focus score ≥ 1) and 13 patients had a negative biopsy (focus score < 1). In one patient, the gland biopsy was inconclusive due to insufficient biopsy volume.

Healthy subjects

Seventy-one age- and gender-matched healthy individuals without known neurological, immunological or malignant diseases served as control subjects. These were recruited among members, friends and neighbours of the hospital staff, and friends and neighbours of the patients. The ages were matched to patient ages within ± 2 years. The mean age was 56.5 ± 13.2 years (median 57.0 years; range 26.0–87.0 years). The mean BMI was 25.0 ± 3.1 kg/m^2 (median 24.8 kg/m^2; 19.5–33.9 kg/m^2). Healthy subjects were also subjected to a 2-day investigation in the hospital after providing informed consent to participate in the study.

Clinical evaluation

All patients and healthy subjects were examined by an experienced internist (EH) and neurologist (ABT). The neurologist classified headaches according to the ICHD-II criteria [7] by performing a structured interview. First, the subject was asked a neutral question about whether they had experienced a headache within the previous year. This was followed by a detailed neurological and headache history covering each of the relevant criteria for reported headaches and other relevant neurological symptoms. The ICHD diagnostic criteria for primary headaches were based on symptoms. According to the criteria, headaches were classified by their phenomenology. Secondary headaches were excluded when they were considered to be due to any disease other than PSS. Headache status was defined as one or more headache attacks during the last 12 months.

A Beck Depression Inventory (BDI) with a cut-off score ≥ 13 was used to assess depression [8]. The Fatigue Severity Scale (FSS) [9] and a fatigue visual analogue scale (VAS) were used to evaluate fatigue.

Laboratory tests

Routine haematological, biochemical and immunological tests were performed as previously described [10]. CSF samples were obtained by lumbar puncture in 54 patients between 13.00 hours and 14.00 hours. All samples were immediately placed on ice and centrifuged at 4 °C at 3000 g for 10 min; the supernatant was then immediately aliquoted and frozen at −70 °C until analysis.

Cerebral MRI

Magnetic resonance imaging was performed with a 1.5-T Philips Gyroscan NT Intra Release 10 (Philips Medical Systems, Best, the Netherlands), as previously described [11]. The interval between clinical and MRI examinations was 14 ± 8 days (median 12.0 days; range 0.0–44.0 days) for patients with PSS, and 24 ± 28 days (median 20.0 days; range 59.0–81.0 days) for healthy subjects. Two experienced radiologists (MB and OJG) rated each scan independently in a blinded manner; they reached a consensus by discussion whenever disagreements occurred. WMHs were evaluated according to the semi-quantitative scale of Scheltens *et al.* [12]. This method took into account the spatial localization, size and number of lesions.

Statistical methods

Continuous data are reported as the mean $\pm$ SD when normally distributed; otherwise, they are reported as the median and range. Categorical data are reported as percentages. McNemars test was used to compare matched pair-wise categorical data. For independent categorical data a Chi-square test was used to compare categorical data when expected frequencies were more than 5; otherwise, the Fisher's Exact Test was used. Logistic regression was used to test for risk factors for development of headache in patients with PSS. The Wilcoxon paired samples test was used to test for significant differences in paired continuous data, and the Mann–Whitney *U*-test was used to test for significant differences in independent continuous data. Correction for multiple testing was not performed. A value of $P \leq 0.05$ was considered significant.

Results

Headaches

Of the 71 patients with PSS, 51 (71.8%) reported one or more headache attacks within the last 12 months (Table 1). Thirty-eight patients (53.5%) reported tension type headaches (TTHs). Thirty patients (42.3%) reported episodic TTHs (ETTHs); 21 (29.6%) had frequent ETTHs (< 15 attacks per month) and nine (12.7%) had infrequent ETTHs (< 1 attack per month). Eight patients (11.3%) reported chronic TTHs; of these, three patients were diagnosed with 'probable chronic TTH', because medication overuse headache could not be ruled out. None of the patients with PSS had chronic migraine.

Table 1 Prevalence of headache in 71 patients with PSS and 71 age- and gender-matched healthy subjects

Type of headache	PSS ($n = 71$)	Healthy subjects ($n = 71$)	P*
All headaches	51 (71.8%)	42 (59.2%)	0.10
All migraine	19 (26.8%)	20 (28.2%)	1.00
Migraine with aura	8 (11.3%)	11 (15.5%)	0.61
Migraine aura without headache	3 (4.2%)	1	0.62
Chronic migraine	0	0	
All TTH	38 (53.5%)	28 (39.4%)	0.12
Frequent ETTH	21 (29.6%)	14 (19.7%)	0.23
Infrequent ETTH	9 (12.7%)	13 (18.3%)	0.50
Chronic TTH	8 (11.3%)	1	0.05
TTH only	32 (45.1%)	22 (31.0%)	0.10
Both migraine and TTH	6 (8.5%)	6 (8.5%)	0.77

*P-values not corrected for multiple significance testing. ETTH, episodic tension-type headache; PSS, primary Sjøgren's syndrome; TTH, tension type headache.

Forty-two healthy subjects (59.2%) reported primary headache within the last 12 months (Table 1). One individual had chronic TTH. The prevalence of migraine was similar between patients with PSS and healthy subjects. One healthy person with migraine also had a primary stabbing headache.

The patients with TTH were younger than patients without TTH (mean age 53.5 ± 12.9 years, median 52.1 years; range 27.1–75.3 years vs. mean age 62.2 ± 11.4 years, median 61.8 years; range 35.7–86.6 years; $P = 0.01$). Patients with chronic TTH were younger than those without chronic TTH (mean age 49.2 ± 11.4 years, median 45.9 years; range 34.2–71.8 years vs. 58.6 ± 12.8 years, median 60.3 years; range 27.1–86.6 years; $P = 0.04$). No differences were found between patients with or without chronic TTH in disease duration, BMI or education.

Laboratory tests and other variables

There were no differences between patients with PSS with or without headache in general, or subtypes of headache, regarding haemoglobin, platelets, leukocytes, erythrocyte sedimentation rate, ANA, anti-nDNA antibodies, FT4, TSH, anti-cardiolipin antibodies, or complement factors C3 and C4. Of the 19 patients with PSS that reported migraines, 18 had anti-SSA and/or -SSB antibodies. Of the 52 patients without migraine, 38 had anti-SSA and/or anti-SSB antibodies (95% vs. 73%; $P = 0.06$). Anti-SSA/-SSB antibodies were detected in four out of eight patients with PSS that had chronic TTH, and 52 out of 63 patients without chronic TTH (50% vs. 83%). Thus, chronic TTH tended to be associated with less anti-SSA/-SSB positivity ($P = 0.06$) in patients with PSS.

Patients with positive biopsies ($n = 57$) showed no differences in headaches or headache categories compared with those with negative biopsies ($n = 13$). Furthermore, for patients with positive lip biopsies, no differences in focus scores were detected in those with or without headaches or headache categories (data not shown).

