

Department of Neurology,
Helsinki University Central Hospital
University of Helsinki,
Faculty of Medicine
Helsinki, Finland

CERVICOCEREBRAL ARTERY DISSECTIONS – RISK FACTORS AND CLINICAL FEATURES

TIINA M. METSO

ACADEMIC DISSERTATION

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SUPERVISOR

Docent Turgut Tatlisumak, MD, PhD
Department of Neurology
Helsinki University Central Hospital
Helsinki, Finland

REVIEWERS

Professor Matti Hillbom, MD, PhD
Department of Neurology
University of Oulu
Oulu, Finland

Professor Pekka Jäkälä, MD, PhD
Institute of Clinical Medicine – Neurology
School of Medicine
University of Eastern Finland
Kuopio, Finland

OPPONENT

Professor Marie-Germaine Bousser, MD, PhD
Department of Neurology
Hôpital Lariboisière
Paris, France

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

- I Metso TM, Metso AJ, Helenius J, Haapaniemi E, Porras M, Salonen O, Hernesniemi J, Kaste M, Tatlisumak T. Prognosis and Safety of Anticoagulation in Intracranial Artery Dissections in Adults. *Stroke* 2007; 38:1837-1842.
- II Metso TM,* Metso AJ,* Salonen O, Haapaniemi E, Putaala J, Artto V, Helenius J, Kaste M, Tatlisumak T. Adult Cervicocerebral Artery Dissection: A Single-Center Study of 301 Finnish Patients. *European Journal of Neurology* 2009; 16:656-661.
- III Debette S, Metso TM, Pezzini A, Engelter ST, Leys D, Lyrer P, Metso AJ, Brandt T, Kloss M, Lichy C, Hausser I, Touzé E, Markus HS, Abboud S, Caso V, Bersano A, Grau A, Altintas A, Amouyel P, Tatlisumak T, Dallongeville J, Grond-Ginsbach C, on behalf of the CADISP-group. CADISP-genetics: a collaborative project searching for genetic risk factors of cervical artery dissections. *International Journal of Stroke* 2009; 4:224–230.
- IV Debette S*, Metso TM*, Pezzini A*, Abboud S*, Metso AJ, Leys D, Bersano A, Louillet F, Caso V, Lamy C, Medeiros E, Samson Y, Grond-Ginsbach C, Engelter ST, Thijs V, Beretta S, Béjot Y, Sessa M, Lorenza Muiesan M, Amouyel P, Castellano M, Arveiler D, Tatlisumak T, Dallongeville J, for the CADISP Group. Association of Vascular Risk Factors with Cervical Artery Dissection and Ischemic Stroke in Young Adults. *Circulation* 2011; 123:1537-1544.
- V Metso TM, Tatlisumak T, Debette S, Dallongeville J, Engelter ST, Lyrer PA, Thijs V, Bersano A, Abboud S, Leys D, Grond-Ginsbach C, Pezzini A, Metso AJ for the CADISP group. Migraine in Cervical Artery Dissection and Ischemic Stroke Patients. *Neurology* 2012; 78:1221-1228.

* Equal contribution

The thesis also contains some unpublished data.

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ABBREVIATIONS

BMI	body mass index
CADISP	Cervical Artery Dissection and Ischemic Stroke Patients
CD	combined dissection (intracranially extending dissection)
CeAD	cervicocerebral artery dissection
CI	confidence interval
CNG	Centre National de Genotypage
CRP	C-reactive protein
CT	computed tomography
CTA	computed tomography angiography
CTD	connective tissue disease
DM	diabetes mellitus
DSA	digital subtraction angiography
EAD	extracranial artery dissection
GWAS	genome-wide association study
IAD	intracranial artery dissection (=ID+CD)
ICA	internal carotid artery
ICAD	internal carotid artery dissection
ICAM	intercellular adhesion molecule
ID	pure intracranial artery dissection
IS	ischemic stroke
MA	migraine with aura
MO	migraine without aura
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
MTHFR	methylenetetrahydrofolate reductase
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio
SAH	subarachnoid hemorrhage
SSQOL	Stroke Specific Quality of Life Scale
TGF β R	transforming growth factor β receptor
TIA	transient ischemic attack
US	ultrasound
VA	vertebral artery
VAD	vertebral artery dissection
vEDS	vascular Ehlers Danlos syndrome

ABSTRACT

Cervicocerebral artery dissection (CeAD) is one of the leading causes of ischemic stroke in the young and middle-aged adults. Although the outcome is good in many CeAD patients, the socioeconomic consequences of stroke at young age may be remarkable. The knowledge about dissections is constantly growing, but most studies are based on small patient series.

Dissection is defined as a tear in the vessel wall, which may lead either to stenosis or occlusion of the artery via formation of a thrombus within the arterial wall, or to formation of a pseudoaneurysm. Most dissections occur in extracranial cervical arteries. Intracranial CeADs may lead to subarachnoid hemorrhage, and they have commonly been regarded a contraindication for anticoagulation, a common treatment for extracranial CeAD.

The pathophysiology of CeAD is poorly understood. CeAD patients probably have a constitutional, partly genetic weakness of the vessel wall, which predisposes to tears in the connective tissue within the vascular wall in occurrence of environmental triggers of the disease, such as acute infection, migraine, or minor trauma.

For this thesis project, we collected a register of all consecutive CeAD patients treated at the Helsinki University Central Hospital, Finland, between 1994 and 2008. In the first part of the thesis, we studied 103 patients with intracranial artery dissections (IAD). IADs could be divided into 2 distinct groups: i) non-aneurysmatic IADs presenting without subarachnoid hemorrhage that are associated with favorable outcomes and safe anticoagulant therapy, and ii) aneurysmatic IADs, characterized by subarachnoid hemorrhage and poorer prognosis.

Secondly, we evaluated characteristics, prognostic factors and vascular risk factors in 301 CeAD patients. We found association of CeAD with male sex, and possible association with smoking and migraine, especially migraine with aura. Stroke severity and recent infection were associated with poorer outcome.

The three other publications for the thesis were part of the CADISP project (Cervical Artery Dissection and Ischemic Stroke Patients), an international consortium focusing on research on CeAD. Its aims are to perform a genetic association study and clinical studies especially on risk factors, stroke-preventive treatment, and outcome predictors. For the clinical part of CADISP, 983 patients with CeAD, 658 patients with ischemic stroke due to causes other than dissection, and 1170 healthy control subjects were included in 8 countries and 18 centers. Our center contributed with 175 CeAD patients (18% of all CeAD patients), 168 ischemic strokes due to other causes (26%), and 269 healthy control subjects.

In the CADISP cohort, vascular risk factors were less frequent in CeAD patients compared with young patients with a non-CeAD ischemic stroke. In comparison with healthy controls, hypercholesterolemia, obesity, and overweight were less frequent in

CeAD patients, whereas CeAD patients had more hypertension. This suggests that hypertension may be a risk factor for CeAD.

Finally, migraine was more common in CeAD patients with stroke than in patients with ischemic stroke due to a cause other than CeAD. We detected no excess of ischemic strokes, specific arterial distribution or other clinical or prognostic features characteristic to migraineous CeAD patients compared to those without migraine.

TIIVISTELMÄ

Kaula- ja aivovaltimodissektoitumien riskitekijät ja taudinkuva

Kaula- ja aivovaltimodissektoituma on yleisimpiä aivoinfarktin aiheuttajia nuorilla ja keski-ikäisillä potilailla. Vaikka suurin osa sairastuneista toipuu hyvin, saattaa aivoinfarkti nuorella iällä aiheuttaa merkittävää ja pitkäaikaista haittaa. Dissektoitumia koskeva tutkimustieto lisääntyy jatkuvasti, mutta taudin harvinaisuuden vuoksi suurin osa julkaisuista on perustunut pieniin potilasmääriin.

Dissektoitumassa valtimon seinämään tulee repeämä, mikä voi johtaa verihyytymän kehittymiseen suonen seinämän sisään ja suonen ahtautumiseen tai tukokseen, tai pseudoaneurysman muodostumiseen. Kaula- ja aivovaltimodissektoituma sijaitsee yleensä kaulan alueen valtimoissa kallonulkoisesti, ja sen hoidossa käytetään yleisesti verenhennuslääkkeitä. Kallonsisäistä dissektoitumaa on pidetty vasta-aiheena verenhennuslääkkeille lisääntyneen lukinkalvonalaisen vuodon riskin takia.

Kaula- ja aivovaltimodissektoituman patofysiologia tunnetaan puutteellisesti. Potilailla ajatellaan olevan altistava valtimoseinämän sidekudoksen rakenteellinen heikkous, mahdollisesti geneettisistä syistä. Heikko seinämä on alttiimpi repeämälle, jonka laukaisee jokin tilapäinen tekijä kuten akuutti tulehdustauti, migreeni tai vähäpätöinen vamma.

Väitöskirjan kaksi ensimmäistä osatyötä perustuu Helsingin ja Uudenmaan sairaanhoitopiirin alueella vuosien 1994-2008 välisenä aikana hoidetuista kaula- ja aivovaltimodissektoitumapotilaista kerättyyn rekisteriin. Ensimmäisessä osatyössä oli mukana 103 kallonsisäisen dissektoituman sairastanutta potilasta. Nämä dissektoitumat jakaantuivat kahteen eri ryhmään: i) ei-aneurysmaattisiin kallonsisäisiin dissektoitumiin, jotka eivät johtaneet lukinkalvonalaiseen vuotoon, joiden ennuste oli hyvä, ja joiden hoidossa verenhennuslääkkeet olivat turvallisia. ii) Lukinkalvonalaiseen vuotoon johtaneisiin dissektoitumiin, joilla oli huono ennuste.

Toisessa osatyössä käsiteltiin kaula- ja aivovaltimodissektoitumapotilaiden taudinkuvaa, ennustetekijöitä ja riskitekijöitä 301 suomalaisen potilaan aineistossa. Enemmistö potilaista oli miehiä, ja dissektoitumapotilailla tupakointi ja migreeni, erityisesti aurallinen migreeni, olivat yleisiä. Vakava aivoinfarkti ja viimeaikaiset tulehdustaudit liittyivät huonompaan ennusteeseen.

Kolme muuta osatyötä ovat osa CADISP-projektia (Cervical Artery Dissection and Ischemic Stroke Patients). Tämän kansainvälisen kaulavaltimodissektoitumien tutkimukseen keskittyvän hankkeen tavoitteet ovat selvittää taudin geneettisiä ja muita riskitekijöitä, sen hoitoa ja ennustetekijöitä. CADISP-hankkeen kliiniseen osaan osallistui 8 maasta yhteensä 18 keskukselta 983 kaulavaltimodissektoitumapotilasta (joita Helsingin alueelta oli 175), 658 aivoinfarktiverrokkia joilla infarkti johtui muusta syystä kuin dissektoitumasta (n=168), ja 1170 tervettä henkilöä (n=269).

CADISP-aineistossa vaskulaarisia riskitekijöitä oli kaulavaltimodissektoitumapotilailla vähemmän kuin aivoinfarktin muusta syystä sairastaneilla verrokeilla. Terveisiin verrokkeihin nähden dissektoitumapotilailla oli vähemmän hyperkolesterolemiaa ja ylipainoa, mutta useammin korkea verenpaine. Hypertensio saattaakin olla kaula- ja aivovaltimodissektoituman riskitekijä.

Viidennessä osatyössä todettiin migreenin olevan yleisempää aivoinfarktin saaneilla kaulavaltimodissektoitumapotilailla kuin muusta syystä aivoinfarktin saaneilla verrokeilla. Migreeniä sairastavat kaulavaltimodissektoitumapotilaat eivät eronneet migreeniä sairastamattomista aivoinfarktien yleisyyden, dissektoituneen valtimon, taudinkuvan tai ennusteen suhteen.

1 INTRODUCTION

Stroke occurs unexpectedly, all of a sudden, but the consequences to the individuals are long-lasting, even life-long. The socio-economic burden is remarkable, especially in the young and middle-aged patients. Cervicocerebral artery dissection (CeAD) leads to stroke in about 3/4 of the cases, and is the most frequent single etiology of ischemic stroke in patients under 50 years of age¹. CeADs can be divided into two subgroups: i) traumatic dissections caused by severe direct, blunt trauma, and ii) spontaneous dissections that occur without preceding events or after minor trauma, although in some cases, this classification may be arbitrary. This thesis focuses on spontaneous CeAD in internal carotid arteries (ICA) and vertebral arteries (VA).

The first publications on non-traumatic CeAD date back to the 50's^{2 3}, when the disease was regarded as a rarity. Until the 1980s, most cases were diagnosed post-mortem, which led to a publication bias towards the most severe forms of the disease. Since then, development and accessibility of vascular imaging methods and better awareness of CeAD among physicians have enabled diagnosis of dissection in patients with stroke, transient ischemic attack (TIA), or very mild symptoms.

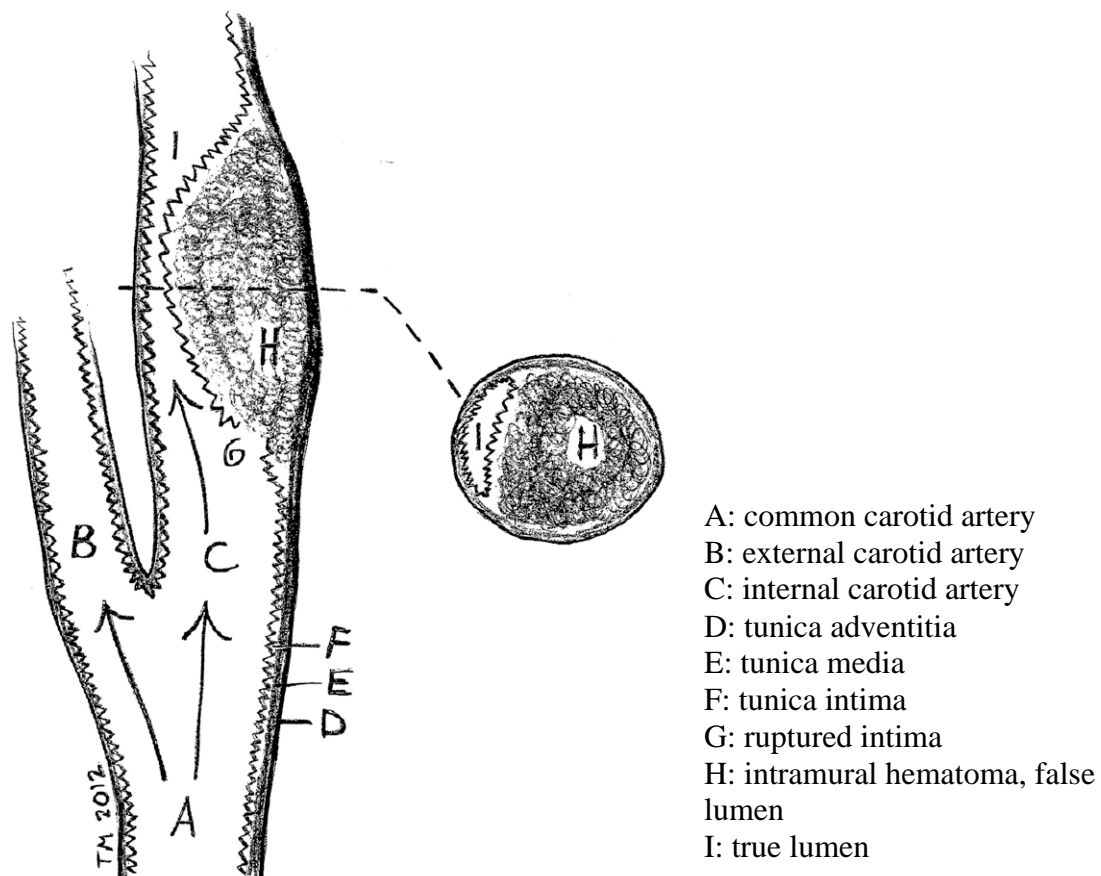
Several factors are associated with cervicocerebral artery dissections, such as connective tissue diseases, minor trauma, recent infections, smoking, and migraine, but the pathophysiology of CeAD is incompletely understood. It is hypothesized that, at least in part of the patients, an underlying genetic defect of the vessel wall predisposes to dissection, triggered by environmental factors. To provide data on CeAD in Finnish patients, we established a register of all consecutive CeAD patients. Due to low frequency of CeAD, collaboration between several stroke centers is essential to study genetic and environmental risk factors, as well as outcome and treatment aspects of the disease. CADISP project (Cervical Artery Dissection and Ischemic Stroke Patients) was set up to resolve these issues.

