CERVICOCEPHALIC ARTERY
DISSECTION
Radiological study with clinical outcome

OUTI
PELKONEN
Department of Diagnostic Radiology,
Department of Neurology,
University of Oulu

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Radiological study with clinical outcome

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Abstract

The aim of this study was to analyze angiographic findings and the presence and topography of cerebral ischemic and/or hemorrhagic lesions in cerebral CT or MRI, and to assess the long-term clinical outcome of a series of 136 consecutive cervicocephalic artery dissection (CCAD) patients. Pulsatile tinnitus was evaluated as a symptom of CCAD. Medical records and films were reviewed retrospectively.

Irregular stenosis was found in angiography in 50% and occlusion in 33% of the dissected cervicocephalic arteries. Irregular stenosis normalized in 81% and occlusion recanalized in 34%. Other findings, such as pseudoaneurysms, intimal flaps, double lumens, and irregular dilatations were rare and often remained unchanged in follow-up.

Pulsatile tinnitus was a presenting symptom in 12% of the CCAD patients, but the majority of patients had concomitant head or neck pain, ischemic brain symptoms, Horner's syndrome, or cranial neuropathies.

Of the 131 patients who underwent brain imaging, 73 (56%) had signs of infarction in cerebral CT or MRI. Occlusion of the dissected vessel was accompanied by infarction in 76%, irregular stenosis in 40%, and other findings only rarely. Of the anterior circulation infarctions, 95% (39/41) were territorial, subcortical, or territorial infarctions with fragmentation and could thus be considered embolic. Subarachnoid hemorrhage was found in CT in 5 of the 22 patients (23%) with intracranial dissection.

The patient's long-term clinical outcome was assessed using two methods: a classification into categories based on neurological symptoms and defects and the modified Rankin Scale (mRS). Of the 136 CCAD patients, 60% recovered with no or mild disability and 79% scored 0–2 on mRS. In the case of dissection of one or more cervicocephalic arteries without occlusion, the figures were 75% and 89%. In the case of occlusive dissection of one or more arteries, only about 35% of the patients recovered well, having no or mild disability, and 61% scored 0–2 on mRS. No significant differences were seen in recovery after intra- and extracranial dissections.

In conclusion: irregular stenosis, which is the most common angiographic finding in CCAD, is associated with brain infarction less frequently than occlusion, and the long-term clinical outcome is good in most cases. Occlusion of the dissected vessel causes more brain infarctions, and only about 35% of the patients recover well, having no or mild disability. More than 10% of CCAD patients have pulsatile tinnitus as a presenting, and sometimes the only symptom.

Keywords: angiography, cerebral infarction, dissection, internal carotid artery, outcome, pulsatile tinnitus, stroke, vertebral artery
To Hannu and Jere
This study was carried out at the Department of Diagnostic Radiology, University of Oulu, during the years 1996–2003.