Fifty-four patients with PSS were subjected to lumbar puncture. Only three of these patients showed detectable IL-1β levels in the CSF; two had TTH and one had migraine with aura. IL-6 was detectable in the CSF of 43 of 54 patients, but there were no differences between those with or without headache or headache categories. Three patients with PSS had an elevated CSF/serum albumin index, indicating impairment of the blood–brain barrier. Of these, all had TTH only, one had chronic TTH. An increased CSF IgG/albumin ratio, which indicated intrathecal IgG synthesis, was detected in nine patients; four were among 40 patients with headache (10%) and five were among 14 patients without headache (36%), ($P = 0.04$). Only one out of 28 patients (4%) with TTH had an increased CSF IgG/albumin ratio compared with eight out of 26 (31%) without TTH ($P = 0.01$). The IgG index was increased in seven patients; three with TTH, one with migraine without aura, and two without headache. This index was not significantly different between patients with or without headache or headache categories.

Two out of the 69 patients (3%) investigated with MRI had cerebral infarcts; both of them ≥ 2 lacunar infarcts. Two healthy subjects (3%) had cerebral infarcts, one with one lacunar infarct and one with ≥ 2 lacunar infarcts. No differences were detected between patients and healthy subjects regarding WMH scores (median 3.0, range 0.0–28.0 vs. median 5.0, range 0.0–30.0; $P = 0.31$). Among patients with PSS, those with TTHs had lower total WMH scores than those without TTHs (median 2.0; range 0.0–16.0 vs. median 5.0; range 0.0–28.0; $P = 0.04$) (Table 2). Adjusted for age in a logistic regression model, this difference was no longer significant.

The patients with PSS had higher FSS scores than the healthy subjects (median 5.3, range 1.2–7.0 vs. 1.9, 1.0–6.0; $P < 0.0005$). The same applied to VAS scores (median 65.0, range 3.0–96.0 vs. 9.0, 1.0–82.0; $P < 0.0005$). Among patients with PSS, the FSS scores were not different in those with headache or any headache category compared with those without headaches (Table 3).

The patients with PSS had higher BDI scores than the healthy subjects (median 9.0, range 0.0–38.0 vs. 2.0, 0.0–16.0; $P < 0.0005$). Among patients with PSS, no differences were detected in BDI scores among those with or without headache in the different headache categories (Table 4).

Table 2 Total WMH scores and different headache categories in 68 patients with PSS

Headache types	Headache present	Headache not present	*P**
All headaches	3.0; 0.0–28.0	7.5; 0.0–20.0	0.06
All migraine	3.0; 0.0–28.0	3.5; 0.0–20.0	0.98
Migraine with aura	4.0; 0.0–27.0	3.0; 0.0–28.0	0.61
All TTH	2.0; 0.0–16.0	5.0; 0.0–28.0	0.04
TTH only	2.5; 0.0–16.0	4.0; 0.0–28.0	0.09
Chronic TTH	2.0; 0.0–10.0	4.0; 0.0–28.0	0.24

**P*-values not corrected for multiple significance testing. WMH, white matter hyperintensities; TTH, tension type headache.

Table 3 FSS scores and different headache categories in 71 patients with PSS

Headache types	Headache present	Headache not present	*P**
All headaches	5.3; 1.6–7.0	5.6; 1.2–6.9	0.78
All migraine	5.3; 1.6–7.0	5.4; 1.2–7.0	0.92
Migraine with aura	5.4; 2.0–6.8	5.3; 1.2–7.0	0.94
All TTH	5.3; 1.7–7.0	5.4; 1.2–7.0	0.98
TTH only	5.3; 1.7–7.0	5.4; 1.2–7.0	0.73
Chronic TTH	6.1; 3.3–6.9	5.2; 1.2–7.0	0.28

**P*-values not corrected for multiple significance testing. FSS, Fatigue Severity Scale; TTH, tension type headache.

Table 4 BDI scores and different headache categories in 71 patients with PSS

Headache types	Headache present	Headache not present	*P**
All headaches	8.5; 0.0–29.0	9.0; 0.0–38.0	0.50
All migraine	9.0; 1.0–23.0	9.5; 0.0–38.0	0.95
Migraine with aura	8.5; 3.0–20.0	9.0; 0.0–38.0	0.86
All TTH	9.5; 0.0–29.0	8.0; 0.0–38.0	0.37
TTH only	10.0; 0.0–29.0	9.0; 0.0–38.0	0.51
Chronic TTH	15.5; 2.0–29.0	9.0; 0.0–38.0	0.15

**P*-values not corrected for multiple significance testing. BDI, Beck Depression Inventory; TTH, tension type headache.

Discussion

This study showed that the only difference between patients with PSS and healthy subjects was that the former group had a higher prevalence of chronic TTHs. These groups were similar in the prevalence of headaches in general and the prevalence of other subtypes of headaches. We expect that these findings reflected the headache spectra in the population with PSS, because nearly all patients with PSS from our

geographic area were recruited into the study. We used widely accepted classification criteria for both PSS (AECC) [6] and headaches (ICHD II) [7], and the headache subtype was assessed based on a structured personal interview by a neurologist. Furthermore, patients with PSS were compared with age- and gender-matched healthy subjects from the same geographic area, and both groups were investigated in the same manner. The prevalence of headaches in general in the control group was similar to that reported in a recent review of headache epidemiology in Europe [13]. Thus, our results reflected the general population in this respect.

Our findings contrasted with previous studies that reported a higher prevalence of migraine in patients with PSS compared with controls. An earlier study found migraine in 46% of patients with PSS, a significantly higher rate than in healthy control subjects [14]. However, that study made the diagnosis of PSS based on subjective and objective mouth dryness phenomena; they did not investigate auto-antibodies and/or salivary gland biopsies. Therefore, that diagnosis did not comply with current PSS criteria. In addition, that study assessed headache with a questionnaire modified from that described by Taylor *et al.* [15]. Recently, Gökcay *et al.* [16] reported an increased prevalence of migraine (54.2%) and also TTH (24.1%) in patients with PSS compared with healthy subjects. They used the ICHD-II criteria for headache and the AECC criteria for PSS. However, the patients with PSS in that study were 10 years younger (mean age 47.1 years) than the patients in our study (mean age 57.1 years), and they did not select healthy controls that were age- and gender-matched.

There are several possible explanations for our finding that chronic TTH occurred more often in patients with PSS than in healthy subjects. First, PSS patients had higher BDI and fatigue scores than the healthy subjects; this may have influenced the headache prevalence. However, in the patients with PSS, a logistic regression with FSS and BDI scores as independent variables failed to detect any association between chronic TTH and fatigue or depression. Furthermore, musculoskeletal symptoms are a common complaint in patients with PSS. A large cross-sectional study in Norway showed an association between chronic headache and musculoskeletal symptoms [17].

Also, according to ICHD-II, headache due to medication overuse has to be ruled out for a definite classification of chronic TTH. In three of our patients with PSS, medication overuse may have explained the chronic headache. In patients with PSS, TTH was not associated with BDI scores, fatigue scores, any laboratory data or PSS medication. Chronic headache is known to have a significant impact on quality of life. Further investigations are needed to address this issue in patients with PSS, because it has implications for both therapy and prophylactic measures.

Study limitations

A limitation of this study was the small sample size. Furthermore, we did not use headache diaries, but relied on retrospective headache reports. In addition, a bias may have been introduced in the selection process for the control group; because the healthy subjects had less depression and fatigue, one might expect fewer headaches, in general, compared with patients with PSS.

The strengths of this study are: a population-based approach with identification of all PSS patients within a limited geographic area, age- and gender-matched healthy control subjects, and the classification of headaches according to ICHD criteria. Also, the classifications were performed by the same neurologist, based on personal interviews with neutral screening questions. Also, the prevalence of headache in the healthy subjects was in accordance with findings in a large epidemiological headache report [13].