2 REVIEW OF THE LITERATURE

2.1 Definition and pathology

Cervicocerebral arteries consist of three layers: i) tunica intima (internal layer with endothelium), ii) tunica media (muscular middle layer), and iii) tunica adventitia (external layer consisting of connective tissue). Cervicocerebral artery dissection is defined as an intramural hematoma within the arterial wall in subintimal, medial, or subadventitial layers. There are two suggested mechanisms for this process: i) Dissection begins with a tear in the inner, intimal layer. This is supported by a recent study ⁴ where a third of dissected vessels showed an intimal flap in high-resolution magnetic resonance imaging (MRI). ii) The intramural hematoma is originated by a rupture of the vasa vasorum – nutrient blood vessels - inside the vessel wall without intimal tear ⁵. In either case, the resulting intramural hematoma propagates within the layers, subsequently creating a false lumen next to the real lumen (Figure 1). The false and true lumens may reconnect distally. The inner surface of the arterial wall, separating the true and false lumens, is called an intimal flap.

Figure 1. Illustration of an internal carotid artery dissection.



It is hypothesized that the plane of dissection (location in the inner or outer arterial layers) relates to the clinical and radiological picture of CeAD^{6,7}. If the splitting of the vessel wall is situated in the medial (middle) or subintimal layers, the inward expanding intramural hematoma narrows the true lumen of the artery or even totally blocks distal blood flow. Both the mechanical barrier and coagulation processes activated by the rupture may induce brain ischemia, which occurs in about 4/5 of the patients^{8,9}. The ischemia can be embolic due to dissection-site thrombosis, which is most common in extracranial artery dissections (EAD)¹⁰⁻¹², or of hemodynamic origin, more often seen in intracranial dissections (IAD)¹³. The degree of stenosis does not seem to relate to occurrence or number of cerebral diffusion-weighted imaging stroke lesions, but the infarctions may be larger in occlusion¹⁴. This is in line with occlusive CeAD leading to more severe strokes¹⁵.

A subadventitial dissection may lead to an aneurysmal dilatation of the artery wall. The layers and surrounding tissues of extracranial arteries are strong, preventing the outermost surface of the artery from rupturing. The aneurysmal CeADs seldom lead to ischemic stroke, and there is evidence that patients with dissecting aneurysms have the best outcome¹⁶. Intracranial arteries have no external elastic membrane between the adventitia and the media, have a thinner adventitia, and less elastic fibers in the media, so that the adventitial and muscular layers are only about 2/3 thick compared to extracranial arteries^{17,18}, and the internal elastic lamina is the strongest of the layers¹⁹. Thus, intracranial subadventitial dissections may more often lead to subarachnoid hemorrhage (SAH)²⁰, discussed in chapters 2.2 and 2.5.3.

2.2 Cervicocerebral dissections in extra- and intracranial arteries

Arterial dissections may occur in any artery of the body. However, the cervical arteries are dissected more frequently than other arteries of the same size, such as the coronary or renal arteries⁵. This can be explained by the exposure to tearing and rotational forces during head movements, as well as compression against the bony structures of the cervical vertebrae. It was suggested that the styloid process may cause mechanical injury to ICA since patients with ICA dissections (ICAD) had longer styloid processes than ischemic stroke controls²¹. ICA and VA are anchored at their origins from the common carotid and subclavian arteries, and distally where ICA enters into the carotid canal, and VA penetrates the intervertebral foramina at its V2 portion and through the dura⁷. The portions of the arteries between these structures are freely mobile. Dissections occur most often extracranially, at the sites of greatest mobility: ICAD in the cervical part starting about 2 cm distal to the carotid bulb, and continuing up to the skull base²², and VA dissections (VAD) from the level of C1 vertebra to C2²³, C6²⁴, or Th1²⁵ vertebrae.

The characteristics of intracranial artery dissections are less well defined than those in EADs. Most of the data come from non-European studies. IAD is currently regarded as a different entity with possibly different etiologic and genetic background²⁶. IADs seem to occur at younger age than EADs²⁷, and the proportion of IADs of all CeADs is thus

higher in children than in adults^{28 29}. IADs are located mostly in vertebral and basilar arteries in adults³⁰, and in anterior circulation in children and adolescents³¹. There are many studies on intracranial dissecting aneurysms in vertebral arteries^{32 33} as they may account for 3 to 7% of SAH cases^{19 34} and 28 % of posterior circulation aneurysms³³. Reports on unruptured IADs – presenting with aneurysms, stenoses, occlusions, and double lumens at imaging - are rarer. Oka *et al.*²⁷ presented 6 original cases and a review of additional 39 patients treated for IS due to intracranial ICAD during years 1980-2004. The mean age of these 45 patients was 21.4 years, but also children were included, which is not usual in many studies on EADs performed in centers of adult neurology, and various studies may not be fully comparable. Two Japanese studies report long-term follow-up of intracranial VAD. The mean age for 11 patients in the paper of Yoshimoto *et al.*³⁵ was 47.3 years, and 7 (64%) were men. Of the dissections, 4 were fusiform or saccular aneurysms and the rest presented with stenosis, occlusion, or double lumen. Nagagawa *et al.*³⁶ had a series of 17 patients (mean age 55.2, 76% men), 5 of which had aneurysms.

Manabe *et al.*³⁰ found IAD in 14 out of 373 consecutive non-emergency outpatients, all having vertebrobasilar dissections. In this patient cohort, CeAD was not initially suspected, and patients were admitted to the neurological and neurosurgical departments due to a variety of symptoms (headache in 46%, focal neurological deficits, dizziness, gait disturbances). Occurrence of IAD was not significantly higher among the headache group (4.7%) than the non-headache group (3.0%). These findings indicate that IADs that do not lead to ischemic or hemorrhagic lesions are more common than previously thought.

Dissections originating extracranially may also extend intracranially. The extent of this phenomenon varies greatly between different publications, and many studies report dissections that are only either extracranial or intracranial. The dural fibers perforate subadventitial and medial layers of VA at dural crossing³⁷, and ICA at proximal and distal dural rings³⁸, anchoring these arteries tightly. This prevents many extracranial dissections from extending intracranially and minimizes mobility of intracranial vessels. However, intracranial and intracranially extending dissections (here referred to as “combined dissections”, CD) may be more frequent than previously thought. In a German study with 250 patients with stroke or TIA from 30 departments of neurology¹⁵, 6.8 % of patients had CD. This was more common in ICAD than in VAD (12.3 vs. 0.9%). Pure IADs (n=36) were excluded from this study. In a small patient series from the USA³⁹, 20% of dissections were intracranial and 20% combined in 20 patients. A Taiwanese study⁴⁰, comprising 73 consecutive CeAD patients in a single center, reported intracranial involvement in 38% (9/24) of anterior circulation dissections, and in 82 % (40/49) of posterior CeADs. Pure IADs were found in 3/24 (12.5%) in anterior circulation and in 27/49 (55%) in posterior circulation dissections.

Reported dissections are mostly single (72-90%)^{41 42}. Multiple dissections occur usually in two vessels – in the same type of artery (ICA or VA) bilaterally, or less often one in ICA and the other in VA. Triple and quadruple dissections constituted 1.6% of all CeADs in a series of 740 consecutive CeAD patients⁴³.

2.3 Epidemiology of cervicocerebral artery dissections

In the past, cervicocerebral artery dissection was considered a rare cause of stroke. The significant development in diagnostic methods has improved recognition of CeAD as the leading etiology of ischemic stroke in the young and middle-aged adults. Digital subtraction angiography (DSA) was developed in the late 1970s by Charles Mistretta, and the first magnetic resonance angiography (MRA) was performed in 1985⁴⁴. In the 1980's, CeAD was reported in about 10% (4 to 22%) of ischemic strokes (IS) in this age group⁴⁵⁻⁴⁷, and since the late 1990's, the proportion has been around 15 to 20%, depending on the upper age limit, population, and the extent of vascular imaging used^{1 48-51}.

In the elderly, traditional risk factors for stroke such as hypertension, diabetes, peripheral artery disease, and atrial fibrillation are more common. The traditional stroke etiologies, large artery atherosclerosis, cardioembolism, and small vessel disease thus predominate in this age group⁵² and simultaneously number of dissections decreases⁵³. Since most ischemic strokes (IS) affect older age groups⁵⁴, dissections are found in only 2-3% of all IS^{55 56}. In a large database of over 3 000 000 US stroke patients with or without thrombolysis, only 0.3% of all patients with IS had CeAD⁵⁷.

Most of the reports on the incidence of CeAD refer to ICAD only. Moreover, only a few population-based studies on CeAD exist. A French report with ICA dissections from years 1987 to 1993⁵⁶ found a rate of 2.9 per 100 000 (95% confidence interval, CI, 1.9-3.9), similar to 2.6 per 100 000 from the United States with ICAD occurring between 1986 and 1992⁵⁸. Both studies date to the era when underdiagnostics of CeAD was common, and the numbers of included dissections were small (36 and 10, respectively). Internal carotid dissections outnumber those diagnosed in vertebral arteries. The VAD/ICAD ratio in three hospital-based studies in the 1990's⁵⁹⁻⁶¹ was in average 0.33 (0.23 to 0.64), which led to an estimated incidence of VAD to be 1 to 1.5 per 100 000⁵. Since that the ratio has slightly increased to an average of 0.53 (0.44 to 0.79) in more recent studies on CeAD from Western countries^{8 62-64}. Lee *et al.*⁶³ also noticed an increase in the incidence rate of VAD from 0.54 per 100 000 during the first half of their study period to 1.52 during the latest years. As they suggested, this difference most likely reflects better diagnostics of VAD by MRA. In their study, however, the overall incidence of CeAD was only 3.01 (95% CI 2.05 to 3.97). It can thus be concluded that at least 1/3 of dissections occur in vertebral arteries, and the overall incidence of CeAD treated in hospitals could be around 3.5 to 5 per 100 000. Male preponderance has been reported in many studies^{64 65}.

However, it is likely that a significant number of CeAD still remain underdiagnosed. Patients with no or very mild symptoms may not seek medical help or are misdiagnosed as having migraine, inexplicable transient dizziness or post-traumatic muscular pain, for example, whereas extensive diagnostics in the patients with severe stroke is not always regarded necessary, particularly among the oldest individuals or those with apparently poor prognostics. Moreover, in regions with several neurological units serving the same population, establishment of comprehensive registries of CeAD patients requires collaboration between the units.

CeAD affects all age groups from early childhood to elderly, with a slightly increased risk in the fifth decade of life. The reported mean ages have been very similar in different studies; 44.0 in a large French cohort ⁸; 45.3 among French and Swiss patients ⁶⁵; 45.8 in a population-based study from the United States ⁶³, and 46.8 in an Italian study ⁹. Women are a few years younger than men at the time of the dissection, with mean age 43.6 to 47.5 in men, and 39.6 to 44 in women in recent studies ^{39 61 64-66}. Although CeAD occurs in children ^{28 29 67}, it can be expected that as the amount of risk factors for CeAD increase with aging, the incidence of CeAD increases towards adulthood. Such factors may include sporting activities, hypertension, and pubertal hormonal changes. In a study comparing stroke subtypes in children (<15 years and 15 to 18 years of age) and young adults (>18 to 45 years) from Indiana, United States ⁶⁸, all cervicocerebral artery dissections in children (n=3) occurred in teenagers (15 to 18 years). There is evidence that skeletal abnormalities may contribute to CeAD in children ⁶⁹.

Patients with internal carotid artery dissections are slightly older than those with vertebrobasilar dissections. In the study of Lee *et al.* ⁶³, ICAD occurred on average at 47.0 years, VAD at 43.4 years. Arnold *et al.* ⁶⁵ reported the mean age of ICAD as 43.0 in women, 48.5 in men, whereas these figures were 40.8 for women and 44.4 for men in VAD.

The characteristics of CeAD seem to be slightly different in non-Caucasian populations. In the Asian countries, VAD is more common, and dissections occur more often in intracranial arteries ^{30 40}. These differences contribute to a greater incidence of subarachnoid hemorrhage (SAH) in Asian patients (chapter 2.5.3). In a Mexican study ⁵¹, VAD (n=72) also exceeded the number of ICAD (n=58), and the patients were younger (mean age 35.4) than in most of the other studies published on CeAD. These features may be due to true ethnic difference with respect to genes, environmental factors, life style or lower life expectancy, as in other types of stroke as well ⁷⁰ - or to referral or diagnostic bias.

2.4 Pathophysiology

Cervicocerebral dissection appears to be a multifactorial disease. The current theory on pathogenesis of CeAD, shared by many researchers ⁴², suggests that a structural defect weakens the arterial wall and predisposes it to a tear, which is triggered by environmental factors. The defect may be genetic, at least in part of the patients, and/or due to transient arteriopathy. Factors that may increase arterial wall vulnerability, predisposing to spontaneous CeAD, are recent infection, hypertension, hyperhomocysteinemia, and migraine ⁴². In addition to dissections due to severe cervical trauma (non-spontaneous CeAD), also minor traumas can act as a triggering factor in some patients.

2.4.1 Genetic risk factors

There are several points suggesting that at least part of CeAD susceptibility is explained by genetic factors with a possible relationship with connective tissue abnormalities. Firstly, risk of CeAD may be elevated in some monogenic connective tissue diseases (CTD). Patient series on vascular Ehlers Danlos syndrome (vEDS) found history of CeAD in 2 to 6% of patients^{71 72}, but the association of CeAD with Marfan syndrome, Loeys-Dietz syndrome, and osteogenesis imperfecta or other monogenic disorders such as autosomal-dominant polycystic kidney disease, alpha-1 antitrypsin deficiency²⁶, and Williams syndrome⁷³ is less clear. However, only a minority of all CeAD patients have a diagnosed CTD²⁶. Secondly, alterations in dermal connective tissue with autosomal-dominant inheritance are found in half of CeAD patients⁴². They resemble those seen in monogenic CTDs but are less dramatic. This indicates the possibility that a mild form of a known CTD or a yet unknown CTD could underlie CeAD, or that there are several genetic polymorphisms, each having a minor influence on the properties of connective tissue⁷⁴. Thirdly, familial CeADs have also been described⁷⁴, constituting no more than 0 to 3% of all CeADs²⁶. Due to CeAD underdiagnostics in the last century, these numbers are expected to increase in the future. Some patients also have family members with dissections in other arteries than cervical (*e.g.* intracranial, renal, and aorta)⁷⁵. Finally, CeAD has been associated with concomitant arterial changes, such as aortic root dilatation, fibromuscular dysplasia, arterial wall hyperdistensibility, and impairment of endothelium-dependent vasodilatation²⁶.

Screening for genetic abnormalities in CeAD patients with no known CTD by candidate gene or linkage studies have not yielded notable or consistent results. The genetic studies may have been underpowered due to small patient numbers; only 4 of the 16 genetic association studies on CeAD so far had >100 patients^{26 76}. The most promising of the results were associations of CeAD with *methylenetetrahydrofolate reductase* (MTHFR) 677TT genotype and *intercellular adhesion molecule 1* (ICAM-1) E469K polymorphism²⁶, but the latter has not been replicated. Three studies (two of which overlap), found the MTHFR 677TT genotype to be more frequent among CeAD patients, but there are also reports suggesting that there is no association^{26 76}. In a recent report⁷⁷, novel mutations in the transforming growth factor β receptor 2 (TGF β R2), were found in 2 (3.6%) patients. Mutations in TGF β R 1 and 2 are also related to Loeys-Dietz syndrome and thoracic aortal aneurysm and dissection⁷⁷.

2.4.2 Migraine

The association between migraine and ischemic stroke has been recognized for some time, and is most likely multifactorial⁷⁸. These conditions share common characteristics such as neurological deficits, headache, and cerebral blood flow changes, and there may also be a causal relationship⁷⁹. According to a recent meta-analysis, migraine with aura (MA), not migraine without aura (MO), is associated with IS⁸⁰. Migraineurs have a two-fold risk for stroke compared to those without migraine, and the association is clearest among young individuals, women, and patients with less vascular risk factors⁷⁸.