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Conflicts of interest

The authors declare no financial or other conflicts of interest.

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Paper III
High headache-related disability in patients with systemic lupus erythematosus and primary Sjögren's syndrome

III

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High headache-related disability in patients with systemic lupus erythematosus and primary Sjögren's syndrome

A. B. Tjensvoll[a], L. G. Gøransson[b], E. Harboe[b], J. T. Kvaløy[c,d] and R. Omdal[b]

[a]*Department of Neurology, Stavanger University Hospital, Stavanger;* [b]*Department of Internal Medicine, Stavanger University Hospital, Stavanger;* [c]*Division of Research and Human Resources, Stavanger University Hospital, Stavanger; and* [d]*Department of Mathematics and Natural Sciencies, University of Stavanger, Stavanger, Norway*

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Background and purpose: It is often argued that patients with systemic lupus erythematosus (SLE) have more headaches than healthy subjects, but this association remains controversial. Thus the magnitude and severity of headaches in SLE were evaluated in comparison with another autoimmune disease, namely primary Sjögren's syndrome (pSS).

Methods: Sixty-seven patients with SLE, 71 pSS patients and 108 healthy subjects were included. The International Classification of Headache Disorders, Headache Impact Test-6 (HIT-6), and the Migraine Disability Assessment (MIDAS) questionnaire were used to classify and assess headache-related disability.

Results: Primary headaches were more prevalent in SLE patients than in healthy subjects (82% vs. 69%, $P = 0.01$). Amongst the headache sufferers, SLE patients ($N = 55$) and pSS patients ($N = 51$) had higher HIT-6 scores (median 51, range 36–67, and median 54, range 36–72, respectively) than healthy subjects ($N = 69$) (median 46, range 36–72; $P = 0.02$ and $P = 0.0009$, respectively). Also, MIDAS scores were higher in SLE (median 0, range 0–110) and pSS patients (median 1, range 0–40) than in healthy subjects (median 0, range 0–10; $P = 0.04$ and $P = 0.003$, respectively).

Conclusion: Patients with SLE and pSS have a higher burden from headaches and more severe headaches than headache sufferers without these diseases. However, evidence of a specific bothersome SLE headache was not possible to identify as the headaches had the same characteristics and similar impact and severity in pSS patients. Depressive mood significantly influenced headache severity.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that can affect almost any organ in the body. The aetiology is largely unknown, but predisposing gene variants and environmental factors, such as UV light, infections and drugs, are important pathogenetic factors [1].

SLE frequently includes neurological involvement, and amongst the central nervous system (CNS) manifestations of SLE, headache has traditionally been considered common and even has a strong weight in the SLE disease activity index (SLEDAI) [2]. The concept 'lupus headache' is defined in the British Isles Lupus Assessment Group 2004 index as a disabling headache that is unresponsive to narcotic analgesia and lasts ≥3 days, and by the American College of Rheumatology (ACR) criteria as a severe, persistent headache that 'may be migraineous, but must be nonresponsive to narcotic analgesia' [3,4]. This type of headache is one of the 19 neuropsychiatric syndromes regarded as part of the SLE disease spectrum [5]. However, some studies have questioned both the claimed prevalence and the severity of headache in SLE [6,7]. These headache issues seem to have gained little attention in other autoimmune diseases.

Primary Sjögren's syndrome (pSS) is another autoimmune disease mainly affecting the exocrine glands and accompanied by dryness of the mouth and eyes, fatigue, and migrating muscle and joint pain. Although it is regarded as a distinct disease, pSS shares several genetic, immunological and clinical features with SLE [8], and both the peripheral nervous system and CNS are frequently involved [9,10].

Correspondence: A. B. Tjensvoll, Department of Neurology, Stavanger University Hospital, pb 8100 Forus, N-4068 Stavanger, Norway (tel.: +47 05151/+47 95731813; fax: +47 51519916; e-mail: tjab@sus.no).

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A number of studies have investigated neurological involvement in pSS, but very few have focused on headache [11,12].

With the strong impact headache has traditionally had in SLE and the possibility that this could represent a myth [13], it is remarkable that no systematic review has explored the impact of headache or tried to quantitate the 'burden of headache' in this condition. Because validated neurological tools are available for assessing these matters, our aim was to investigate whether headache has a greater impact on SLE patients' lives than in the normal population and to compare it with another distinct autoimmune disease, namely pSS.

Patients and methods

SLE patients

Stavanger University Hospital serves a population of 310 000 inhabitants and all patients with systemic autoimmune diseases are allocated to this hospital. A total of 86 patients, all Caucasian, fulfilled the 1982 revised ACR criteria for SLE [14]. Informed consent to participate in the study was provided by 70 patients (81%). One patient with a brain tumour and two patients who withdrew their consent were excluded from the study. Therefore, 67 patients were identified for the study (SLE full group).

Fifty-five (82%) of the 67 patients with SLE reported having a headache (primary) during the last 12 months and were included in the headache impact analysis. Demographic and selected data for the SLE headache group are given in Table 1. In this group, 45 patients (82%) used medication for SLE, eight (15%) used antimalarial medication, eight (15%) used prednisolone only, one patient received intravenous cyclophosphamide infusions and 29 patients (53%) were on combination medication. Twenty-two SLE patients (40%) used cardiovascular medication and nine (16%) were on beta-blockers.

pSS patients

Seventy-two (73%) of the 99 patients who fulfilled the American European Consensus Criteria for pSS gave informed consent to participate in the study [15]. One patient was excluded due to a brain tumour. Thus, 71 patients were included in the study (pSS full group).

Fifty-one (72%) of the 71 pSS patients reported having a headache during the previous year and were included in the pSS headache group. Demographic and other relevant data for this group are provided in Table 1. Twenty-four (47%) pSS patients were on medication for pSS, 12 patients (24%) used antimalarials, one used prednisolone only, one received intravenous cyclophosphamide and 10 patients (20%) were on combination medication. Thirteen pSS patients (25%) used cardiovascular medication, including two (4%) on beta-blockers.

Table 1 Demographic and other select data in headache group patients and healthy subjects

Subjects	SLE $N = 55$	pSS $N = 51$	Healthy subjects $N = 69$
Female–male, %	87–13	82–18	87–13
Mean age ± SD, years	43.3 ± 13.9	53.8 ± 12.4	46.7 ± 12.6
Disease duration, years	11.0; 0.5–29.0	6.1; 0.4–24.1	NA
SLEDAI	2.0; 0–26	NA	NA
SLICC	2.0; 0–8	NA	NA
BDI	8.0; 0.0–27.0	9.0; 0.0–29.0	2.0; 0.0–16.0
MSG biopsy, focus score ≥1	NA	40/50[a] (80%)	NA
ANA	53/55 (96%)	46/51 (90%)	NA
anti-DNA ab	30/55 (55%)	1/51	NA
aPL	19/55 (35%)	6/51 (12%)	NA
anti-SSA ab	16/55 (29%)	41/51 (80%)	NA
anti-SSB ab	9/55 (16%)	22/51 (43%)	NA

Data are given as median; range or proportions unless otherwise noted. SLEDAI, SLE disease activity index [2]; SLICC, Systemic Lupus International Collaborating Clinics/ACR damage index [16]; BDI, Beck Depression Inventory score [21]; MSG, minor salivary gland; ANA, antinuclear antibodies; aPL, anti-phospholipid antibodies; ab, antibodies; SSA, Sjögren's syndrome A antigen; SSB, Sjögren's syndrome B antigen.
[a]The MSG biopsy was inconclusive in one patient due to insufficient biopsy volume.

Healthy subjects

A total of 108 healthy subjects with no immunological, neurological or malignant diseases served as control subjects and were recruited amongst the friends and neighbours of the patients and the friends, friends of friends, and neighbours of hospital staff (healthy subjects, full group). In this group, 69 persons (64%) had experienced a headache in the last year and constituted the healthy subjects headache group, Table 1.

Clinical evaluation

All patients and healthy subjects were subjected to a 2-day stay at the hospital for research purposes only and were examined by an experienced internist (EH) and experienced neurologist (ABT). Disease activity in the SLE patients was assessed by the SLEDAI and cumulative organ damage by the Systemic Lupus International Collaborating Clinics/ACR damage index [16]. Headaches were diagnosed and classified

according to the International Classification of Headache Disorders (ICHD II) criteria using a structured interview with a neutral opening screening question about having had a headache during the last year [17]. Headache status was defined as one or more headache attacks during the last year. The structured interview included a detailed neurological and headache history covering relevant information necessary to diagnose and classify headaches and differentiate them from other neurological conditions. Secondary headaches considered to be due to conditions or diseases other than SLE or pSS were excluded. 'Migraine' and not 'migraine-like' or 'migraineous headache' was used, because the criteria A–D in the ICHD classification of migraine were fulfilled outside the context of an SLE disease flare and not attributed to another disorder.

The impact of headache was assessed using the Migraine Disability Assessment (MIDAS) questionnaire and the Headache Impact Test-6 (HIT-6) [18,19]. MIDAS assesses headache-related disability over a 3-month period due to activity limitations or lost time in three domains (paid work or school, household work and non-work activities), whereas HIT-6 measures the headache impact during the previous 4-week period. HIT-6 is considered a more global assessment of headache impact that also takes into account fatigue, mood and pain severity [20]. Both questionnaires assess headache in general, categorizing headache impact into four severity grades: minimal (grade I), mild (grade II), moderate (grade III) and severe (grade IV). Headache disability is considered moderate or severe (grades III–IV) for MIDAS scores >10 and HIT-6 scores >55. The questionnaires were answered by the patients and healthy subjects during the headache interview. Subjects were asked to rate the headache type they considered most bothersome if having more than one type. Depression was assessed by the Beck Depression Inventory (BDI) [21].

Laboratory analyses

Routine haematological, biochemical and immunological tests were performed in the hospital's routine laboratories as described previously [10].

Statistical analysis

Continuous data are reported as mean ± SD when normally distributed, otherwise as median and range. Categorical data are reported as numbers and percentages. The ANOVA F test was used to compare independent continuous data between groups when normally distributed (i.e. age). The Kruskal–Wallis test was used to compare independent continuous data between groups when not normally distributed, and the Mann–Whitney U test without correction for multiple testing for *post hoc* analysis. Logistic regression was used to test for risk factors for headache impact with headache impact as the dependent categorical variable (MIDAS >10, HIT-6 > 55) and age, gender, BDI score and headache group (SLE, pSS and healthy subjects) as the independent variables. Linear regression was also used to test for risk factors for total HIT-6 score as these scores were normally distributed. The chi-squared test was used to compare categorical data. $P < 0.05$ was considered significant.

The study complied with the Helsinki Declaration and was approved by the Regional Research Ethics Committee.

Results

Demographics and headache impact

Post hoc analysis revealed that pSS patients were older than healthy subjects ($P = 0.004$) and SLE patients ($P < 0.0001$), but no difference was found between SLE patients and healthy subjects ($P = 0.15$; Table 1). The prevalence of headache and headache category in the three full groups of subjects are given in Table S1 and amongst the headache sufferers (SLE, pSS and healthy subjects) in Fig. 1. Headache prevalences differed between the full groups of subjects, *post hoc* analyses revealing more headaches in SLE patients compared with healthy subjects (82% vs. 64%, $P = 0.01$). No differences existed between SLE and pSS patients or pSS and healthy subjects. MIDAS and HIT-6 scores are shown in Fig. 2, and categorization by impact grades I–II (minimal, mild) versus III–IV (moderate, severe) is shown in Figs 3 and 4. The impact data in headache subtypes in SLE and pSS

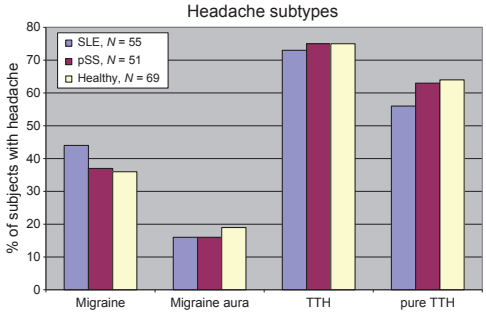

Figure 1 Headache categories in SLE, pSS and healthy subjects with headache. SLE, systemic lupus erythematosus; pSS, primary Sjögren's syndrome; TTH, tension type headache.

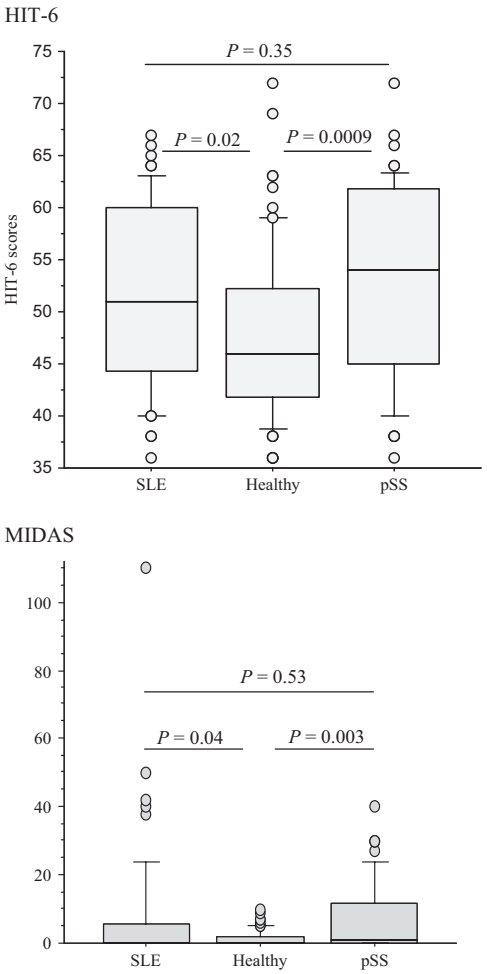

Figure 2 Boxplot of headache-related disability in SLE, pSS and healthy subjects. Whiskers indicate the 10–90 percentiles. HIT-6, Headache Impact Test-6; MIDAS, Migraine Disability Assessment; SLE, systemic lupus erythematosus; pSS, primary Sjögren's syndrome.