One of the many links between migraine and stroke could be CeAD. Both migraine and CeAD occur predominantly in young and middle-aged adults. Migraine is more common among women and women with CeAD are younger than men (see Chapter 2.3). A number of studies have found high frequencies of migraine among CeAD patients^{63 65 81-87}. Silbert *et al.*⁸⁸ reported migraine rates similar to the general population⁸⁸, but this study lacked a control group. Whether CeAD is related to MA or MO or both, is not clear. The studies on the topic have mostly had small patient numbers and heterogeneous control groups: *i.e.* healthy controls from hospital staff^{82 84}, spouses and friends⁸⁷ or random selection from population⁸⁶, and part of the control subjects were ischemic stroke patients^{81 82 84}. Most of the studies used the International Headache Society criteria of migraine⁸⁹, but there were some methodological differences between studies. For example, in the study of Pezzini *et al.*⁸², patients with both MO and MA were included in both groups (as MO and MA patients) thus increasing the frequency of MO, whereas Artto *et al.*⁸⁶, considered aura as a “dominant” feature, and the patients with both MO and MA were included only in the MA group. In addition, the confounding factors used in multivariate regression models were inconsistent.

Compared to healthy controls, the frequencies of both MA and MO seem to be increased in CeAD. In a French study with 47 CeAD patients and 52 controls⁸¹, a history of migraine was reported in 49 % of CeAD patients and in 21 % of healthy controls (odds ratio, OR, 3.6; 95% CI 1.5-8.6, $p=0.005$). This was mostly due to MO (OR 3.2, 95% 1.2-9.0; $p=0.025$), but since there were only 6 CeAD patients and 4 healthy controls with MA (OR 1.7; $p=0.45$), no firm conclusions can be drawn on MA. Migraine was associated with CeAD also in an Italian study⁸² with 72 CeAD patients: migraine history was positive in 59.7 % of the patients, compared to 30.6 % in 72 non-CeAD IS patients and 18.1 % in 72 healthy controls (OR 3.14; 95% CI 1.41–7.01, and OR 7.41; 95% CI 3.11–17.64 for the comparisons, respectively). The frequencies of MA were, again, low: 6 CeAD, 9 non-CeAD IS patients, and 6 healthy controls had MA. In comparison to the percentage of CeAD patients with MA of all migraineurs in these two studies (26 and 14%), the study of Silbert *et al.*⁸⁸ reported 43 % of the migraineurs to have MA.

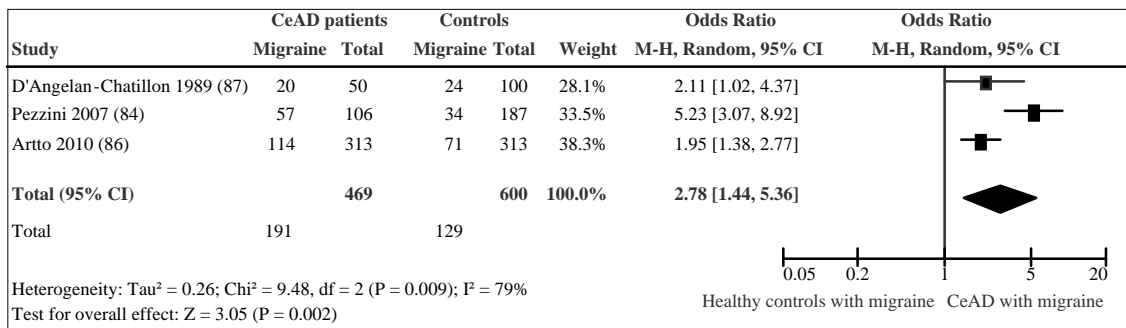
In a more recent Italian study⁸⁴, partly overlapping with the previous one⁸², with 106 CeAD and 227 non-CeAD IS patients and 187 healthy controls, both MO and MA were associated with CeAD (OR 5.45 95% CI 3.03–9.79 for MO; and OR 4.06, 95% CI 1.63–10.2 for MA compared to healthy controls). MO, not MA, was more frequent in the CeAD group compared to the non-CeAD IS patients. Artto *et al.*⁸⁶ reported that MA was more common in 313 CeAD patients than in 313 healthy controls (OR 2.41, 95% CI 1.53–3.80), and that the association of MO and CeAD was parallel, but did not reach statistical significance (OR 1.64, 95% CI 0.98–2.76).

A meta-analysis on studies in English language comparing migraine in CeAD patients and healthy controls is presented in Figure 2. The meta-analysis was performed using unadjusted ORs with Review Manager (RevMan), Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011. Since the two Italian studies overlap^{82 84}, only the latter was used in the comparisons. Migraine was more common among

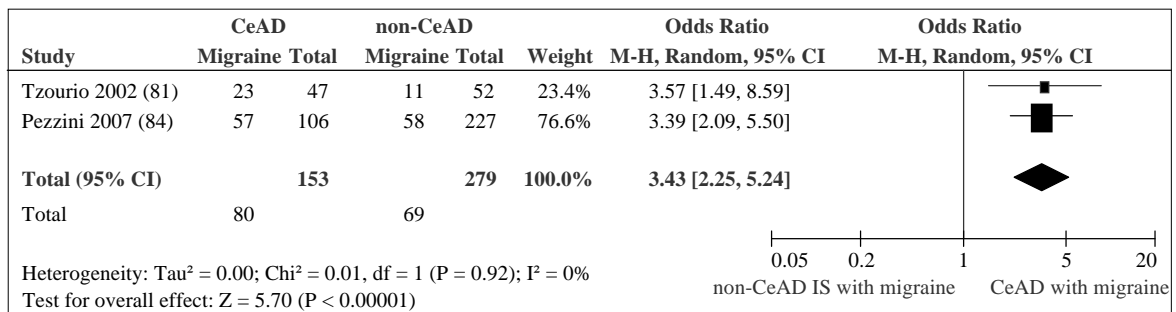
CeAD patients compared to healthy controls (Figure 2a). In a subgroup analysis, both MO (OR 2.25, 95% CI 1.04-4.88) and MA (OR 2.21 [1.52-3.21]) were more frequent among CeAD patients (data not shown). Similarly, migraine was more common among CeAD patients compared to non-CeAD IS group (Figure 2b). However, this was due to MO only (for MO: OR 4.28 [2.66-6.88]; for MA: OR 1.99 [0.68-5.89], data not shown). This shows that healthy individuals and non-CeAD IS patients differ as referents. In a recent meta-analysis these two kind of control groups were combined ⁸⁵, and the difference in MA between CeAD patients and all referents did not reach statistical significance (OR 1.50 [0.76-2.96]).

Figure 2. Studies on migraine in CeAD patients vs. controls

a) Migraine in CeAD patients vs. healthy controls



b) Migraine in CeAD vs. non-CeAD IS patients



CeAD: cervicocerebral artery dissection, IS: ischemic stroke, M-H: Mantel-Haenszel, CI: confidence interval

In addition to the high prevalence of migraine among CeAD patients, some findings support the hypothesis that migraine and CeAD may have causal relationship – and/or perhaps share common pathogenic mechanisms. Levels of elastases – enzymes that degrade elastic fibers in extracellular matrix, thus weakening the vessel wall – have been found to be elevated in patients with migraine ⁹⁰, especially in patients with MA. Endothelium-dependent vasodilatation is impaired in both CeAD and migraine patients, suggesting that there may be a common generalized vascular disorder predisposing to both conditions ⁸². Another link between migraine and CeAD may be patent foramen ovale

(PFO), although the association is speculative with few supporting data. Its association with stroke and migraine has been under debate in recent years. It can be hypothesized that paradoxical microscopic emboli that, especially during Valsalva-provoking activities, travel to posterior circulation via PFO and cause visual migraine auras⁹¹. In a recent study of 981 young stroke patients⁹², migraine with aura was associated with an interatrial right-to-left shunt. In a Swedish study⁵⁰, PFO was found in 5 of the 7 patients with probable or possible arterial dissection. However, Swiss investigators⁹³ assumed PFO and CeAD to be different diseases by comparing findings of cerebral ischemia with diffusion-weighted imaging in patients with CeAD and PFO. The lesions caused by CeAD were more often large, multiple and territorial, whereas PFO led more often to single, non-territorial infarcts.

There are several interesting findings about migraine in CeAD patients. As in general populations, also among CeAD patients women have more migraine than men⁶⁵. Migraine was more common among VAD patients that did not develop brain ischemia than among those with stroke in one study⁹⁴. However, there were only 21 patients in the non-ischemic group. Migraineurs tend to develop headache or neck or facial pain associated with dissection more often than the non-migraineurs⁹⁵. In a North-American series of 177 CeAD patients, only 13% of those with previous headaches, mostly migraine, did not have headache as a presenting symptom of CeAD⁶². One explanation for this association could be sensitization of migraineurs for pain⁹⁶, amplifying the painful stimulus caused by dissection. Migraine characteristics were different between CeAD and non-CeAD IS groups in the study of Tzourio *et al.*⁸¹: in CeAD patients, the age of onset of migraine was higher and there were more attacks during the past 3 months. The OR for migraine was higher for patients with multiple dissections (6.7; 95% CI 1.9-24.1; $p=0.002$) compared to non-CeAD IS than for single CeAD (OR 2.9; 95% CI 1.1-7.6; $p=0.037$)⁸¹. Moreover, the prevalence of CeAD patients with both migraine and the *TT677 MTHFR* genotype was higher among patients with multiple dissections (3/16; 18.8%) compared to those with single-vessel CeAD (12/90; 13.3%) and healthy controls (5/187; 2.7%, $p=0.0008$)⁸⁴. There is some evidence that migraine may alleviate or resolve after CeAD; this happened among 8/29 (28%) CeAD patients with migraine⁸⁸.

2.4.3 Infection and inflammation

Infections have been suggested as a predisposing factor for the arterial wall damage in CeAD. Guillon *et al.*⁹⁷ reported more infections (31.9%) in 47 CeAD patients compared to 52 non-CeAD IS controls (13.5%, $p=0.032$; OR 3.0; 95% CI, 1.1 to 8.2) during 4 weeks before the onset of symptoms. Recent infections were most common in patients with multiple dissections (50%; OR 6.4; 95% CI 1.7 to 24.0). Infection had no association with ischemic manifestations in CeAD⁹⁷. Grau *et al.* found as many as 58.1% infections during the preceding week in CeAD patients and 32.8% in non-CeAD IS patients ($p=0.01$)⁹⁸, and the association was not related to mechanical factors in infectious diseases (cough, vomiting). CeAD patients have also been reported to have higher plasma levels of high-sensitivity C-reactive protein (CRP) in the convalescence phase (>9 months after CeAD), independent from vascular risk factors⁹⁹. This was thought to reflect long-standing

inflammatory mechanisms and not acute reaction to stroke, which usually does not last longer than 3 months⁹⁹. In another study, 18 patients with spontaneous CeAD had more often leukocytosis and elevated CRP in the acute phase compared with 25 traumatic (both minor and major trauma were included) CeAD patients¹⁰⁰. Patients with a subsequent clinical infection were excluded. In a German study, a generalized inflammatory arteriopathy, seen with high-resolution MRI and positron emission tomography, and lasting for 6 months, was seen in a quarter of CeAD patients¹⁰¹. This was related particularly to the patients with >2 CeADs, which supports the finding of Guillon *et al.*⁹⁷ of infections being related to multiple dissections. A French study demonstrated that periarterial edema, recent infection, and elevated CRP were more common in spontaneous than traumatic ICAD using high-resolution MRI¹⁰².

Infections may predispose to CeAD via indirect inflammatory and immunological mechanisms, where cytokines and proteases could weaken the arterial wall by inducing extracellular matrix degradation⁹⁷. This may cause a transient inflammatory arteriopathy, increasing the risk of multiple dissections¹⁰¹. The individual inflammatory response may depend on genetic variability, which is consistent with the excess of ICAM-1 E469K polymorphism in CeAD patients¹⁰³. It can thus be concluded that inflammatory or genetic mechanisms may underlie the generalized arteriopathy in CeAD. This kind of arteriopathy was seen in superficial temporal artery biopsies of CeAD patients, taken during the first weeks after dissection¹⁰⁴.

2.4.4 Vascular risk factors

CeAD is presumably a non-atherosclerotic disease, and patients have been thought to have very few vascular risk factors⁴², particularly compared with non-CeAD IS controls. According to a systematic review of the risk factors for the disease, CeAD patients have less hypertension, hypercholesterolemia, diabetes, smoking, and coronary artery disease than non-CeAD IS patients¹⁰⁵. Two studies have been designed for comparing CeAD patients and healthy controls in this aspect^{6 106}. According to the study of Arnold *et al.*¹⁰⁶, there were no differences in the prevalence of hypertension, diabetes mellitus (DM), hypercholesterolemia, and current smoking between 119 CeAD patients and 263 healthy controls, but body mass index (BMI) was lower in CeAD patients.

Hypertension has been associated with CeAD compared to healthy controls in a few studies^{6 103 107}. In an Italian study⁶ of 153 CeAD patients, and as many non-CeAD IS patients and healthy controls, hypertension was more frequent in CeAD patients presented with stroke *vs.* healthy controls, whereas the rates of hypercholesterolemia, current smoking, and DM were similar. This suggests that patients with hypertension might have increased risk for stroke when CeAD occurs. In a rather small study with two cohorts of German CeAD patients (31 and 65 patients), hypertension was reported in 22% of all CeAD patients together and 6% of the healthy controls¹⁰³. Another German study of the same size (95 CeAD patients and 95 healthy controls)¹⁰⁷ about the association of homocysteine with CeAD reported higher blood pressure values in CeAD patients

($p=0.016$), but there was no statistical difference in history of hypertension between CeAD patients (28%) and healthy controls (15%, OR 2.056, $p=0.082$).

Hyperhomocysteinemia has been associated with cardiovascular diseases, although treatment with vitamins B6, B12, or folic acid has not reduced the risk of arterial ischemic events¹⁰⁸. CeAD patients were reported of having increased levels of homocysteine¹⁰⁵ in two studies, and the MTHFR C677T polymorphism was associated with homocysteine levels¹⁰⁷. Post-methionine load homocysteinemia was described in a patient with CeAD¹⁰⁹. MTHFR catalyzes the homocysteine re-methylation to methionine¹⁰⁸. These findings are in keeping with the MTHFR C677T polymorphism being related with CeAD (see Chapters 2.4.1 and 2.4.2) and to the various mechanisms of homocysteine: it thickens vessel wall, increases matrix metalloproteinase activity, and enhances thrombus formation¹⁰⁸. These changes may lead to endothelial dysfunction or damage¹⁰⁹.

2.4.5 Trauma

According to a common belief, mild mechanical traumas to cervical vessels may trigger CeAD. They include hyperextension, rotation, or lateroversion of the neck⁴² such as sports activities¹¹⁰, sneezing, coughing or vomiting, carrying heavy objects, whiplash injury, prolonged sustained head rotation, intercourse, and child delivery^{42 111}. However, these traumas are often non-dramatic and common, can occur every day to anyone, similar traumas lead to CeAD usually only once, and they are not consistently defined across studies. Nevertheless, several studies report traumas to be common among CeAD patients with frequencies from 12 to 34%¹⁰⁵. The frequency of various traumas was assessed in a systematic interview comparing CeAD and non-CeAD IS patients in the acute phase¹¹². The number of patients was quite small (47 CeAD patients), but the sum of all mechanical factors (*e.g.* heavy lifting, sexual intercourse, mild direct neck trauma, sports activities during 24 hours before first symptoms, and cervical manipulative therapy in the past 30 days) was slightly increased in the CeAD group. It is not known whether cervical manipulation causes arterial damage or whether patients seek for manipulative therapy because of neck- or headache that is caused by CeAD. Smith *et al.*¹¹³ reported spinal manipulative therapy to be associated with CeAD also after controlling for preceding pain, but several confounding factors such as recall bias and age of the control group may affect these results.

2.5 Clinical features of cervicocerebral artery dissections

2.5.1 Local manifestations

Local symptoms of CeAD can occur separately or in combination with ischemia and are often ipsilateral to dissection. They include pain in neck, face, ear or eye, headache, Horner's syndrome (without anhidrosis), tinnitus, neck swelling, and cranial nerve dysfunction^{42 88 114 115}. Headache is a common presentation, and reported in 45-71% of all CeAD patients^{9 55 62 64 65} and even more (82%) in VAD¹¹⁶. Neck pain occurs in 25-58%⁶²

^{64 65}. In a study of 20 patients with pain as the only symptom of CeAD ¹¹⁷, headache was mostly different from previous headaches, intense, and more often throbbing than blunt. The onset of pain ranged from very sudden (reaching maximum in 1 minute) to progressive (>24 hours). Neck pain was usually constrictive and less intense ¹¹⁷. Pulsatile tinnitus is related to the proximity of the damaged ICA to the tympanic membrane ⁷. Tinnitus has been reported in 5-11% ^{62 64 65 116}, cranial nerve palsies, mostly in lower cranial nerves, in 5-13% of patients ^{65 114}, and Horner's syndrome in 29-37% of ICAD patients ^{9 64}. Horner's syndrome may occur also in VAD ¹¹⁴, but instead of being a sign of vessel wall rupture as in ICAD (due to peripheral interruption of sympathetic nerve supply to the eye), it is caused by brain stem ischemia.