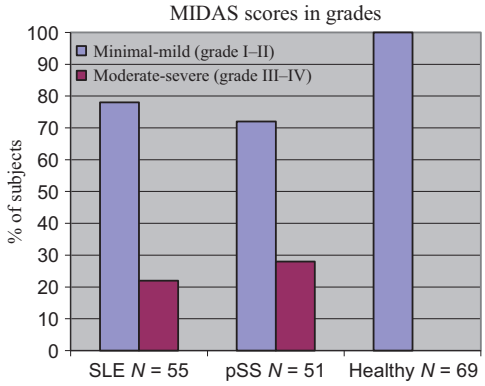

Figure 3 Severity of headaches assessed with MIDAS scores in SLE, pSS and healthy subjects. MIDAS, Migraine Disability Assessment; SLE, systemic lupus erythematosus; pSS, primary Sjögren's syndrome.

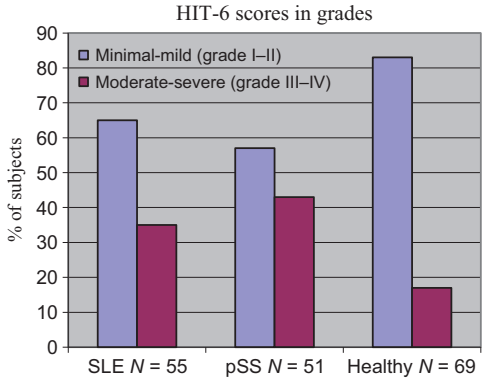

Figure 4 Severity of headaches assessed with HIT-6 scores in SLE, pSS and healthy subjects. HIT-6, Headache Impact Test-6; SLE, systemic lupus erythematosus; pSS, primary Sjögren's syndrome.

patients and healthy subjects are shown in Table 2. No associations between headache impact and autoantibodies or medication for SLE or pSS were found (data not shown).

Comparisons between subject groups with headache

MIDAS scores (Fig. 2) were different between the three groups ($P = 0.011$). *Post hoc* analysis revealed higher MIDAS scores in the SLE (median 0, range 0–110) and pSS patients (median 1.0, range 0–40) compared with healthy subjects (median 0, range 0–10; $P = 0.04$ and $P = 0.003$, respectively). No difference was found between the SLE and pSS groups.

HIT-6 scores (Fig. 2) were also different between the three groups ($P = 0.003$). *Post hoc* analysis revealed higher scores in SLE (median 51, range 36–67) and pSS patients (median 54, range 36–72) compared with healthy subjects (median 46, range 36–72; $P = 0.02$ and $P = 0.0009$). No difference was found between SLE and pSS patients.

Table 2 Headache-related disability in SLE, pSS and healthy subjects based on headache categories

	SLE, $N = 55$			pSS, $N = 51$			Healthy subjects, $N = 69$		
	Migraine	Pure TTH	*P*	Migraine	Pure TTH	*P*	Migraine	Pure TTH	*P*
No. of subjects	24/55	31/55	NA	19/51	32/51	NA	25/69	44/69	NA
MIDAS score	7.5; 0–110	0.0; 0–9	0.0007	2.0; 0–30	0.0; 0–40	0.33	2.0; 0–9	0.0; 0–10	0.002
MIDAS III–IV	12/24 (50%)	0	0.0001	7/19 (37%)	7/32 (22%)	0.25	0	0	
HIT-6 score	60.5; 36–67	46.0; 38–62	0.0001	57.0; 42–72	50.0; 36–67	0.03	53.0; 40–72	44.0; 36–58	<0.0001
HIT-6 III–IV	15/24 (63%)	4/31 (13%)	0.0002	12/19 (63%)	10/32 (31%)	0.03	10/25 (40%)	2/44 (5%)	0.0004

Data are given as median; range or proportions unless otherwise noted. SLE, systemic lupus erythematosus; pSS, primary Sjögren's syndrome; TTH, tension type headache; MIDAS, Migraine Disability Assessment; HIT-6, Headache Impact Test-6; III–IV, moderate to severe grades of headache impact.

The number of subjects with moderate to severe headache impact based on MIDAS scores (grades III–IV) was different between the three headache groups ($P < 0.0001$). In *post hoc* analysis the SLE patients had more moderate to severe headache disability compared with healthy subjects (22% vs. none with grades III–IV, $P < 0.0001$). The same was found for pSS patients (27% vs. none, $P < 0.0001$). No difference in MIDAS grades III–IV was found between SLE and pSS patients ($P = 0.50$, Fig. 3).

The moderate to severe headache impact according to HIT-6 scores was different between groups ($P = 0.007$). *Post hoc* analysis revealed that more SLE patients had impact grades III–IV compared with healthy subjects (35% vs. 17%, $P = 0.03$) and more pSS patients had grades III–IV compared with healthy subjects (43% vs. 17%, $P = 0.002$). No difference in HIT-6 grades III–IV was found between SLE and pSS patients ($P = 0.36$, Fig. 4).

Depression

BDI scores were different between groups ($P = 0.0001$, Table 1). *Post hoc* analysis revealed higher BDI scores in SLE and pSS patients compared with healthy subjects ($P < 0.0001$ for both), but no difference was found between SLE and pSS patients ($P = 0.21$).

In a backward stepwise regression analysis including gender, age, BDI score and headache group as independent variables and MIDAS score >10 (grades III–IV) as the dependent variable, differences between groups disappeared when adjusting for BDI and age. On adjusting for BDI in a logistic regression model with HIT-6 score >55 as the dependent variable, differences between groups again disappeared. In a stepwise linear regression model for HIT-6 scores, differences between groups disappeared when adjusting for depression, age and gender. The differences also disappeared when adjusting only for BDI.

Discussion

This study confirms previous reports of headaches, particularly migraines, being common in patients with SLE. The new finding in this study is that the burden of headache, or the impact of headache on patients' lives, is considerably higher in SLE patients with headache than otherwise healthy subjects who also suffer from headaches. This finding supports the concept of headache as a strong and influential phenomenon in SLE as previously argued by several authors. Using validated headache impact

instruments, it was found that SLE patients have both more headache-related disability and greater severity of disability (severity grade).

A somewhat surprising finding was that patients with pSS reported a similar impact of headache on their lives as SLE patients. Both the magnitude and severity of impact were identical in these two diseases and considerably higher than in 'healthy' headache sufferers.

Depression influences headache-related disability, and the SLE patients experienced more depression than healthy subjects [22]. Thus, a more depressive state may partly explain the high ranking that headaches have traditionally had in SLE patients, in our study illustrated by the high impact. Using specific questionnaires for headache-related disability, our findings are in accordance with a recently reported large international inception cohort study that found an association between headache and health-related quality of life [23]. Thus, high headache-related disability in SLE and pSS patients may reflect the burden of chronic disease, although a biological mechanism such as intrathecal cytokine effect cannot be ruled out [24].

As in the general population, SLE patients with migraine had more headache-related disability than those with non-migraine headache [25]. However, the proportion of migraines amongst headache sufferers was similar in SLE and pSS patients and healthy subjects; therefore, it cannot explain the greater headache impact in patients compared with healthy subjects.

Our data indicate that the headache issue in SLE may be explained, at least in part, by the influence of co-factors such as depression and does not represent a specific CNS manifestation of SLE. However, this finding was not specific for the SLE patients; the same influence on headache impact appeared in pSS patients.

Study limitations

The study has some limitations. First, the sample size was small. Second, a lack of headache diaries may have led to recall bias. Third, employment and education status was not systematically recorded. MIDAS scores are highly influenced by work and school status. Many patients do not work due to disease, and this may have resulted in lower MIDAS scores reported by the patients.

The strengths of the study are a near population-based approach with identification of all SLE and pSS patients within a limited geographical area; classification of SLE, pSS and headache according to international criteria; and the assessment of headache-related disability using valid and reliable tools for impact measures. Furthermore, the same neurologist performed personal interviews with the neutral screening question and headache classifications, and impact questionnaires were filled out during the interview.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Headache prevalence in SLE, pSS and healthy subjects (full groups)

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Paper IV
Migraine in patients with systemic lupus erythematosus is associated with reduced cerebral gray matter volume but not with measures of glial activation or anti-NR2 or anti-P antibodies

IV

EUROPEAN JOURNAL OF NEUROLOGY

ORIGINAL ARTICLE

Migraine in patients with systemic lupus erythematosus is associated with reduced cerebral grey matter volume but not with measures of glial activation or anti-NR2 or anti-P antibodies

A. B. Tjensvoll[a], M. B. Lauvsnes[b], S. Hirohata[c], M. K. Beyer[d], O. J. Greve[e], I. Kvivik[f], J. T. Kvaløy[g,h], E. Harboe[b], L. G. Gøransson[b,i] and R. Omdal[b,i]

[a]*Department of Neurology, Stavanger University Hospital, Stavanger;* [b]*Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway;* [c]*Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Tokyo, Japan;* [d]*Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo;* [e]*Department of Radiology, Stavanger University Hospital, Stavanger;* [f]*Department of Pathology, Stavanger University Hospital, Stavanger;* [g]*Division of Research and Human Resources, Stavanger University Hospital, Stavanger;* [h]*Department of Mathematics and Natural Sciences, University of Stavanger, Stavanger; and* [i]*Department of Clinical Science, University of Bergen, Bergen, Norway*

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Background and purpose: Migraine is frequent in patients with systemic lupus erythematosus (SLE), but the pathogenesis and pathophysiology are poorly understood. Migraine is assumed to be a consequence of abnormal neuronal excitability. Based on the hypothesis that the threshold for migraine is lower in SLE patients due to cerebral disturbances, whether structural abnormalities of the brain or relevant biomarkers are associated with headaches in SLE was investigated.

Methods: Sixty-seven SLE patients and age- and gender-matched healthy subjects participated. Volumes of grey matter (GM) and white matter (WM) were estimated from cerebral magnetic resonance images with SPM8 software. Anti-NR2 and anti-P antibodies and protein S100B were measured in cerebrospinal fluid.

Results: In regression analyses, larger GM volumes in SLE patients reduced the odds for headache in general [odds ratio (OR) 0.98, $P = 0.048$] and for migraine in particular (OR 0.95, $P = 0.004$). No localized loss of GM was observed. Larger WM volumes in patients increased the odds for migraine (OR 1.04, $P = 0.007$). These findings could not be confirmed in healthy subjects. Neither anti-NR2 and anti-P antibodies nor S100B were associated with headaches in SLE patients.

Conclusions: Systemic lupus erythematosus patients with migraine have a diffuse reduction in GM compared to patients without migraine. This finding was not observed in healthy subjects with migraine, and selected biomarkers did not indicate specific pathophysiological processes in the brain. These findings indicate that unknown pathogenic processes are responsible for the increased frequency of migraine in SLE patients.

Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that may influence the brain through various mechanisms. Headache, especially migraine, is frequent and constitutes part of the neuropsychiatric SLE syndromes (NPSLEs) thought to be specific manifestations of the disease [1]. The so-called 'lupus headache' is defined as a severe, persistent headache that 'may be migrainous, but must be non-responsive to narcotic analgesia' [2]. Whether such a headache really exists is debated. In a recent controlled study, considerably more migraine was observed in SLE patients than in healthy subjects

Correspondence: A. B. Tjensvoll, Department of Neurology, Stavanger University Hospital, pb 8100 Forus, N-4068 Stavanger, Norway (tel.: +47 05151/+47 95731813; fax: +47 51519916; e-mail: anne.tjensvoll@lyse.net).

[3], in line with the results of previous studies [4,5]. However, why migraine should be more common in SLE patients is not clear.

Migraine is a disorder characterized by an imbalance in neuronal excitability, and it affects several regions in the brain [6]. It is possible that the threshold for migraine may be lower in SLE patients because of immunological, biochemical or structural disturbances. Several brain abnormalities, such as white matter (WM) hyperintensities, infarcts and loss of grey matter (GM), have been documented in magnetic resonance imaging (MRI) studies of SLE patients [7–9]. A recent meta-analysis reported similar structural abnormalities in migraine patients in the general population [10].

The NR2 subunit type of the *N*-methyl-D-aspartate (NMDA) receptor is considered to have a significant role in migraine [11]. Some patients with autoimmune diseases develop antibodies to NR2 subunits. These antibodies cause prolonged opening of the NMDA receptor ion channel on the postsynaptic membrane and lead to continuous depolarization with excessive Ca^{2+} influx into the cell [12]. This is followed by neuronal dysfunction and eventually cell death [13]. In humans, anti-NR2 antibodies are associated with cognitive dysfunction and mental depression, as well as loss of hippocampal GM, in patients with SLE and in those with primary Sjögren's syndrome [14–16]. One might therefore speculate that anti-NR2 antibodies contribute to neuronal dysfunction in the brains of patients with lupus and thereby increase migraine susceptibility.

Antibodies against ribosomal P proteins (anti-P antibodies) constitute another pathogenic antibody that occurs in patients with SLE. Previous studies have reported associations between anti-P antibodies and NPSLE, especially psychosis, in SLE patients [17,18]. Moreover, this antibody binds to neurons and leads to influx of Ca^{2+} and neuronal dysfunction or apoptosis [19]. It is therefore an obvious candidate for involvement in cerebral disturbances and lowering of the migraine threshold in SLE patients.

Astroglial cells play an active role in regulating and controlling synaptic transmission and in providing an optimal environment for neuronal functioning [20]. The subtype of astroglial cells in intimate contact with cerebral blood vessels secretes protein S100B when activated in response to damage or homeostatic disturbances. Vasculopathy and endothelial activation in cerebral blood vessels, as well as other immune and inflammatory stressors, in SLE patients could influence astroglial function and lead to increased concentrations of S100B in cerebrospinal fluid (CSF), as was observed in a previous study of patients with NPSLE [21].

To further elucidate potential mechanisms for the high prevalence of migraine in SLE patients, it was investigated whether structural, immunological or biochemical abnormalities in the brain, as revealed by MRI imaging and detection of anti-NR2 antibodies, anti-P antibodies and protein S100B in CSF, were associated with migraine or any other headaches in SLE.

Patients and methods

The overall recruitment period of patients and healthy subjects took place from 2003 to 2006. The study complied with the Helsinki Declaration and was approved by the Regional Research Ethics Committee. Written informed consent was obtained from all participants.

Systemic lupus erythematosus patients

Nearly all patients with SLE in Rogaland County, Norway, are allocated to Stavanger University Hospital. This study can thus be regarded as close to population based. Eighty-six patients, all Caucasian, fulfilled the 1982 revised American College of Rheumatology (ACR) criteria for SLE, and 70 patients (81%) consented to participate in the study. Three patients were excluded: two patients withdrew their consent, and one was excluded because of a brain tumor. Thus, 67 patients were included. Selected demographic, clinical and laboratory data are shown in Table 1.