2.5.2 Ischemic manifestations

Local symptoms may precede ischemia by minutes or days ⁵, they may begin simultaneously or ischemia may be the only symptom. Among 42 consecutive extracranial ICAD patients with stroke ¹¹⁸, 9 (21%) had no previous local symptoms. For the remaining 33 patients, the time interval between local signs and ischemia was less than a week for 82%. Ischemic symptoms due to CeAD – cerebral infarction, TIA, and rarely retinal ischemia or isolated ischemia of the spinal cord - are similar to those seen in strokes caused by other etiologies ⁴². Ischemic symptoms in ICAD lead to contralateral limb dysfunction or neglect, for example, and in VAD to nausea, vertigo, Horner's syndrome, ataxia, and dysphagia. Also visual disturbances such as diplopia, blurred vision, and visual field abnormalities, resembling migraine aura, have been described ¹¹⁹.

The frequency of ischemic stroke in diagnosed patients is around 50-70%. Stroke was reported in 51% of 76 Italian patients, and TIA in 17% ¹²⁰. In 136 German patients ⁶⁴, stroke occurred in 71% in ICAD and 85% in VAD, and TIA in 13% and 11%, respectively. In a French-Swiss study of 186 first-ever unilateral VAD ⁹⁴, 77% had stroke and 13% TIA, and those with ischemic symptoms were older, more often male and smokers. In a study of 181 Swiss patients with 200 ICADs ¹²¹, 116 (58%) of dissections led to ischemic stroke, 22 (11%) to TIA, and 7 (3.5%) to amaurosis fugax or retinal ischemia. Patients with ischemia had more often high-degree stenosis or occlusion and hypercholesterolemia, less Horner's syndrome and cranial nerve palsies. However, it might be that the differences in the occurrence of Horner's syndrome and cranial nerve palsies are in part due to recruitment bias, since young patients with ischemic symptoms are more likely to be diagnosed than those with minor symptoms, whereas patients with Horner's syndrome are suspected to have CeAD more likely than those with neck pain only. Thus, the proportion of non-ischemic CeAD patients may be greater than reported ⁴².

It was suggested that intracranial dissections lead to ischemia more often than EADs, and that the delay from the first transient symptoms (pain, Horner's syndrome) to stroke could be shorter for IADs ¹²². In a series of 10 intracranial ICAD patients ¹²², there was symptom fluctuation in 5 patients during the first 2 weeks. This was in line with hypoperfusion being a common cause for ischemia in IADs.

2.5.3 Subarachnoid hemorrhage

Dissecting aneurysms in intracranial arteries may rupture causing SAH. A common guideline is to avoid anticoagulation in intracranial and combined dissections¹¹⁶. Dissecting aneurysms also have a higher risk of rebleeding than non-dissecting saccular aneurysms³³. The risk of SAH in dissecting aneurysms is higher in “entrance-only” – lesions than in entry-exit –aneurysms with reconnection into the true lumen and less pressure against the outermost artery wall¹²³. The symptoms of SAH do not differ from those in non-CeAD SAH¹³.

Bleeding complication has been reported to be more frequent in VAD than in ICAD both in early³¹ and recent publications¹⁹. Mizutani *et al.*¹⁹ reported SAH in 57% of intracranial VAD and in 39% of ICAD. In a Taiwanese single-center series of 73 extra- and intracranial CeAD patients⁴⁰, anterior circulation CeAD led most often to ischemia: 19 patients out of 24 had ischemic stroke, 2 both ischemia and SAH. Posterior circulation CeAD patients had similar occurrence of ischemia and SAH (21/49 had ischemia, 22 patients SAH, 1 had both). Since most SAH patients are treated in neurosurgical units, the reported bleeding frequencies in CeAD may be underestimated in patient populations from neurological units only. In two large series of CeAD patients treated in departments of neurology, SAH rate was around 1%^{8 65}. It should be noted that most studies on symptoms, clinical characteristics and outcome of CeAD describe the ischemic subpopulation of CeAD patients.

2.6 Diagnosis of cervicocerebral artery dissections

The radiological signs of dissection include long tapered or filiform stenosis, a dissecting aneurysm, intimal flap and double lumen, a tapered occlusion (in ICAD usually >2cm above carotid bifurcation) and intramural hematoma or wall thickening^{42 124}.

2.6.1 Digital subtraction angiography

The former golden standard DSA is performed currently only occasionally, mainly before performing endovascular procedures, because it is invasive and does not allow direct visualization of the arterial wall^{42 114}. The rate of neurologic complications is around 0.9-4%, and of puncture-site hematoma 4%¹²⁵, and DSA may even cause iatrogenic dissections¹²⁶.

2.6.2 Ultrasound

Cervical ultrasound (US) is sometimes used as a screening tool on an emergency basis for patients with suspected CeAD. It may show stenosis or occlusion of the vessel, or more rarely hypoechogenic wall hematoma, false lumen, hyperechogenic flap or pseudoaneurysm¹²⁷. However, it is operator-dependent, not reliable in CeAD near the skull base, within the transverse foramina, and intracranial arteries¹²⁸, and its sensitivity

in diagnosing VAD¹²⁸ or CeAD with low-grade stenosis or local symptoms only¹²⁷ is low. In the study of Arnold *et al.*¹²⁷, 1/3 of the ICAD with isolated Horner's syndrome remained false-negative in US examination. Dittrich *et al.*¹²⁹ found US to be negative in 11/86 (12.8%) patients diagnosed subsequently with CeAD by computed tomography angiography (CTA) or MRA. Seven of these were followed-up with repetitive US, and in five, US remained normal. The diagnosis should always be confirmed by CTA or MRA⁴²¹²⁷. US may be useful in follow-up if CeAD was seen in the initial US imaging¹¹⁴.

2.6.3 CT-angiography

Development of multidetector CT angiography has made CTA a useful tool in CeAD diagnostics¹³⁰. For the present, CTA or MRA are regarded as equally good in diagnosing CeAD¹³⁰, but they have some differences. CTA is an irradiative method but usually more easily available. Vertinsky *et al.*¹²⁴ compared multidetector CTA and MR imaging. CT/CTA visualized more often intimal flaps, pseudoaneurysms, and high-grade stenoses, and was considered to be a better method for VAD¹²⁴, which is often a diagnostic challenge¹¹⁴, but MRI/MRA was superior in diagnosing ischemic complications¹²⁴. Atherosclerotic ICA may be difficult to distinguish from dissection with CTA, but Leclerc *et al.*⁸⁹ found an eccentric lumen at the upper portion of ICA in all 12 stenotic ICADs but in none of the 22 atherosclerotic controls, in whom the location of maximum stenosis was lower than in ICAD.

2.6.4 Magnetic resonance imaging

MRI combined with MRA is considered the best method for diagnosing the intramural hematoma in CeAD⁴²¹¹⁴, if one keeps in mind the time interval of a couple of days in development of methemoglobin in the intramural hematoma¹³¹. High-resolution MRI, a novel technology to visualize vessel wall, is able to distinguish intraluminal thrombus from intramural hematoma and may be even better in showing intimal flaps and wall thickening than CTA or routine MRI/MRA⁴, and may become routine imaging procedure in the future.

2.7 Treatment of cervicocerebral artery dissections

2.7.1 Thrombolysis

CeAD patients have received thrombolytic agents in the acute phase of cerebral ischemia, since CeAD diagnosis is seldom clear before initiation of thrombolysis¹³². There are no randomized controlled trials on thrombolysis versus placebo in CeAD patients. A recent meta-analysis¹³² gathered previous case reports and series published on CeAD thrombolysis. Rates of symptomatic intracranial hemorrhage (3.1%), overall mortality (8.1%), and outcome (41% had modified Rankin Scale 0-1) of 180 thrombolysed CeAD patients were compared to data from the Safe Implementation of Thrombolysis in Stroke - International Stroke Thrombolysis Register (SITS-ISTR). There were no marked

differences in the safety or outcome between CeAD patients and other ischemic stroke patients in SITS-ISTR study.

There is, however, some evidence that thrombolysed CeAD patients have worse outcome than patients with other causes for IS. In a series of 48 Finnish thrombolysed young stroke patients, CeAD was associated with unfavorable outcome¹³³. Admission NIHSS is a strong predictor of outcome, and median NIHSS in CeAD patients was 10.5 compared to 7 in all thrombolysed patients in this series¹³³. In a large US cohort of almost 48000 thrombolysed IS patients and nearly 3 million IS patients without thrombolysis, characteristics of those with CeAD were compared with the rest⁵⁷. There were 488 (1%) thrombolysed CeAD patients and 7374 (0.2%) non-thrombolysed CeAD patients with stroke. The odds for moderate to severe disability were approximately 3-fold in CeAD patients, in both thrombolysed and non-thrombolysed groups, also when adjusted for age, sex, and admission NIHSS. This may in part be due to flow-limiting mechanical barrier, intimal flap, and exposure of the thrombogenic subintima. Thrombolytic agents may be less effective in the resulting platelet-rich thromboembolism⁵⁷.

2.7.2 Anticoagulation and antithrombotic medication

CeAD patients usually receive anticoagulation or antithrombotic agents for the first months after diagnosis. The rationale is to prevent further ischemic events. There are no randomized controlled studies comparing the medications, and the indications for choosing anticoagulation or antithrombotic agents - mostly warfarin or aspirin - vary by country and district. This is why systematic meta-analyses are to be interpreted with caution. According to reviews that meta-analyze non-randomized studies comparing anticoagulants and antithrombotics, the rates of death or disability do not differ between patients receiving these treatments^{134 135} so it is recommended to choose the medication on a case-to-case basis⁴². However, in a recent non-randomized study that included 198 German patients with a follow-up of about 2.5 years¹⁵, IS recurrence was more frequent (16.7%) with antiplatelets than with anticoagulation (2.0%; HR 0.11; 95% CI 0.02-0.69; $p=0.02$). It should be noted that only patients with IS or TIA were studied, while the previous meta-analyses included also non-ischemic ICAD and VAD patients¹³⁵ or ICAD patients¹³⁴.

An ongoing project tries to evaluate if randomization into anticoagulation and antithrombotic medication would be feasible^{136 137}. However, the frequency of post-CeAD ischemic events is low and acquiring firm results from a randomized trial would require large patient populations (n=2000-3000).

Since most of the recanalizations occur during the first few months after CeAD (see Chapter 2.8.1), anticoagulation is usually used for six months, but there are no studies focusing on the optimal length of the medical treatment. In case of incomplete recanalization, a change into a long-term antithrombotic medication is common.

2.7.3 Treatment of intracranial dissections

The long-term treatment of non-ruptured intracranial dissections is not established. In IADs, the mechanism of ischemia is more often hemodynamic than in EADs¹³. Due to the risk of rupture and subsequent SAH, some authors have regarded anticoagulation contraindicated¹³ or at least advice to perform a lumbar puncture before initiation of the treatment^{116 138}. In cases of progressive or persistent ischemic symptoms despite medication, operative methods are also an option^{13 139}.

Oka *et al.*²⁷ presented 6 patients with intracranial ICAD of their own together with 39 previous patients from studies published between 1980-2008. Anticoagulation was given to 14 patients of which one also had a surgical operation and one received antiplatelets as well, and antiplatelets were given to an additional 10 patients, of which outcome data were provided for 7. Of these 21 patients, 13 had good recovery. No comparison of outcomes between patients treated with or without anticoagulation/antiplatelet medication can be made due to incomplete data. The patients in the study of Oka *et al.*²⁷ were divided into 3 groups: A) single attack and severe outcome; B) single attack and mild to moderate outcome; and C) recurrent attack and various outcomes. For group A, outcome is poor regardless of treatment, and patients in group B do fine with conservative treatment. They performed superficial temporal artery - middle cerebral artery bypass surgery for 2 of their own patients, one of which recovered well. To differentiate group B and C patients, the authors recommended close clinical and radiological follow-up for the first 2 weeks, and consideration of early surgical management in case of any new symptoms or findings for the group C.

Self-expanding stent placement appeared to be safe and effective in 8 patients with ICAD causing occlusion or critical stenosis and thus hemodynamic insufficiency¹³⁹. The dissection was traumatic in 4. Of the 8 ICADs, 3 were intracranial lesions with initial NIHSS 5-10 and 0-1 at discharge.

Surgical or endovascular interventions are more commonly used in the aneurysmal forms of IAD¹³. Ruptured aneurysms should be treated early by neurosurgical methods¹⁴⁰. The indications for choosing conservative or operative treatment for patients with unruptured aneurysms are not clear. Naito *et al.*¹⁴¹ recommended endovascular management for VAD if the aneurysm is large or growing. Therefore, careful follow-up with repetitive angiography at about 3 weeks is advisable^{36 140}. The options for surgical or endovascular treatments include proximal occlusion and trapping with or without bypass, coil embolization, stenting, and stenting with coil^{13 32 140}. It should be noted that because the aneurysm wall in CeAD does not include all the vessel wall layers, it may be weak. Many dissecting aneurysms are wide-necked or fusiform, which limits the use of aneurysmal clipping and coiling¹³.

2.8 Prognosis in cervicocerebral artery dissections

2.8.1 Recanalization

Recanalization occurs most often by the first 6 months. It is seen more often in stenotic (48-77%) than in occlusive (35-44%) or aneurysmal (13-25%) CeAD^{62 63 142}. In the study of Schwartz *et al.*⁶², partial recanalization was seen in 2 weeks, whereas total or near-total recanalization took in average 4.7 months. Baracchini *et al.*¹²⁰ investigated 74 CeAD patients with neurovascular US daily while at hospital, monthly after discharge and every 6 months thereafter. Complete or hemodynamically significant (stenosis <50%) recanalization occurred in 72% of ICAD and in 65% of VAD. In this study, the recanalization rates between stenotic and occlusive CeAD did not differ statistically significantly. Recanalization has not been independently associated with outcome in most studies^{142 143}. In a Mexican population of 72 VAD and 56 ICAD patients⁵¹, those with recanalized VAD had a better prognosis (OR 3.2, 95% CI 1.1–8.8; $p=0.02$). However, the results were not adjusted for age, sex, or baseline NIHSS. Moreover, the patient population may differ from European series: ICAD patients were markedly disabled at 6 months: only 27% had modified Rankin Scale (mRS) 0-2.

2.8.2 Neurological outcome

Outcome in ischemic CeAD is generally good and depends mostly on the severity of initial stroke, as in strokes due to other etiologies¹⁴⁴. The mortality rate in CeAD is low (<5%) according to recent series⁴². It is, however, likely that some CeAD patients with severe strokes and subsequent death remain undiagnosed, as well as many with oligo- or asymptomatic CeAD. Occlusion due to ICAD leads to worse prognosis compared to patients with atherothrombotic stroke etiology¹¹. This may be due to lack of pre-existing collaterals in CeAD. Indeed, occlusive ICAD patients with ≥ 2 activated collaterals (ophthalmic artery, anterior or posterior communicating arteries seen in transcranial Doppler within 24 hours of symptom onset) had a better outcome than those with none or 1 collateral in a recent study¹⁴³. The proportion of patients with good functional outcome – defined usually as mRS 0-2 at 3 months - is around 70-90%^{63 144 145}, and less among patients with ischemic stroke¹⁴⁶. A summary of studies published during the last 10 years on outcome in CeAD is presented in Table 1.

Age-related factors were discussed in the CADISP study¹⁴⁷. Although young CeAD patients with stroke (<34 years) had more often excellent outcome than the oldest (>54 years) ones (69 vs. 58% had mRS 0-1 at 3 months), the difference was not statistically significant in multivariable analysis adjusted with sex, prospective vs. retrospective recruitment, admission NIHSS, occlusion, site of the dissection, and country of inclusion.

Table 1. Studies on outcome in CeAD in English language, published 2002-2012

Study †	Year	No of patients (%)	Brain infarction (%)	mRS 0-2 (%) at 3 months	mRS 0-1 (%) at 3 months
Dziewas et al. (64)	2003	All 126	96 (76)	NA	88 (70)
		ICAD 78 (63)	55 (71)	NA	54 (69)
		VAD 46 (37)	39 (85)	NA	32 (70)
Beletsky et al. (145)	2003	All 105/116*	78 (67)	93 (89)	NA
		ICAD 49 (42)	29 (59)	NA	NA
		VAD 67 (58)	49 (73)	NA	NA
Cimini et al. (146)	2004	All 10	10 (100)	5 (50)	3 (30)
		ICAD 8 (80)	8 (100)	3 (38)	1 (13)
		VAD 2 (20)	2 (100)	2 (100)	2 (100)
Arauz et al. (51)	2006	All 130	6 (5)	72 (55) at 6 months	NA
		ICAD 58 (45)	NA	16 (27)	NA
		VAD 72 (55)	NA	56 (78)	NA
Arnold et al. (65)	2006	All 383/696*	410 (59)**	282 (74)	215 (56)
		ICAD 501 (75)	NA	NA	NA
		VAD 163 (25)	NA	NA	NA
Lee et al. (63)	2006	All 48	27 (56)	44 (92)	NA
		ICAD 32 (67)‡	13 (41)	29 (91)	NA
		VAD 18 (33)‡	15 (83)	17 (94)	NA
de Bray et al.	2007	All 103	66 (64)	NA	72 (70) at 6 months
		ICAD 68 (69)	41 (60)	NA	NA
		VAD 30 (31)	25 (83)	NA	NA
Fischer et al. (148)	2009	All 108	79 (73)	NA	71 (66)
		ICAD 87 (82)	NA	NA	56 (65)
		VAD 19 (18)	NA	NA	14 (74)

† Studies that include consecutive, non-selected non-SAH CeAD patients (ICAD and/or VAD)

CeAD: cervicocerebral artery dissection; mRS: modified Rankin Scale; NA: not assessed

*Follow-up data were not available for all patients. **Outcome was presented only for patients with stroke.

‡Number of dissections

J M de Bray, G Marc, V Pautot *et al.* Fibromuscular Dysplasia May Herald Symptomatic Recurrence of Cervical Artery Dissection. *Cerebrovasc Dis* 2007; 23(5-6):448-452.

Practically all patients with local signs only have a favorable outcome measured by mRS, but some may suffer from prolonged pain⁸⁸. However, the quality of life measured by Stroke Specific Quality of Life Scale (SSQOL) was impaired also in patients with local signs only ($p < 0.038$ compared to SSQOL before CeAD) and in those with excellent functional outcome (mRS 0-1; $p = 0.013$) in 99 Swiss patients¹⁴⁸.

The aneurysmal form of IAD, leading to SAH, is not a benign disease. High mortality rates have recently been reported, especially among conservatively treated patients. Of 24 Japanese conservatively treated VAD SAH patients¹⁴⁹, 16 (67%) died. Outcome in SAH is related to rebleeding, which occurs in 24-71%¹⁵⁰. In a Japanese series of 62 VAD SAH patients¹⁵⁰, rebleeding was more likely in dissections near PICA origin (46%) than more distal ones (21%) and if angiography revealed “stenosis and dilatation” or “lateral protrusion” –patterns. The authors recommended early surgical management when these signs are present. Only 4/22 (18%) of the patients with rebleeding had “good recovery” on Glasgow Outcome Scale compared to 58% of those without. Mortality was 21% among patients with an intervention, and 56% among conservatively treated subjects.

Prognosis of unruptured IAD presenting with stenosis or occlusion seems to be better than in aneurysmal IAD. Oka *et al.* presented a summary of reported cases of ischemic intracranial ICAD²⁷. In studies published in 1990 or before, death occurred in 10/12 (83%) of ischemic intracranial ICAD patients, but only 7/33 (21%) were dead or severely disabled in later reports (1994-2008)²⁷ with a relatively benign outcome. In the review article of Oka *et al.*, the largest series of intracranial ICAD patients by Chaves *et al.*¹²² presented 10 patients with 9 ischemic strokes and 1 TIA. All patients had excellent or good functional outcome at 3 months.

According to the few studies on prognosis of non-aneurysmal intracranial VAD, unruptured intracranial VAD has a tendency to spontaneous healing. In 1994, Kitanaka *et al.*¹⁵¹ followed-up five unruptured VAD patients with pearl and string sign. There were angiographic changes during the first months in all affected arteries. Every one recovered well. The authors also presented a review of 12 previous intracranial unruptured VADs, of which 4 were ischemic. They concluded that the best treatment option in ischemic intracranial VAD is conservative treatment without antithrombotics when there is improvement in angiography. Some years later, characteristics of 11 patients with 13 intracranial VADs, 4 of which were aneurysms, were reported³⁵. Cases with initial SAH were excluded. During follow-up, 9 patients received antiplatelet drugs, 2 had no medical treatment. Out of the 13 VADs, 8 (62%) were spontaneously recanalized or progressed to complete occlusion. One patient was later on treated by intravascular coil embolization because of persistent aneurysmal dilatation. Good recovery was first achieved in all, but two had a mild recurrent ischemic event, and one patient died 1.5 years later of SAH, which was presumably unrelated to the initial VAD.

2.8.3 Recurrences

Most patients (around 70%) develop one single CeAD and no recurrent events⁴¹. It seems that if the patient has more than one dissection during his/her life, it is more common for multiple CeAD to occur simultaneously or during the first months after the initial dissection than after a long time interval. Early recurrences could be due to a transient arteriopathy¹⁰¹, and late recurrences due to longstanding connective tissue alterations⁴². Multiple dissections (*i.e.* more than one CeAD at the time of the first CeAD diagnosis) have been reported in 10-28% of cases^{41 42}, usually around 15%. The recurrences tend to be oligo- or asymptomatic⁴¹ and diagnosed more often if repetitive, frequent imaging is performed. According to a recent review⁴², in studies published before 2008, new stroke or TIA after initial diagnosis has been reported in 0-11.9% during a mean follow-up period of 1.0 to 9.3 years. In studies until 2009, a recurrent CeAD was diagnosed in 0-8.3% with a follow-up of 0.5 to 9.3 years⁴², with an exception of 25% in the study by Dittrich *et al.*⁴¹. They reported as many as 19% recurrences during the first 4 weeks, and 6% during 5 to 7 months after the first event in 36 CeAD patients investigated with repetitive MR⁴¹. Of these 9 recurrences, 4 occurred in more than one artery. Also in the study of Baracchini *et al.*¹²⁰, there were more recurrences than reported in previous studies: 20 (26%) during the hospital stay, and additional 2 at 3 and 12 months. Interestingly, the early recurrences occurred in initially unaffected arteries, whereas the

later recurrent symptoms were due to lesions in the same arteries as the initial CeAD. All 6 patients with family history of CeAD had a recurrence.

Less is known about recurrences in ischemic forms of IADs. Unusual for EADs, Oka *et al.*²⁷ reported early aggravation of symptoms in half of their patients (3/6), which was due to propagation of the dissection. One of the three patients received anticoagulation before recurrent symptoms. Mizutani *et al.*¹⁹ followed-up 190 patients with IAD for a mean of over 3 years. Of these, 93 were ischemic IADs. There were 18 (9.5%) recurrences of which 12 occurred within the first month. Majority (n=13) of the recurrences presented with headache only, and the rest with infarction (n=4) or SAH (n=1).

Among 177 US CeAD patients⁶², recurrent stroke was detected in 15 (8.5%) of cases, half of which during the first 2 weeks. Recurrent CeAD occurred in 2 (1.1%). Weimar *et al.*¹⁵ studied recurrent ischemic stroke after CeAD in 198 patients, which occurred in 5.2% at hospital before discharge, 11% during the first year, and in 14% during the first 3 years. In a US population of 69 extra- and/or intracranial CeAD patients¹⁵², new TIA, ischemic stroke, or death was reported in 16% during hospital stay and an additional 12% after discharge within a year. CeAD patients had less recurrent strokes than young stroke patients of other etiologies in a French⁴⁸ and a Finnish series¹⁵³. This may be due to fewer vascular risk factors in CeAD patients¹⁵⁴.

3 AIMS OF THE STUDY

To investigate the long-term prognosis of intracranial artery dissections and analyze whether anticoagulation treatment is safe in this patient subgroup (I).

To study the clinical features of cervicocerebral artery dissection in a patient population from Southern Finland (II).

To plan, prepare, and realize a multinational European project (CADISP) on cervical artery dissections to study several clinical features and genetics of this disease (III).

To study the distributions of vascular risk factors in cervical artery dissection patients in comparison with 2 control groups: i) age- and sex -matched ischemic stroke patients with a cause other than dissection and ii) healthy control subjects (IV).

To study occurrence and characteristics of migraine in patients with cervical artery dissection (V).

4 PATIENTS AND METHODS

This study consists of two parts. 1) The two first publications (I, II) were carried out at the Departments of Neurology (I, II) and Neurosurgery (I), Helsinki University Central Hospital, Helsinki, Finland. 2) Publications III, IV, and V are based on the international CADISP project (Cervical Artery Dissection and Ischemic Stroke Patients, www.cadisp.org). The Finnish patients in the CADISP study were treated in the Department of Neurology, Helsinki University Central Hospital, and they partly overlap with the patients in publications I and II.

The study protocols were approved by relevant local authorities in all participating centers and were conducted according to the national rules concerning ethics committee approval and informed consents.

4.1 Data collection

A flow diagram of patient selection is presented in Figure 3.

4.1.1 Finnish patients (I, II)

The publications I and II are retrospective, descriptive, register-based studies. The Helsinki University Central Hospital serves as the only neurological emergency unit and a teaching hospital for a defined population of 1.5 million in Southern Finland. Potential candidates were identified using electronic search of the hospital's databases for diagnoses related to CeAD, ischemic stroke, and SAH, and their medical records were reviewed. The patients living in the hospital catchment area and with the discharge diagnosis of CeAD were included.

The diagnosis was made based on MRA, CTA or, rarely, DSA. For diagnosing intramural hematoma in CT-angiography, the following criteria were applied: The diameter of the artery was greater than in the contralateral side and proximally/distally to the dissection, and the residual lumen was eccentric in location relative to the surrounding hematoma. Radiological images were analyzed by neuroradiologists, and for patients in whom CeAD was considered possible, the images were re-analyzed. Uncertain cases were excluded. All patients included in the study had one or more of the typical diagnostic radiological findings: intramural hematoma, intimal flap or double lumen, dissecting aneurysm, long filiform stenosis, rat tail-shaped or flame-like occlusion, or an occlusion (if in ICA, >2cm above carotid bifurcation) that recanalized into a long filiform stenosis. Recanalization was defined as a radiologically normalized artery after stenosis, and as reperfusion after occlusion. The register of CeAD patients in Helsinki University Central Hospital area includes the following for each patient: age, sex, domicile town, brain vascular imaging results, putative risk factors, BMI, blood tests during hospital stay (On admission: complete blood count, blood glucose, electrolytes, renal and liver function tests, creatine

kinase, cardiac enzymes, activated partial thromboplastin time, whether thromboplastin time or international normalized ratio; 24 to 72 hours after admission: lipid profile), several neurological scores including National Institutes of Health Stroke Scale (NIHSS), Glasgow Coma Scale, mRS, and Barthel Index were recorded on admission, discharge, and at 3 months. Repeat angiography was typically performed at 3-6 months. In case of residual stenosis or dissecting aneurysm, another angiography was performed at 12 months. mRS 0–2 at 3 months was considered a favorable outcome, and mRS 0–1 an excellent outcome.

Intracranial dissections (IAD) treated in the neurological unit were divided into two: A dissection located completely within the cranium was classified as “purely intracranial dissection,” (ID) and a dissection starting extracranially but extending intracranially as “combined dissection” (CD). For the first sub-study (I), only intracranial dissections (IDs and CDs) were included. These patients were called “non-SAH patients”. All cases of diagnosed CeAD treated at the Department of Neurology between January 1994 and October 2004 were reviewed. Out of 256 patients with CeAD, 81 had IAD. Immediately after CeAD diagnosis and exclusion of SAH with negative noncontrast brain CT or MRI scan, all patients received intravenous full-dose heparin sulfate, or subcutaneous low-molecular-weight heparin. Within a few days, oral warfarin was initiated and continued for at least 3 months. Heparin was continued until warfarin treatment achieved target plasma levels (international normalized ratio, 2.0 to 3.0). The clinical features were presented separately for ID, CD, ICAD, and VAD.

To ensure that all patients with IAD treated in the catchment area were recruited, we reviewed all medical records and images of patients hospitalized in the Department of Neurosurgery between August 1998 and October 2004 with the diagnosis of SAH. All IADs were included, also in other than carotid or vertebrobasilar arteries. The radiological findings in the patients matching the criteria (n=22) were typically fusiform aneurysm, double lumen, and/or intramural hematoma, or fusiform aneurysm with arterial wall irregularity together with no notable arteriosclerosis. Risk factors, clinical features and outcome were presented for SAH and non-SAH CeAD patients.

For the second sub-study (II) we recruited all non-SAH CeAD cases treated at our neurological department at the Meilahti Hospital between January 1994 and August 2007, and all patients diagnosed at the two other neurological units of our hospital (Jorvi and Peijas Hospitals) between January 2000 and August 2007. We excluded patients (n=133) who i) lived outside the catchment area, ii) were treated as CeAD, but the radiological diagnosis could not be verified, or iii) had cervicocerebral artery dissection in other than internal carotid or vertebrobasilar arteries. In this study, intracranial and extracranial dissections were also analyzed separately. The patients were followed-up until the end of August 2008. The rates of vascular risk factors were compared to the prevalence of risk factors in the general Finnish population, obtained from Statistics Finland (http://www.stat.fi/index_en.html) and Finnish database for healthcare professionals (<http://www.terveysportti.fi>).

4.1.2 CADISP patients (III-V)

The primary aim of the CADISP consortium was to perform a genetic association study to identify genetic susceptibility factors of CeAD. For this purpose, consecutive patients, aged ≥ 18 years by the time of enrolment, with internal carotid artery or vertebral artery dissections were recruited in 20 centers from 9 countries. To solve whether the genes possibly to be found are specific for CeAD, consecutive patients with ischemic stroke due to causes other than dissection (non-CeAD IS) were also recruited by the same centers. Non-CeAD IS patients were matched on sex and age with CeAD patients. All but 2 centers (London, Munich) also participated in a clinical study including detailed screening of putative environmental risk factors and clinical and radiological characteristics. For each participant, a venous blood sample was collected, and a detailed standardized questionnaire was filled in by a stroke physician. The CADISP clinical study comprises 983 CeAD and 658 non-CeAD IS patients recruited in 18 centers from 8 countries (Argentina, Belgium, Finland, France, Germany, Italy, Switzerland, and Turkey). Since substantial difference in genes, risk factors and life habits were to be expected between patients from different countries, the country of inclusion was taken into account in the statistics.

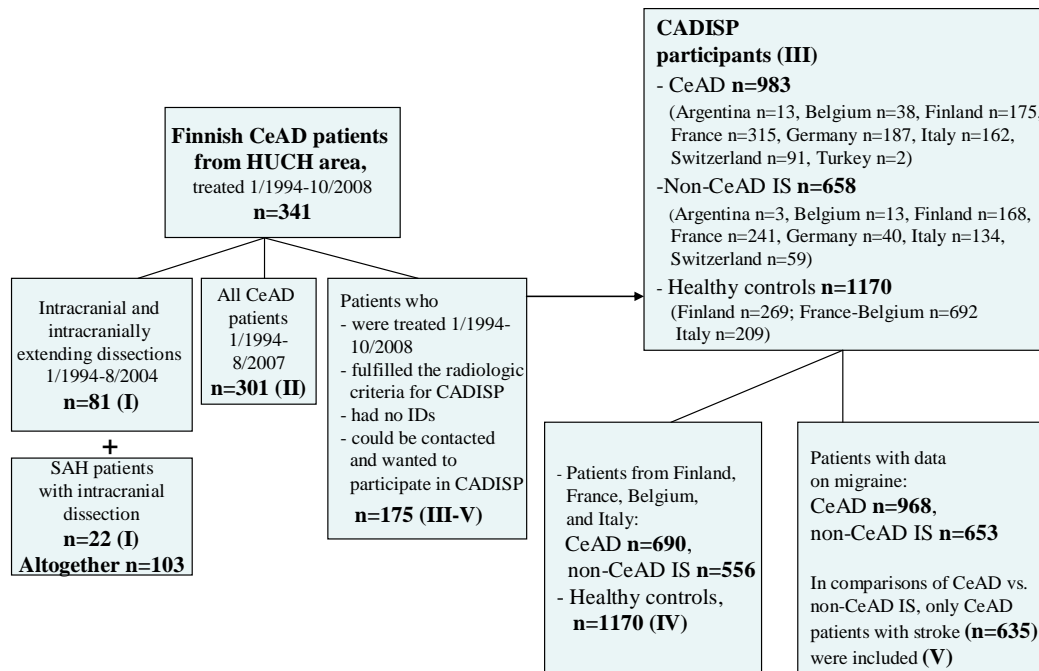
Patients were recruited both prospectively and retrospectively. Those recruited retrospectively had the qualifying event before the beginning of the study in each center and were identified through local registries of CeAD patients. All eligible patients were invited to take part in the study. The great majority ($>96\%$) of patients had a qualifying event between 1999 and 2009.