Sixty-two patients completed cerebral MRI scanning; two were excluded from analyses due to poor image quality, and seven were excluded due to cortical infarcts. Thus, 53 SLE patients were eligible for the part of the study that included MRI scans. Cerebral MRI scanning was performed within 11.7 ± 10.6 days (median 9.0, range 2–75 days) following the clinical examination.

Healthy subjects

Age- (±2 years) and gender-matched subjects without immunological, neurological or malignant diseases were recruited from hospital staff, friends and neighbors of hospital staff and unrelated friends and neighbors of the patients. The healthy subjects whose corresponding SLE patients had ineligible MRI scans were excluded from the MRI analyses. None had cortical infarcts. MRI scanning in the healthy subjects was performed within 19.9 ± 29.2 days (median 16.0, range 39–87 days) following the clinical examination.

Table 1 Selected demographic and clinical data in SLE patients and healthy subjects

	SLE patients (N = 67)	Healthy subjects (N = 67)	P value
Women/men (%)	58/9 (87/13)	58/9 (87/13)	
Age, years	42.4 (20–76)	42.4 (21–77)	
SLEDAI, scores	2.0 (0–26)	NA	NA
SLICC-DI, scores	2.0 (0–11)	NA	NA
Disease duration, years	11.0 (1–32)	NA	NA
ANA (%)	65 (97)	NA	NA
Anti-DNA ab (%)	35 (52)	NA	NA
aPL (%)	26 (39)	NA	NA
Anti-NR2 ab in CSF[a]	0.38 (0.1–2.2)	NA	NA
Anti-P ab in CSF, μg/ml[b]	<0.001 (<0.001–0.13)	NA	NA
S100B in CSF, pg/ml[c]	221 (110–420)	NA	NA
BDI scores	6.0 (0–27)	2.0 (0–9)	<0.0001
Fatigue VAS scores	49.0 (1–980)	12.0 (1–72)	<0.0001
Arterial hypertension	34 (51%)	19 (28%)	0.001
Present use of			
Corticosteroids	44 (66%)	NA	NA
Antimalarials	34 (51%)	NA	NA
No SLE drugs	12 (18%)	NA	NA

SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; SLICC-DI, Systemic Lupus International Collaborating Clinics/ACR damage index; ANA, antinuclear antibodies; ab, antibodies; aPL, anti-phospholipid ab; CSF, cerebrospinal fluid; BDI, Beck Depression Inventory; VAS, visual analogue scale. Arterial hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Data are given as median (range) or proportions. [a]N = 52, value given as a ratio of signal against an internal calibrator with defined signal intensity; [b]N = 51; [c]N = 50.

Clinical evaluation

All patients and healthy subjects were clinically examined by an experienced internist (EH) and a neurologist (ABT). Headaches were classified according to the International Classification of Headache Disorders (ICHD II) criteria by means of a structured interview [22]. The presence of headache was defined as one or more headache attacks during the last year. The Beck Depression Inventory (BDI) [23] was used to assess depression, and fatigue was assessed by a fatigue Visual Analogue Scale (fVAS). Arterial hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. Investigations were performed during a 2-day stay in the hospital for research purposes only.

Laboratory analyses

Routine hematological, biochemical and immunological analyses were performed in the hospital's routine laboratory. CSF samples were obtained between 1 and 2 p.m. by lumbar puncture in 52 SLE patients (78%) who agreed to undergo this procedure. Samples were immediately placed on ice and centrifuged at 4°C at 3000 g for 10 min. Supernatants were immediately aliquoted and frozen at −70°C until analysis.

Screening for antinuclear antibodies was performed with the HEp-2000 assay (Immunoconcepts, Sacramento, CA, USA), and the presence of anti-double-stranded (ds) DNA was confirmed by enzyme-linked immunosorbent assay (ELISA) with the QUANTA Lite ENA 6 assay (Inova Diagnostics, San Diego, CA, USA). Anti-dsDNA antibodies were verified by Nova Lite dsDNA *Crithidia luciliae* 708 200 indirect immunofluorescence assay (Inova Diagnostics). Anti-phospholipid antibodies were considered positive if the patients had a positive anti-cardiolipin immunoglobulin M (IgM) or IgG antibody test, were lupus-anticoagulant positive or any combination of these. Anti-cardiolipin IgM and IgG and lupus anticoagulant were measured as previously described [3]. Anti-NR2 antibodies in CSF were analyzed by electrochemiluminescence as previously described [16]. Protein S100B was analyzed in CSF with the Human S100B ELISA kit (Abnova, Jhongli City, Taiwan) according to the manufacturer's instructions. Anti-P antibodies in CSF were analyzed as previously described [17].

Magnetic resonance image acquisition and preprocessing

All subjects were examined with a 1.5-T Philips Gyroscan NT Intera Release 10 (Philips Medical Systems, Best, The Netherlands). MRI images were preprocessed using default settings in the VBM8 extension (Gaser, http://dbm.neuro.uni-jena.de/vbm/download/) of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). The MRI protocol and details regarding the preprocessing of MRI images have been described previously [24]. Global GM and WM volumes for each individual were estimated with the VBM8 tool.

The two-sample t test in SPM8 was applied to compare GM volumes voxel-wise between SLE patients with and without any headache and between those with and without migraine in order to reveal potential localized GM loss. All voxels with a <10% probability of being GM were excluded to avoid possible edge effects between different tissue types. Family-wise error correction was applied for multiple testing, and $P < 0.05$ was used as the significance threshold.

Statistics

Continuous data are reported as mean ± SD when normally distributed; otherwise as median and range.

Categorical data are reported as numbers and percentages. McNemar mid-*P* test was used to compare pairwise categorical data [25]. Global GM and WM volumes, BDI and fVAS scores in SLE patients and healthy subjects were compared by paired-sample statistics. Correction for family-wise error was not performed. Univariable logistic regression analyses were used to test for possible explanatory variables for headache and headache subtypes. Variables with *P* values ≤0.25 in univariable analyses and variables thought to be of clinical interest regardless of their *P* values were then tested in multivariable logistic regression analyses. Forward and backward stepwise model selections were performed. Goodness-of-fit of the models was checked by the Hosmer and Lemeshow test, Cook distance plots and standardized residuals. Three models were established where dependent variables were all headaches, migraine and pure tension-type headache (TTH). Predictors in all three models were age, gender, GM volume, WM volume, BDI scores, fVAS scores, body mass index, anti-NR2 and anti-P antibodies, and protein S100B; all except gender were continuous variables. Variables that lacked significant effect, as determined by multivariable regression analysis, were excluded from the final models with the exception of age and gender, which were regarded as important variables regardless of their significance level. A *P* value of <0.05 was considered significant.

Results

Headache prevalence in the 67 SLE patients and matched healthy control subjects are shown in Fig. 1. Twenty-four SLE patients had migraine; nine of these had migraine with aura. Headache prevalence in the matched groups with eligible MRI scans ($N = 53$) are shown in Table 2. Four out of the 53 SLE patients with eligible MRI scans and two healthy subjects had lacunar infarcts. There were no differences in GM or WM volumes between the patients and the matched healthy subjects (Table 3). Anti-NR2 and anti-P antibodies were analyzed in CSF in 52 and 51 patients, respectively, and S100B in 50 patients. Numbers of analyzed patients in the different headache groups are shown in Fig. 2. Brain volumes, presence of antiphospholipid antibodies, and levels of anti-NR2 and anti-P antibodies and S100B in the different headache groups are shown in Table 4.

There were no associations between headaches and routine immunological variables such as antinuclear antibodies, anti-DNA, anti-SSA/SSB and anti-phospholipid antibodies. Anti-NR2 and anti-P antibodies, S100B, fVAS and BDI scores and body mass indices

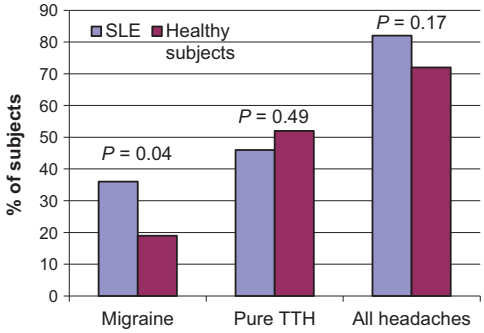

Figure 1 Headache in 67 SLE patients and 67 matched healthy subjects. SLE, systemic lupus erythematosus; TTH, tension-type headache.

Table 2 Headache and arterial hypertension in SLE patients with eligible MRI scans and matched healthy subjects

	SLE patients ($N = 53$)	Healthy subjects ($N = 53$)	*P* value
All headaches	44 (83%)	39 (74%)	0.24
Migraine	19 (36%)	11 (21%)	0.08
Pure TTH	25 (47%)	28 (53%)	0.56
Arterial hypertension	24 (45%)	16 (30%)	0.11

SLE, systemic lupus erythematosus; MRI, magnetic resonance imaging; TTH, tension-type headache. Arterial hypertension, systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg.

Table 3 Brain volumes in SLE patients and healthy subjects

	SLE patients ($N = 53$)	Healthy subjects ($N = 53$)	*P* value
TIV	1347 (1140–1651)	1387 (1155–1639)	0.13
GM volume	556 (450–680)	562 (466–657)	0.36
GM volume/TIV	0.41 (0.36–0.46)	0.41 (0.37–0.44)	0.16
WM volume	531 (410–679)	553 (406–711)	0.07
WM volume/TIV	0.40 (0.34–0.42)	0.40 (0.35–0.43)	0.18

SLE, systemic lupus erythematosus; TIV, total intracranial volume; GM, grey matter; WM, white matter. Volume (range) given in cm^3.

did not contribute significantly in the regression models and were thus not included in the final models for any of the headache categories. In the model including all headaches in SLE patients, increasing GM volumes decreased the odds for having headaches [odds ratio (OR) 0.98, $P = 0.048$]. Two patients were removed from this model due to standardized residuals of >3. In the model comparing SLE patients with and without migraine, increasing GM volumes reduced the odds for having migraine (OR 0.95, $P = 0.004$), whilst increasing WM volumes increased the odds for having migraine (OR 1.04, $P = 0.007$). No associations

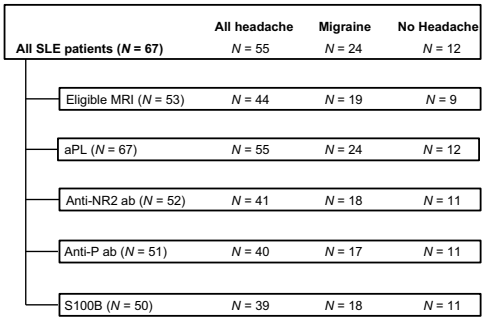

Figure 2 Numbers of analyzed patients in the headache groups. SLE, systemic lupus erythematosus; MRI, magnetic resonance imaging; aPL, anti-phospholipid antibodies; ab, antibodies.

between pure TTH in the SLE patients and brain volumes were revealed, nor any associations between headache and brain volumes in the healthy subjects (data not shown). No localized differences in GM volumes were revealed in voxel-wise comparisons between SLE patients and healthy subjects or between SLE patients with and without all headaches, migraine or TTH.

Discussion

Systemic lupus erythematosus patients with headaches, especially those with migraine, were found to have less cerebral GM compared to SLE patients without headaches. This finding could not be confirmed in the healthy control subjects. No localized loss of GM was found to be associated with headaches.

Global brain atrophy is common in patients with SLE, and GM loss in non-SLE patients suffering from major depression has been reported [26]. Although SLE patients had more depression than the healthy control subjects (Table 1), BDI scores did not affect the risk of headache. The influence of GM volume on headache in SLE patients persisted when adjustment was made for depression. Localized GM loss has been reported in patients with NPSLE and also in migraineurs in the general population [8,27]. However, in our study, the GM volume loss could not be localized to specific brain structures in the voxel-wise analyses.

A paradoxical finding was that SLE patients with migraine had larger WM volumes than patients without migraine. The association remained after adjusting for age, and more complex interactions could possibly be responsible for this.

Headaches were not associated with the presence of neuronal antibodies anti-NR2 and anti-P. Hence, our results do not support the hypothesis that immunological processes due to these antibodies are operative mechanisms.

Anti-phospholipid antibodies have been implicated as a pathogenic factor for non-thrombotic NPSLE in several studies, although conflicting results also exist [4,28]. In the present study, the presence of anti-phospholipid antibodies was not a significant predictor for headaches.

One possible cause of neuronal imbalance is dysfunction of glial cells. Astrocytes modify neuronal excitability and might become activated in SLE patients, as was previously observed in a study of patients with NPSLE [29]. Such a hypothesis could not be confirmed, as the concentration of S100B did not differ between SLE patients with or without migraine.

This study has some limitations. First, a larger sample of patients and healthy control subjects might have revealed effects that could not be detected by us. Secondly, concentrations of antibodies may fluctuate over time, and the cross-sectional design may have limited our ability to detect associations. Thirdly, headache diaries were not used and this may have led to recall bias. A bias may also have been introduced by using 1-year headache prevalence and not taking

Table 4 MRI and selected immunological data for SLE patients in the different headache groups

	All headaches, $N = 55$	Migraine, $N = 24$	No headaches, $N = 12$
GM volume	549 (450–680)	544 (450–633)	566 (516–675)
WM volume	523 (410–643)	512 (454–643)	533 (471–679)
aPL in serum	19/55 (35%)	7/24 (29%)	7/12 (58%)
Anti-NR2 ab[a,b]	0.37 (0.1–1.7)	0.33 (0.1–1.4)	0.44 (0.2–2.2)
Anti-P ab, μg/ml[a]	<0.001 (<0.001–0.08)	<0.001 (<0.001–0.04)	<0.001 (<0.001–0.13)
S100B, pg/ml[a]	228 (110–420)	222 (110–393)	190 (127–302)

MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; GM, grey matter; WM, white matter; aPL, anti-phospholipid antibodies; ab, antibodies. Data are given as median (range) or proportion unless otherwise noted. Volume (range) given in cm^3.
[a]Measured in CSF; [b]anti-NR2 antibody values are given as a ratio against an internal calibrator with defined signal intensity.

into account previous headaches that hypothetically might have influenced brain volume.

The strengths of the study include a near population-based, controlled and age- and gender-matched design, as well as headache assessment by structured interview with the same neurologist. In addition, cortical infarcts were excluded from analyses and validated methods for VBM analyses with conservative correction for multiple testing were used.

Our results indicate that unknown disease processes in patients with SLE result in GM loss and may increase headache and migraine susceptibility.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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