Pure IADs and iatrogenic dissections were excluded from the CADISP study. CeAD patients had to present with a mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double lumen, or occlusion ≥ 2 cm above the carotid bifurcation revealing an aneurysmal dilatation or a long tapering stenosis after recanalization. The non-CeAD IS patients had a recent IS confirmed on brain imaging, and MRA or CTA, performed within 7 days after the IS, were negative for CeAD; excluded were patients with iatrogenic IS, cardiopathies at very high embolic risk, arterial vasospasm after SAH, or autoimmune or monogenic disease possibly explaining the IS.

One center (Helsinki) also collected healthy controls as part of the CADISP project, since Finnish referents for genetic analyses were lacking (see 4.3). These Finnish healthy controls (n=269) were recruited prospectively within the Helsinki area; most of them (n=233) were recruited randomly with the help of the Finnish Population Register Center; the rest were spouses of CADISP patients (n=17) and unrelated friends or hospital staff (n=19). Rest of the healthy controls that were used in sub-study IV but not in genetic analyses comprise a random selection from pre-existing population-based surveys for France, Belgium, and Italy (MONitoring NationaL du rISque Artériel [MONA-LISA]-Lille study for northern France and Belgium, n=383; MONA-LISA-Strasbourg study for central-eastern France, n=309; and Vobarno study for northern Italy, n=209). See sub-study IV for details. The Finnish and Italian healthy controls are individuals without a

history of vascular disease (peripheral artery disease, stroke, or myocardial infarction). The healthy controls were used in the sub-study IV, from which 293 CeAD and 102 non-CeAD IS patients from Germany, Switzerland, Argentina, and Turkey were excluded because country-, sex-, and age-matched referents with detailed vascular risk factor data were not available.

Figure 3. Patient selection into sub-studies I-V



HUCH: Helsinki University Central Hospital; CeAD: cervicocerebral artery dissection; ID: pure intracranial artery dissection; IS: ischemic stroke

4.2 Variable definition

The risk factors were defined as follows: *Hypertension*: antihypertensive treatment or blood pressure >140/90 mmHg during nonacute phase; *Hypercholesterolemia*: antidyslipidemic treatment or total cholesterol value >5.0 mmol/l, LDL >3, HDL < 1 or triglycerides >2 for sub-studies I and II, and total cholesterol ≥6.20 mmol/L or low-density lipoprotein cholesterol ≥4.1 mmol/L for sub-studies III-V, measured within 48 hours after admission to the hospital; *Diabetes*: antidiabetic treatment or fasting blood glucose ≥7 mmol/l during non-acute phase. *Hormonal therapy*: use of oral contraceptives or postmenopausal substitution therapy at time of event. *Smoking*: Smokers were divided into current (smoking within a month) and past smokers. *Previous infection*: for sub-studies I and II, a history of respiratory or gastrointestinal tract infection within 1 month before admission. For sub-studies III-V, an infection in the week preceding the dissection with i)

at least 1 typical symptom of infection together with fever (temperature $>38^{\circ}\text{C}$), or ii) at least 1 typical symptom of infection together with serologic, cultural, or radiologic findings indicating an acute infection, or iii) the combination of at least 2 typical corresponding symptoms¹⁵⁵. A recent *trauma* was a physical impact on the head or neck (*e.g.* extreme neck movements, cervical manipulation, lifting up heavy loads) <1 month before the first symptoms of CeAD. If the trauma led to a visit to a physician or hospitalization, it was considered major. Lifetime history of *migraine* was classified according to the International Headache Society criteria⁸⁹.

4.3 Genetic analyses (III)

The aim of the sub-study III was to present the strategy of the CADISP network. The majority of CADISP patients were included in both genetic and clinical parts. This thesis focuses on the clinical aspects of CADISP. The genetic analyses are described in more detail in the sub-study III. Briefly, we planned (III) and performed (Debette *et al.*, submitted) a genome-wide association study (GWAS) where hundreds of thousands of single nucleotide polymorphisms (SNPs), distributed across the chromosomes, are genotyped. This approach does not require any hypothesis of the underlying pathophysiology beforehand. The genome-wide association analyses were performed at the Centre National de Genotypage, CNG (<http://www.cng.fr/>). In addition to the GWAS, we also selected SNPs for candidate genes, based on previous genetic studies on CeAD, vEDS, aortic aneurysms and dissections, and intracranial aneurysms (see Chapter 2.4.1 and sub-study III). The genotype frequencies were primarily compared between CeAD patients and healthy controls. In a secondary analysis the significant findings were tested separately for non-CeAD IS patients, in order to confirm that the findings were specific for CeAD and did not reflect a more general susceptibility for ischemic stroke. The study setting also allowed us to search for interactions between polymorphisms and environmental factors or CeAD characteristics (*i.e.* risk factors, dissection site). A pre-existing database of >14000 controls from CNG was used in the analyses, together with 213 Finnish healthy controls.

4.4 Statistics

A two-tailed value of $p < 0.05$ was considered statistically significant. The analyses were performed with a commercially available, statistical software package SPSS for Windows (I: version 12.0.1; II: version 14.0.1; V: PASW 18.0) and Statistical Analyses System software version 9.2 (SAS Institute, Cary, NC, sub-study IV).

4.4.1 Sub-studies I, II

Groupwise comparisons were made using T-test, Mann–Whitney U-test, Kruskal–Wallis H-test, chi-square, Fisher’s exact, and Newcombe–Wilson tests. Stratified analysis was performed when these tests were statistically significant to exclude potential confounders

(e.g. presence *vs.* absence of infarction/sex/ICAD *vs.* VAD/ IAD *vs.* EAD). In the sub-study II, logistic regression was used to test whether the results in chi-square and stratified analyses remained statistically significant after controlling for potential confounders. The following comparisons with logistic regression were performed for this thesis: ID *vs.* CD; non-SAH *vs.* SAH patients; EAD *vs.* IAD; ICAD *vs.* VAD; mRS 0-1 *vs.* mRS 2-6 (unpublished data). The thesis also contains some novel unpublished data on risk factors, symptoms, and outcome for sub-studies I and II (Tables 2-6).

4.4.2 Sub-study IV

We compared the prevalence of vascular risk factors between i) CeAD patients *vs.* healthy controls, ii) non-CeAD IS patients *vs.* healthy controls, and iii) CeAD *vs.* non-CeAD IS patients. The groups were compared using logistic regression models adjusted for age, sex, and country of inclusion. In secondary analyses, we tested whether associations with CeAD were maintained in the following CeAD subgroups comparing them to all referents: ICAD or VAD, presence or absence of cerebral ischemia, and retrospective or prospective recruitment. Because few referents <35 years of age were available, we performed sensitivity analyses including only individuals ≥ 35 years of age.

4.4.3 Sub-study V

All CADISP patients with migraine data available were included (CeAD: n=968; non-CeAD IS: n=653). CeAD patients with or without migraine were compared. When comparing CeAD and non-CeAD IS patients, only CeAD patients presenting with ischemic stroke were included (CeAD_{stroke}, n=635). This way the groups differed in one aspect only (*i.e.* etiology of stroke). The groups (CeAD_{stroke} *vs.* non-CeAD IS; and CeAD patients with *vs.* without migraine) were compared by using chi-square, Mann-Whitney U, and T tests, and logistic regression, adjusted for the following possible confounding factors: age, sex, country of inclusion, and prospective/retrospective recruitment. CeAD and non-CeAD groups differ in terms of vascular risk factors (sub-study IV). Vascular risk factors were thus added as covariates to the comparisons regarding migraine and its subtypes. Since women have migraine more frequently than men¹⁵⁶, the analyses were performed separately for both sexes. A subgroup analysis of patients without patent foramen ovale (PFO) was run because of epidemiological association of PFO and migraine¹⁵⁷.

5 RESULTS

5.1 Prognosis and safety of anticoagulation in intracranial artery dissections (I)

There were 81 non-SAH patients with either purely intracranial or combined dissection (Tables 2, 3). The majority of these were located in vertebrobasilar arteries (VAD: n=59, 73%; ICAD: n=22, 27%). Patients with ID were a few years younger (ID 41.5 vs. CD 46.0 years), although this difference was not statistically significant. The patients with purely intracranial ICAD were the youngest (mean age 34.0 years), and those with combined VAD were the oldest (47.4 years). Majority (n=76) received warfarin during the first months, and the rest used aspirin. No recurrences or new infarctions were detected clinically or radiologically during the first 3 months. None of our patients developed clinical or imaging signs of SAH. One patient died at the acute phase (day 3) due to severe brain infarction. Complete recanalization was observed in 31/43 (72.1%) of the initially stenosed arteries. Of the 34 initially occluded arteries, 7 (20.6%) recanalized totally and 10 (29.4) partially. None of the occlusions in the ID group (n=8) recanalized totally. Recanalization was not a predictor of outcome.

The patients with ID and CD were compared for this thesis using multivariable regression analyses (Table 2). There were no statistical differences between ID and CD regarding age, sex, location of dissection (ICAD/VAD), risk factors, occurrence of brain infarction or occlusion, admission NIHSS, symptoms, or outcome, although there was a trend towards more pain, preceding trauma, unconsciousness, and less hypertension and brain infarction in ID.

We found 22 SAH patients with dissection between 1998 and 2004 (Table 3). The lesions were located mainly in the posterior circulation. Two patients had a bilateral dissection. The radiological findings were: fusiform dilatation only (n=11/24, 45.8%), fusiform dilatation and stenosis (n=11, 45.8%), or fusiform dilatation with slow filling up with contrast agent (n=2, 8.3%). During the same period, there were 67 non-SAH ID or CD patients. Thus, in our center, SAH rate of all intracranial dissections was 25%. SAH patients were slightly older and more often women. The SAH and non-SAH patients had as often headache, which is a typical symptom of SAH. A striking difference between the two groups was a clear deterioration in the clinical condition of SAH patients: 80% of them were unconscious during hospital stay compared to <8% among non-SAH patients, and admission NIHSS and 3-month mRS were higher in the SAH group. All non-SAH patients without brain infarction achieved mRS 0-2 by 3 months.

The non-SAH and SAH groups were compared statistically for this thesis (Table 3) Severity of stroke (admission NIHSS) was the most important predictor of outcome at 3 months. Although strokes were more severe and outcome worse in the SAH group, the type of CeAD manifestation (non-SAH or SAH) did not have an independent influence on 3-month mRS.

These findings indicate that non-SAH and SAH –type intracranial dissections can be distinguished early. Aneurysmatic IDs lead to SAH and have a poor prognosis, whereas non-aneurysmatic IADs presenting without SAH are associated with a favorable outcome and can be safely treated with anticoagulant therapy.

Table 2. Characteristics of purely intracranial and combined dissections

	ID n=23	CD‡ n=57	ID vs. CD* OR <i>unadjusted</i> (95% CI)	ID vs. CD* OR <i>adjusted</i> † (95% CI)
Age (years ± SD)	41.5 (10.4)	46.0 (12.0)	1.03 (0.99-1.08)	1.04 (0.99-1.09)
Age range	21-56	15-68		
Women/Men (%)	8/15 (34.8/65.2)	17/40 (29.8/70.2)	1.26 (0.45-3.51)	1.05 (0.35-3.18)
ICA/VA (%)	5/18 (21.7/78.3)	17/40 (29.2/70.8)	0.65 (0.21-2.05)	0.53 (0.16-1.73)
Risk factors				
Trauma*	10 (43.5)	16 (28.1)	1.97 (0.72-5.39)	1.80 (0.63-5.14)
Hypertension*	5 (21.7)	25 (43.9)	0.36 (0.12-1.09)	0.39 (0.12-1.31)
Hypercholesterolemia*	15 (65.2)	34 (59.6)	1.27 (0.46-3.48)	1.81 (0.57-5.76)
Smoking*	8 (34.8)	18 (31.6)	1.16 (0.42-3.22)	1.33 (0.45-3.88)
Migraine*	9 (39.1)	15 (26.3)	1.80 (0.65-5.01)	1.49 (0.47-4.71)
Manifestations				
Pain	19 (82.6)	38 (66.7)	2.38 (0.71-7.97)	2.21 (0.64-7.61)
Occlusion*	8 (34.8)	28 (49.1)	0.55 (0.20-1.51)	0.52 (0.17-1.54)
Brain infarction	17 (73.9)	50 (87.7)	0.40 (0.12-1.35)	0.28 (0.07-1.10)
Unconscious during hospital stay	3 (13.0)	3 (5.3)	2.70 (0.50-14.50)	1.91 (0.33-11.03)
Median NIHSS at admission if infarction (± IQR)	4 (1.5)	4 (6.25)	0.99 (0.92-1.07)	0.99 (0.91-1.06)
mRS 0-1 at 3 months if infarction*	10 (58.8)	29 (58.0)	1.03 (0.34-3.16)	1.31 (0.30-5.67)
mRS 0-2 at 3 months if infarction*	13 (76.5)	37 (74.0)	1.14 (0.32-4.13)	2.80 (0.36-22.10)

ID: pure intracranial dissection; CD: combined dissection (=extracranial dissection extending intracranially); OR: odds ratio; CI: confidence interval; SD: standard deviation; ICA: internal carotid artery; VA: vertebral artery; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; mRS: modified Rankin Scale

Values are n (%) unless otherwise indicated. *Novel unpublished data. ‡ One patient with both ID and CD is not included in this column.

† Logistic regression, adjusted for age, sex, and CeAD location (ICA/VA), and mRS additionally adjusted for NIHSS.

Table 3. Comparison of non-SAH and SAH patients

	non-SAH patients n=81	SAH patients n=22	non-SAH vs. SAH*, OR <i>unadjusted</i> (95% CI)	non-SAH vs. SAH*, OR <i>adjusted</i> ‡ (95% CI)
Age (years ± SD)	44.8	50.9	0.95 (0.90-0.99)	0.93 (0.88-0.98)
Age range	15-68	32-67		
Women/Men (%)	26/55 (32.1/67.9)	11/11 (50/50)	0.47 (0.18-1.23)	0.29 (0.10-0.84)
Pain	58 (71.6)	19 (86.4)	0.40 (0.11-1.48)	0.34 (0.09-1.31)
Unconscious during hospital stay	6 (7.4)	18 (81.8)	0.02 (0.005-0.070)	0.01 (0.002-0.062)
Median NIHSS at admission if infarction or SAH (± IQR)	4 (6.75)	12 (21.0)	0.93 (0.88-0.98)	0.91 (0.86-0.97)
Median GCS at admission (± IQR)	15 (0)	11 (9)	1.32 (1.16-1.51)	1.35 (1.17-1.56)
mRS 0-1 at 3 months if infarction*	40 (58.8)	3 (13.6)	9.05 (2.44-33.53)	4.08 (0.86-19.44)
mRS 0-2 at 3 months if infarction*	51 (75.0)	7 (31.8)	6.43 (2.25-18.04)	3.11 (0.67-14.35)

SAH: subarachnoid hemorrhage; OR: odds ratio; CI: confidence interval; SD: standard deviation; IQR: interquartile range; NIHSS: National Institutes of Health Stroke Scale; GCS: Glasgow Coma Scale; mRS: modified Rankin Scale

Values are n (%) unless otherwise indicated. Bold font indicates statistical significance. *Novel unpublished data.

‡ Logistic regression, adjusted for age and sex, and mRS additionally adjusted for NIHSS.

5.2 Clinical features of cervicocerebral artery dissections in a patient population from Southern Finland (II)

The characteristics of the patient population of sub-study II are presented in Table 4. A total of 301 consecutive CeAD patients with a mean age of 46.6 years were included. Of them, 280 (93%) had uniarterial and 21 (7%) had multiple dissection. Intracranial or combined dissections constituted 32% of all dissections. However, the location of dissection (intra/extracranial) could be defined only for 234 patients of which 95 (41%) were IDs or CDs. A clear male preponderance was observed (68%, $p<0.001$), and men were older than women (47.7 vs. 44.0, $p=0.006$, OR 1.33, 95% CI: 1.09–6.31). More than 1/3 of the patients had a lifetime history of migraine. MA (63%) was more frequent than MO. Current smoking was reported by 39% of men and 29% of women.

5.2.1 Extracranial vs. intracranial and combined dissections

There were very few differences when comparing EADs with IDs and CDs both in univariate and multivariate analyses (Table 4). Intracranial and combined dissections located more often in vertebrobasilar arteries and they were more often occlusive. Partly due to this, VAD led more frequently to brain infarction. The risk factor profile between these groups was similar, and the groups had as often cervical pain or headache. The groups had similar outcomes.

Table 4.

a) Characteristics of CeAD patients according to dissection site (extra-/intracranial/undetermined)

	EAD	ID & CD	Undetermined
Number of patients (%)	139 (46)	95 (32)	67 (22)
Age, mean (\pmSD)	46.0 (10.6)	45.9 (12.3)	48.5 (9.1)
Women/Men (%)	46/93 (33/67)	33/62 (35/65)	18/49 (27/73)
ICAD/VAD (%)	77/62 (55/45)	38/57 (40/60)	42/25 (63/37)
Multiple dissection*	13 (9)	6 (6)	2 (3)
Risk factors			
Hypertension*	55 (40)	39 (41)	29 (43)
Hypercholesterolemia*	72 (52)	52 (55)	50 (75)
Smoking*	48 (35)	25 (26)	35 (52)
Migraine*‡	46/126 (37)	29/87 (33)	22/60 (37)
Previous infection*	24 (17)	12 (13)	14 (21)
Previous trauma*	63 (45)	39 (41)	20 (30)
Brain infarction	87 (63)	74 (78)	60 (90)
Pain*	113 (81)	70 (74)	48 (72)
Occlusion*	32 (23)	41 (43)	60 (90)
Median NIHSS on admission if infarction (IQR)	2.5 (6)	3 (5)	4 (7.75)
mRS 0-2 at 3 months if infarction	69/86 (80)	57/75 (76)	43/58 (74)
mRS 0-1 at 3 months if infarction	46/86 (54)	40/75 (53)	27/58 (47)

b) Differences between extracranial and intracranial CeAD

	EAD vs. ID&CD* OR <i>unadjusted</i> (95% CI)	EAD vs. ID&CD* OR <i>adjusted</i> (95% CI) †
Age, mean (\pm SD)	1.00 (0.98-1.02)	1.00 (0.97-1.02)
Women/Men	0.93 (0.54-1.61)	1.00 (0.56-1.76)
ICAD/VAD	1.86 (1.10-3.16)	1.88 (1.10-3.22)
Multiple dissection	1.53 (0.56-4.18)	1.47 (0.53-4.07)
Risk factors		
Hypertension	0.94 (0.55-1.60)	0.92 (0.53-1.61)
Hypercholesterolemia	0.89 (0.53-1.50)	0.93 (0.53-1.64)
Smoking	1.48 (0.83-2.63)	1.40 (0.78-2.53)
Migraine‡	1.13 (0.64-1.97)	1.19 (0.66-2.15)
Previous infection	1.44 (0.68-3.05)	1.33 (0.62-2.85)
Previous trauma	1.19 (0.70-2.02)	1.23 (0.72-2.11)
Brain infarction	0.45 (0.25-0.81)	0.52 (0.27-0.98)
Pain	1.55 (0.83-2.90)	1.73 (0.89-3.33)
Occlusion	0.39 (0.22-0.69)	0.41 (0.23-0.74)
Median NIHSS on admission if infarction (IQR)	0.98 (0.94-1.03)	0.96 (0.91-1.01)
mRS 0-2 at 3 months if infarction	1.28 (0.61-2.71)	1.17 (0.39-3.52)
mRS 0-1 at 3 months if infarction	1.01 (0.54-1.87)	0.96 (0.46-2.01)

Values are n (%) unless otherwise indicated. Bold font indicates statistical significance. CeAD: cervicocerebral artery dissection; EAD: extracranial dissection; ID: pure intracranial dissection; CD: intracranially extending dissection *i.e.* 'combined' dissection. Undetermined: Due to occlusion it was uncertain whether the dissection extended intracranially; OR: odds ratio; CI: confidence interval; SD: standard deviation; ICAD: internal carotid artery dissection; VAD: vertebrobasilar artery dissection; NIHSS: National Institutes of Health Stroke Scale; IQR: interquartile range; mRS: modified Rankin Scale
 *Novel unpublished data. ‡Only patients with available migraine data are included.
 † Logistic regression, adjusted for age, sex, and CeAD location (ICA/VA), and mRS additionally adjusted for NIHSS.

5.2.2 ICAD vs. VAD

Dissections occurred equally often in ICA (n=157, 52%) and VA (n=144, 48%) (Table 5). ICAD patients had two times more frequently previous infections, and ICAD was more often extracranial than VAD. VAD led to brain infarction more often, but admission NIHSS score was higher among ICAD patients. ICAD patients had a poorer prognosis assessed by 3-month mRS.

In multivariable analyses, there was no longer statistically significant difference in outcome between ICAD and VAD; outcome was mostly dependent on admission NIHSS. Multiple dissections were as frequent between ICAD and VAD. ICAD and VAD groups did not differ statistically regarding age, sex, vascular risk factors, migraine, and previous trauma. However, in a subgroup analysis, patients with extracranial ICAD were older than extracranial VAD patients (48.7 vs. 42.7 years, $p=0.001$, T-test), but in intracranial dissections this was vice versa, although not statistically significant (ICAD 45.1; VAD 46.4 years, $p=0.616$).

Table 5. Comparison of patients with ICAD and VAD

	ICAD (n=157, 52%)	VAD (n=144, 48%)	ICAD vs. VAD* OR <i>unadjusted</i> (95% CI)	ICAD vs. VAD* OR <i>adjusted</i> (95% CI) †
Age, mean (±SD)	47.3 (10.3)	45.8 (11.5)	1.01 (0.99-1.03)	1.02 (1.00-1.05)
Women/Men (%)	43/114 (27/73)	54/90 (37/63)	0.63 (0.39-1.02)	0.64 (0.37-1.14)
EAD/ID&CD (%)*	77/38 (67/33)	62/57 (52/48)	1.86 (1.10-3.16)	1.88 (1.10-3.22)
Multiple dissection*	13 (8)	8 (6)	1.54 (0.62-3.82)	1.39 (0.52-3.69)
Risk factors				
Hypertension*	67 (43)	56 (39)	1.17 (0.74-1.85)	1.04 (0.60-1.82)
Hypercholesterolemia*	86 (55)	88 (61)	0.77 (0.49-1.22)	0.57 (0.32-1.01)
Smoking*	61 (39)	47 (33)	1.31 (0.82-2.11)	1.41 (0.79-2.50)
Migraine*‡	47/138 (34)	50/135 (37)	0.88 (0.54-1.44)	0.63 (0.51-1.70)
Previous infection*	33 (21)	17 (12)	1.99 (1.05-3.75)	1.76 (0.83-3.71)
Previous trauma*	59 (38)	63 (44)	0.77 (0.49-1.23)	0.81 (0.48-1.38)
Brain infarction	99 (63)	122 (85)	0.29 (0.17-0.51)	0.18 (0.09-0.35)
Pain*	112 (71)	119 (83)	0.52 (0.30-0.91)	0.65 (0.34-1.26)
Occlusion*	67 (43)	66 (46)	0.88 (0.56-1.39)	0.50 (0.28-0.92)
Median NIHSS on admission if infarction (IQR)	7 (13)	2 (4)	1.20 (1.13-1.27)	1.19 (1.11-1.27)
mRS 0-2 at 3 months if infarction	57/96 (59)	112/123 (91)	0.14 (0.07-0.30)	0.90 (0.26-3.08)
mRS 0-1 at 3 months if infarction	31/96 (32)	82/123 (67)	0.24 (0.14-0.42)	0.55 (0.24-1.24)

Values are n (%) unless otherwise indicated. Bold font indicates statistical significance.

ICAD: internal carotid artery dissection; VAD: vertebralbasilar artery dissection; OR: odds ratio; SD: standard deviation;

CI: confidence interval; EAD: extracranial dissection; ID: pure intracranial dissection; NIHSS: National Institutes of Health Stroke Scale;

CD: intracranially extending dissection i.e. 'combined' dissection; mRS: modified Rankin Scale

*Novel unpublished data. ‡Only patients with available migraine data are included.

† Logistic regression, adjusted for age, sex, and dissection site (extra-/intracranial), and mRS additionally adjusted for admission NIHSS.

5.2.3 Outcome and recanalization

A favorable outcome (mRS 0-2) at 3 months was observed in 83% of all patients, and excellent outcome (mRS 0-1) in 63%. All patients without brain infarction achieved mRS 0-2. Age had no correlation on favorable outcome in univariate analyses. In univariate analyses, poor outcome was associated with ICAD, higher admission NIHSS, brain infarction, and occlusion. Total recanalization occurred in 153 patients (54%). Younger age was related to recanalization, whereas recanalization occurred less often among smokers and those with occlusion. Patients with recanalization had returned to work more often by 3 months, whereas recanalization did not associate with better outcome measured by mRS. Six (2%) new CeADs were observed during the follow-up (mean 4 years).

Presence or absence of brain infarction and NIHSS at admission remained the strongest predictors of outcome in multivariable logistic regression performed for this thesis. Recent infections and older age were also associated with worse outcome (Table 6). In addition to younger age, non-smoking, and stenosis, previous cervical trauma was related to higher recanalization rate in logistic regression (data not shown).

Table 6. Predictors of excellent outcome (mRS 0-1)

	mRS 0-1	mRS 2-6	OR (95% CI)	OR (95% CI) †
Number of patients (%)	188 (63.3)	109 (36.7)		
Age, mean (±SD)	45.4 (10.7)	48.1 (11.1)	0.98 (0.96-0.999)	0.96 (0.92-0.995)
Women/Men (%)	60/128	72/37	0.91 (0.55-1.51)	0.72 (0.29-1.82)
ICA/VA (%)	85/103 (45/55)	68/41 (62/38)	0.50 (0.31-0.81)	0.63 (0.25-1.64)
ED	96 (51.1)	41 (37.6)	0.028*	0.99 (0.44-2.24)
ID/CD	59 (31.4)	36 (37.6)		
Undetermined	33 (17.6)	32 (29.4)		
Multiple dissection	14 (7.4)	7 (6.4)	1.17 (0.46-3.00)	1.09 (0.26-4.68)
Risk factors				
Hypertension	79 (42.0)	41 (37.6)	1.20 (0.74-1.95)	0.82 (0.35-1.89)
Hypercholesterolemia	108 (57.4)	62 (56.9)	1.02 (0.64-1.65)	1.48 (0.63-3.48)
Diabetes	12 (6.4)	5 (4.6)	1.42 (0.49-4.14)	4.10 (0.30-56.38)
Smoking	69 (36.7)	36 (33.0)	1.18 (0.72-1.93)	1.33 (0.54-3.27)
Migraine	66 (35.1)	34 (31.2)	1.11 (0.64-1.84)	0.64 (0.26-1.58)
Previous infection	25/188 (13.3)	24/109 (22.0)	0.54 (0.29-1.01)	0.24 (0.07-0.65)
Previous trauma	87 (46.3)	35 (32.1)	1.82 (1.11-2.98)	1.04 (0.44-2.45)
Brain infarction	75 (60.1)	106 (97.2)	0.04 (0.01-0.14)	0.05 (0.01-0.27)
Pain	151 (80.3)	78 (71.6)	1.62 (0.94-2.81)	0.66 (0.25-1.78)
Occlusion	72 (38.3)	59 (54.1)	0.53 (0.33-0.85)	1.21 (0.48-3.06)
Recanalization	103 (56.9)	50 (50.0)	1.32 (0.81-2.45)	0.93 (0.36-2.37)
Median NIHSS at admission if infarction	2 (4)	6 (13)	0.78 (0.72-0.85)	0.78 (0.70-0.87)

Values are n (%) unless otherwise indicated. Bold font indicates statistical significance.

mRS: modified Rankin Scale; OR: odds ratio; CI: confidence interval; SD: standard deviation;

ICAD: internal carotid artery dissection; VAD: vertebralbasilar artery dissection; EAD: extracranial dissection;

ID: pure intracranial dissection; CD: intracranially extending dissection i.e. 'combined' dissection.

Undetermined: Due to occlusion it was uncertain whether the dissection extended intracranially.

NIHSS: National Institutes of Health Stroke Scale; IQR: interquartile range. * *p*-value (chi-square)

† Logistic regression with age, sex, site of dissection (ED or ID/CD and ICA/VA), risk factors, pain, occlusion, multiple dissection, recanalization and admission NIHSS as covariates.

5.4 Vascular risk factors in cervical artery dissection (IV)

We assessed the frequency of vascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, current smoking, and BMI) between 690 (mean age 44.2±9.9 years; prospective 232, 34%) Belgian, French, Finnish, or Italian CeAD patients, 556 age-, sex-, and country-matched non-CeAD IS patients (44.7±10.5 years), and 1170 healthy referents (45.9±8.1 years). About ¾ of the CeAD patients had ischemic stroke or TIA, majority (56%) were men, and 65% had ICAD. Most strokes in the non-CeAD IS group were cardioembolic (37%) or of undetermined origin (41%).

Compared with healthy controls, CeAD patients had less often hypercholesterolemia (19 vs. 29%, *p*<0.0001), and their BMI was lower (24.5 vs. 25.9, *p*<0.0001). After sensitivity analysis excluding participants <35 years, also diabetes was less frequent among CeAD

patients (OR 0.43, 95%CI 0.23-0.81, $p=0.009$). However, CeAD patients had more hypertension (25 vs. 19%, $p<0.0001$). In the secondary analyses, we assessed vascular risk factor separately for ICAD/VAD, presence or absence of cerebral ischemia, and prospective/retrospective recruitment, all compared with healthy referents, and the results remained practically identical. However, in the subgroup of VAD, the association between smoking and CeAD became statistically significant (OR 1.39, 95%CI 1.02–1.89, $p=0.03$).

In comparison with non-CeAD IS patients, all vascular risk factors were less frequent in CeAD patients (P for all <0.0001), but in logistic regression adjusted also for all vascular risk factors, the difference in diabetes was no longer significant. In secondary analyses, country of inclusion or stroke etiology (large-artery atherosclerosis, small-vessel disease, and cardioembolism vs. patients other determined cause or undetermined cause) did not affect the results.

5.5 Migraine and cervical artery dissection (V)

5.5.1 CeAD_{stroke} vs. non-CeAD IS

Migraine was more common in CeAD_{stroke} patients (35.7 vs. 27.4%, $p=0.003$) in a multivariate model, adjusted for age, sex, country, prospective/retrospective inclusion, hypertension, hypercholesterolemia, smoking, diabetes, BMI, and use of oral contraceptives or hormone replacement therapy. The difference was due to MO (20.2 vs. 11.2%, $p<0.001$), since the frequencies of MA were not different (13.1 vs. 15.8%, $p=0.322$).

Non-CeAD IS patients with PFO had more migraine, especially MA, compared with other IS etiologies (overall migraine 36 vs. 23%, $p=0.001$; MO 12 vs. 11%, $p=0.559$; MA 23.6 vs. 12.4%, $p<0.001$). When patients with PFO ($n=197$ non-CeAD IS and 36 CeAD_{stroke} patients) were excluded, and analyzed were only patients in whom echocardiography was done, the difference between CeAD_{stroke} and non-CeAD IS groups regarding overall migraine became even clearer (37.8 vs. 23.4, $p>0.001$), but the difference in MA remained statistically insignificant (12.2 vs. 12.4%, $p=0.938$).

5.5.2 CeAD patients with and without migraine

In univariate analysis, CeAD patients with and without migraine differed in 6 aspects. The migraineurs were a bit younger and slimmer, they were more often female, had more often headache and tinnitus, and slightly less often hypercholesterolemia. After adjustment for age, sex, prospective/retrospective inclusion and country of inclusion, only sex and frequency of headache remained statistically significant. There was no difference in terms of hypertension, diabetes, smoking, admission NIHSS score, prior minor trauma, dissected vessel (ICA or VA), vessel patency (occluded or non-occluded), occurrence of ischemia, multiple dissections, or dissecting aneurysms.

6 DISCUSSION

6.1 Intracranial dissections (I)

The sub-studies I and II included both intra- and extracranial dissections. In our sample, the proportion of intracranial or intracranially extending dissections of all cervicocerebral dissections was approximately 1/3. Our results indicate that if initial brain CT does not reveal bleeding, the risk of subsequent SAH from dissection is very low. About $\frac{3}{4}$ of patients with ID or CD occurred without SAH, had favorable prognosis, and could be treated with anticoagulants. The rest $\frac{1}{4}$ had SAH and poorer prognosis. Even if we showed anticoagulation in non-SAH patients to be safe, there is, however, no evidence of its efficacy or benefits in IADs.

The distinction of ischemic and hemorrhagic dissections has become clearer during the past years⁷. The favorable outcome in initially unruptured IADs was recently confirmed in two relatively large patient series. Among 178 South-Korean patients with intracranial unruptured VADs¹⁵⁸, none had SAH during follow-up (mean 46 months). All patients with headache only (n=76), and majority (92 out of 102) of those with ischemic symptoms achieved mRS 0 to 1. A Japanese study of 206 IADs in 190 patients by Mizutani *et al.*¹⁹ had two groups: unruptured IADs (n=98) and SAH patients (n=108). Only one patient in the non-SAH group had bleeding complications during a follow-up of over 3 years. When headache preceded onset of SAH, the delay between pain and bleeding was 0 to 3 days in 96%, and the longest delay was 11 days. The authors state that the repair process after artery injury begins shortly after disruption and is completed in about 2 months. In agreement with our study, there were more women in the SAH group than in the non-SAH group.

Our patient population had similar characteristics with 25 Australian patients with pure intracranial dissection¹⁵⁹. The non-SAH patients were younger than those with SAH, and ischemic manifestations were most common in the anterior circulation whereas SAH occurred mostly in the posterior circulation. Treatment with antiplatelet or anticoagulant therapy did not lead to bleeding complications. However, the differences in outcome between non-SAH and SAH patients were not statistically significant in that study¹⁵⁹. This may in part be due to a small patient number, and different cut-off for good recovery: they considered mRS 0 to 3 favorable outcome¹⁵⁹.

6.2 Clinical features of cervicocerebral artery dissections in a Finnish patient population (II)

Our study sample of 301 patients was a representative population of CeAD patients, since it included practically all hospitalized CeAD cases in a large population of 1.5 million inhabitants. The mean age was similar to other publications on CeAD⁴², and we confirmed the previous results about male preponderance in CeAD and that CeAD occurs

later in men ⁶⁵. The sex differences are most likely multifactorial, and may be related to different rates of risk factors (hypertension, migraine, trauma) and to hormonal status between men and women ¹⁶⁰. These factors also change with increasing age ¹⁴⁷.

We observed a high frequency of migraine among CeAD patients in sub-study II. This finding led to a more detailed study on this subject ⁸⁶ with a proper control group. However, the exact mechanism for the association of CeAD and migraine is not yet clear.

According to Statistics Finland, the average prevalence of adult (15–64 years) smokers in Finland from 1994 to 2006 was 27% for men (range: 26–30%) and 20% for women (18–20%) (http://www.stakes.fi/tilastot/tilastotiedotteet/2011/liitetaulukot/Tr44_11_liitetaulukot.pdf). Compared to these figures, CeAD patients were more often smokers, but there was no proper control group in the sub-study II.

ICAD patients had less brain infarctions and had more frequently previous infection than patients with VAD, although the latter was no longer statistically significant after adjustment for age, sex and dissection site. These findings were confirmed later in the large CADISP cohort, which partly overlaps with the patient population in sub-study II ¹⁶¹. In CADISP ¹⁶¹ and some other publications ^{63 65}, ICAD patients were older than those with VAD. In our series this difference was not statistically significant. Interestingly, the difference became significant in the subgroup of patients with EAD, while in IADs this was vice versa. The difference in age of ICAD vs. VAD between the CADISP study and sub-study II can thus be explained by the fact that purely intracranial dissections were excluded from CADISP. The CADISP study comparing ICAD and VAD reported that the proportion of women is greater in VAD than in ICAD ¹⁶¹. There was a similar trend in the sub-study II which did not reach statistical significance. A small series of Lee *et al.* ⁶³ had opposite results, whereas in a Swiss population there was no sex difference between ICAD and VAD. A later study from CADISP, reporting sex differences in CeAD, showed that after adjustment for age, women no longer had more VAD than men ¹⁶⁰. ICAD and VAD seem to differ regarding risk factors, and occurrence and severity of stroke. This may in part be explained by the differences in embryonic origin of these arteries ¹⁶¹ and the mechanical stress to which they are exposed. These factors emphasize the importance of taking into account the site of the dissection when analyzing factors related to CeAD.

In our study, patients with extracranial or intracranial and combined dissections had similar outcomes. The publications comparing extra- and intracranial dissections in Caucasian patients are scarce, and the patients presenting with and without SAH should not be regarded as one entity. A recent study from the US ¹⁵² reported more frequently (35 vs. 16%, $p=0.018$) neurologic deterioration (new TIA/ischemic stroke or death within 1 year) among patients with intracranial involvement, but only 69 patients were included. Of these 69 patients, 23 (33%) were intracranial or extended intracranially. This is in agreement with our results (32%).

Previous infection is a known risk factor for worse outcome in brain infarcts ¹⁶². The sub-study II confirmed these results and showed that this is true also in ischemic stroke due to

CeAD, even after adjustment for confounding factors. Recanalization had no association with outcome measured by mRS, but the patients in whom recanalization occurred, returned more often to work by 3 months. Modified Rankin Scale may be too coarse to assess subtle differences in recovery.

6.3 CADISP study protocol (III)

Several lines of evidence support the idea that genetic risk factors may contribute to CeAD, for example autosomal-dominantly inherited dermal connective tissue alterations, some cases of familial CeAD, and CeAD occurrence in monogenic connective tissue diseases²⁶. CeAD is a relatively rare disorder, but large patient numbers are needed for GWAS analyses. The international CADISP study has allowed establishing the largest register of CeAD patients to date. Most of the patients in the clinical part of CADISP are European (altogether 18 patients were from Argentina and Turkey), but also a few centers from the USA participated in the genetics part. There are major genetic differences between people from different countries, also within Europe. This population stratification was taken into account using statistical methods. CADISP was the first group that performed systematic evaluation of CeAD genetics. CADISP GWAS analysis is completed, and it was successful even though the number of patients was lower than what is recommended for similar studies, and yielded very interesting results (Debette *et al.*, submitted). Previous genetic studies on CeAD have been mostly negative. This is in part due to small sample sizes and the fact that they used candidate gene approach which requires an a priori hypothesis^{26 76}. Some findings on previous candidate genes related to CeAD²⁶ could not be confirmed. Initially, healthy controls from the pre-existing databases (see Chapter 4.1.2) were planned to be used in the GWAS. However, we were able to use the large registry of more than 14000 anonymized control individuals at the CNG.

Deciphering genetic secrets of CeAD and examining numerous issues in a large multicenter registry does not only serve for shedding light on pathophysiology of CeAD, but gives a solid example for future studies targeting at other understudied etiologies of ischemic stroke, such as fibromuscular dysplasia and moyamoya disease.

6.4 Vascular risk factors (IV)

CeAD patients differ from both non-CeAD IS patients and healthy population in terms of vascular risk factors. When assessing the difference between CeAD and referents, it is important to know if the control group represents ischemic or healthy people. Regarding vascular risk factors, comparing CeAD and non-CeAD IS patients shows that the CeAD group is basically healthy with fewer vascular risk factors¹⁰⁵ but it does not reveal information that is needed for understanding the pathology in CeAD. Therefore, it is important to also have a healthy population for the comparisons.

It seems that hypertension is a risk factor for CeAD. It was hypothesized ⁶ that hypertension-induced changes in the arterial wall are more marked in the internal layers. This would increase the risk of an internally located dissection, leading to stenosis and occlusion more often than a subadventitial tear. It is, however, not known whether the mechanism of dissection in patients with hypertension is due to a long-standing elevated pressure against the vessel wall or to short, steep daily blood pressure changes ⁶. It is possible that the association is vice versa: the changes in the connective tissue properties may lead to elevated blood pressure. Calvet *et al.* ¹⁶³ compared 32 CeAD patients with 32 healthy controls who had similar blood pressures in order to measure carotid wall properties. CeAD was associated with increased stiffness of the vessel wall. In sub-study IV, the association of hypertension and CeAD was more pronounced in the subgroup of ischemic CeAD patients. This is in agreement with the results of Pezzini *et al.* ⁶. One explanation for this could be higher magnitude of hypertension-induced changes in the inner parts of the arterial wall compared to the outer layers – resulting in stenoses and occlusions, and thus in infarctions, more often than dissection affecting the outer layers ⁶. Hypertension alone may not, however, have a major role in CeAD pathogenesis since frequency of hypertension increases with age but CeAD occurs in younger individuals.

CeAD patients tend to be healthy and often do a lot of sports. This can indirectly be confirmed by our finding that their BMI is lower than both non-CeAD IS patients and healthy controls. It is also in agreement with the study of Arnold *et al.* ¹⁰⁶ with mean BMI 22.9 for CeAD patients and 24.5 for healthy controls. The negative association of CeAD and hypercholesterolemia is a novel finding. Previous studies have reported similar hypercholesterolemia rates for CeAD patients and healthy controls. The results may in part depend on the reference values used (for example, hypercholesterolemia was defined as ≥ 6.2 mmol/l in the CADISP study, > 5.7 in an earlier Italian study ¹⁶⁴, and > 5.2 in the study of Arnold *et al.* ¹⁰⁶) and the size of study populations. However, the previous and current results implicate that elevated cholesterol is not a risk factor for CeAD. Whether it is a protecting factor remains to be confirmed. It was discussed ¹⁶³ that a heterogeneous echostructure in the arterial wall is more prone to tear and dissection. With aging and atherosclerosis, collagen and elastin cross-links come more abundant and the vessel wall becomes more homogenous. Hypercholesterolemia, diabetes, and high BMI could accelerate this process ^{163 165}. This could be one explanation why CeAD occurs at a younger age.

There was a trend for current smoking being more common among CeAD patients than healthy controls in sub-study IV (OR 1.22, 95% CI 0.99–1.50, $p=0.07$), and the difference became statistically significant in the subgroup of VAD. In sub-study II, smokers had a lower rate of recanalization, although recanalization had no correlation with outcome, nor did smoking itself. Even though the association of smoking and CeAD is not strong, smoking might be an additional risk factor for the disease. It is known that smoking is a risk factor for impaired wound healing and post-surgical infections ¹⁶⁶. The suggested mechanisms could also be related to CeAD pathology: detrimental vasoactive effect in tissues with fragile blood supply, impaired inflammatory healing response, and alteration of collagen metabolism ¹⁶⁶. It can be speculated that in non-smokers, small tears in the

cervical artery wall are more often healed spontaneously without causing any CeAD symptoms.

6.5 Cervical artery dissection and migraine (V)

In the sub-study V we confirmed previous results of migraine being common among CeAD patients. In the interpretation of results from various studies of migraine in CeAD, the control group used should be taken into account. In the sub-study V, the referents were patients with ischemic stroke due to another cause than CeAD. CeAD patients had more MO, and the proportion of MA were similar among CeAD and non-CeAD IS patients. This is in agreement with previous studies^{81 82}. It is also known that IS patients have more MA than healthy controls⁸⁰. Based on these facts, it seems justified to conclude that both MO and MA are associated with CeAD patients compared to healthy controls. The few studies on this subject support this idea^{82 86}. We can also state that the non-CeAD IS patients are not a neutral control group regarding migraine, and non-CeAD IS patients and healthy controls should not be combined in meta-analyses⁸⁵.

The frequency of migraine was similar in CeAD patients with and without stroke. This indicates that the occurrence of ischemic stroke in CeAD patients is independent of migraine history. In a study of Arnold *et al.*⁹⁴, ischemic CeAD patients had less migraine than non-ischemic but the difference disappeared in a multivariate analysis.

We did not observe differences in vascular risk factors among CeAD patients with or without migraine. It has been debated whether migraineurs from the general population have more vascular risk factors than the non-migraineurs or not. A higher risk of ischemic events (*e.g.* coronary heart disease and stroke) and vascular risk factors have been associated with MA¹⁶⁷. However, in a study of Pezzini *et al.*⁹², with 981 young stroke patients but no healthy controls, patients with MA had less cardiovascular risk factors than non-migraineurs. Similarly, according to Schwaiger *et al.*¹⁶⁸, prevalence, severity, and 5-year progression of atherosclerosis did not differ significantly between migraineurs and nonmigraineurs. As we know from sub-study IV, CeAD patients are generally quite healthy and have few vascular risk factors, except for hypertension, and thus statistically significant differences among CeAD patients with or without migraine – if they exist – would require extremely large patient groups. The only factor that distinguished CeAD patients with and without migraine was higher frequency of headache in the acute phase. This may be related to sensitization to pain⁹⁶.

The association of CeAD and migraine seems clear, although it is not known whether there is a causal relationship or both conditions have a common predisposing factor. This issue is to be explored in future studies.

6.6 Strengths and limitations

The strength of the sub-studies I and II was relatively large patient population and single-center design. In our region, practically all CeAD and SAH patients are diagnosed and treated in the neurological and neurosurgical units of our hospital, which use the same electronic healthcare records. Therefore, the patient material is practically population-based. Moreover, for the sub-study I, patients from both neurologic and neurosurgical units were recruited.

The strengths of the CADISP study are i) large sample size, made possible by international multicenter recruitment, ii) collection of a homogenous patient population by using strict inclusion and exclusion criteria, iii) use of a detailed, standardized questionnaire, iv) two control groups: non-CeAD IS patients from the same centers as CeAD patients, and healthy controls, and v) for the genetic part, systematic search for polymorphisms associated with CeAD, as well as using candidate gene approach, which allows to confirm previous studies.

The limitations of the study are as follows. Since the patient records of SAH patients were checked retrospectively and many of them died, the data concerning risk factors and symptoms could not be assessed reliably. The sub-study II lacked a control group, and comparisons of CeAD patients and healthy population regarding vascular risk factors and migraine were done indirectly. Despite using the standardized questionnaire in CADISP, we had no data on frequency of migraine in non-Finnish healthy controls. The recruitment of healthy controls was done as part of CADISP in one center only, and for many centers healthy controls were not available at all. The collection of data for healthy controls was heterogeneous across countries: for French/Belgian and Italian healthy controls, weight and height were measured, whereas for others the data was based on self-reported values. In addition, for the Finnish healthy controls, blood pressure or cholesterol levels were not measured during recruitment process. CeAD patients were recruited in neurological departments. Therefore, some patients with very mild or no symptoms were likely to be underdiagnosed and unrecruited, as well as those with severe and lethal strokes.

7 CONCLUSIONS

Dissections in intracranial parts of ICA and VA or basilar artery can be safely treated with anticoagulants if there is no evidence of acute SAH at admission. These patients have a favorable prognosis (I). CeAD occurs predominantly in men. It is possibly associated with smoking and migraine, especially migraine with aura. Older age, stroke severity, and recent infection may predict poorer outcome (II).

In relatively rare diseases such as CeAD, multicenter registries are an important way to collect reliable information (III). CeAD patients have less vascular risk factors than patients with ischemic stroke due to a cause other than CeAD. Compared to healthy controls, CeAD patients have more hypertension but less hypercholesterolemia and overweight (IV).

CeAD patients have more migraine without aura compared to non-CeAD IS patients. CeAD patients with migraine are more often women and have more often headache as CeAD symptom than patients without migraine (V).

The increase in the knowledge about CeAD as one of the most important single etiologies of ischemic stroke in young adults has been rapid in the past years. Yet, many dissections remain undiagnosed. Studies on the field thus concentrate on characteristics of diagnosed CeAD patients, while the fraction of undiagnosed CeADs with mild symptoms is unknown. The results may not be directly applicable to all CeAD cases, but they can be regarded valid for the patient population that is diagnosed and treated in our hospitals. Fortunately, CeAD without ischemia is usually a benign disease with a relatively low rate of symptomatic recurrences.

In this thesis, several potential risk factors for CeAD were examined. In contrast with individuals having treatable risk factors such as overweight, diabetes, hypertension, elevated cholesterol values, and a physically inactive life style that are at risk of other cerebrovascular diseases, CeAD patients typically have no significant comorbidities. Migraine and hypertension were common among CeAD patients, but for the present we do not know the pathogenesis of CeAD sufficiently, and we have no primary prevention for the disease. To reach these goals, studies like this one are much needed, providing information about the clinical characteristics, risk factors and comorbidities.

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