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Oulu, January 2004

Outi Pelkonen
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AICA</td>
<td>anterior inferior cerebellar artery</td>
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<tr>
<td>ACA</td>
<td>anterior cerebral artery</td>
</tr>
<tr>
<td>ACAD</td>
<td>anterior cerebral artery dissection</td>
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<tr>
<td>ASA</td>
<td>acetylsalisylic acid</td>
</tr>
<tr>
<td>CBF</td>
<td>cerebral blood flow</td>
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<tr>
<td>CBV</td>
<td>cerebral blood volume</td>
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<tr>
<td>CCAD</td>
<td>cervicocephalic artery dissection</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>DSA</td>
<td>digital subtraction angiography</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted imaging</td>
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<tr>
<td>EPI FLAIR</td>
<td>echo planar imaging, fluid-attenuated inversion recovery</td>
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<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>FMD</td>
<td>fibromuscular dysplasia</td>
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<tr>
<td>HU</td>
<td>Hounsfield Unit</td>
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<tr>
<td>ICA</td>
<td>internal carotid artery</td>
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<tr>
<td>ICAD</td>
<td>internal carotid artery dissection</td>
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<td>IVUS</td>
<td>intravascular ultrasound</td>
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<td>MCA</td>
<td>middle cerebral artery</td>
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<td>MCAD</td>
<td>middle cerebral artery dissection</td>
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<tr>
<td>MDCT</td>
<td>multidetector computed tomography</td>
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<tr>
<td>MIP</td>
<td>maximum-intensity projection</td>
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<td>MR</td>
<td>magnetic resonance</td>
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<td>MRA</td>
<td>magnetic resonance angiography</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>mRS</td>
<td>modified Rankin Scale</td>
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<td>PC</td>
<td>phase contrast</td>
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<td>posterior cerebral artery</td>
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<tr>
<td>PCAD</td>
<td>posterior cerebral artery dissection</td>
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<td>PD</td>
<td>proton density</td>
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<tr>
<td>PICA</td>
<td>posterior inferior cerebellar artery</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>PICAD</td>
<td>posterior inferior cerebellar artery dissection</td>
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<tr>
<td>PWI</td>
<td>perfusion-weighted imaging</td>
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<tr>
<td>RF</td>
<td>radio frequency</td>
</tr>
<tr>
<td>SAH</td>
<td>subarachnoid hemorrhage</td>
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<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
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<tr>
<td>T</td>
<td>tesla</td>
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<tr>
<td>TCD</td>
<td>transcranial Doppler ultrasound</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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<tr>
<td>TOF</td>
<td>time-of-flight</td>
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<tr>
<td>TR</td>
<td>time of repetition</td>
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<tr>
<td>T1</td>
<td>longitudinal relaxation time</td>
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<tr>
<td>T2</td>
<td>transversal relaxation time</td>
</tr>
<tr>
<td>VA</td>
<td>vertebral artery</td>
</tr>
<tr>
<td>VAD</td>
<td>vertebral artery dissection</td>
</tr>
<tr>
<td>VENC</td>
<td>velocity encoding</td>
</tr>
<tr>
<td>V1</td>
<td>vertebral artery from origin to entry into the foramen transversarium of a cervical vertebra, usually C6</td>
</tr>
<tr>
<td>V2</td>
<td>C6 to C2 level of the vertebral artery</td>
</tr>
<tr>
<td>V3</td>
<td>vertebral artery from the C2 foramen transversarium to the dura mater</td>
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<tr>
<td>V4</td>
<td>intradural segment of the vertebral artery</td>
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<tr>
<td>2D</td>
<td>two-dimensional</td>
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<tr>
<td>3D</td>
<td>three-dimensional</td>
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List of original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals:


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1 Introduction

Dissection occurs when the intima or media of the arterial wall disrupts, causing an intramural hematoma to develop in the subintimal, medial, or subadventitial layers (Hart & Easton 1983, de Bray et al. 1994, Lal et al. 1994, Provenzale et al. 1995). Spontaneous dissection of the internal carotid artery was first described in 1954 by Jenzer (1954). In 1983, Hart & Easton (1983) reviewed over 180 cervicocephalic artery dissections (CCAD) reported in the literature. Most CCADs, however, remained undiagnosed at that time or were diagnosed postmortem. Along with the development of imaging modalities, CCAD has become an increasingly well known cause of acute strokes and transient ischemic attacks (TIA) in young adults, explaining up to 22–32% of strokes in patients under 40 years of age (Norrving et al. 1986, Bogousslavsky & Regli 1987). The average annual incidence of spontaneous internal carotid artery dissections (ICAD) in all age groups has been estimated to be 2.6 per 100,000 (Schievink et al. 1993). CCAD may occur spontaneously, but extracranial dissections may be caused by many everyday activities, including sudden severe stretching, compression, or both or prolonged extension, flexion, or rotation of the neck. Traumas to the neck or head, common vascular risk factors, and arteriopathies are considered to be associated with CCAD. Some dissections occur as clinically silent. Some patients may have only mild symptoms, such as pulsatile tinnitus or Horner’s syndrome, but CCAD may also cause brain infarctions with persistent neurologic symptoms and signs or even death. Angiography has long been the golden standard in diagnosing CCAD, showing indirect signs of dissection in the vessel lumen. It is still the best imaging modality to show filiform stenosis with very slow blood flow, changes due to fibromuscular dysplasia (FMD), and other irregularities of the vessel wall (Schulze et al. 1992, Link et al. 1996). There are no randomized trials of the different treatment regimens in CCAD, and both treatment and prognosis remain controversial.

The purpose of this retrospective study was to evaluate the angiographic spectrum and course and the long-term clinical outcome of CCAD. Pulsatile tinnitus was evaluated as a presenting symptom. Brain manifestations were analyzed and anterior circulation infarctions evaluated in order to find out if the etiology of CCAD-related brain infarctions is embolic or hemodynamic. Long-term clinical outcome was assessed by using two methods: classification into categories based on neurological symptoms and defects and the modified Rankin Scale (mRS). Comparisons were made between the initial findings in the dissected vessels and the frequency and pattern of infarctions and also with the clinical outcome.
2 Review of the literature

2.1 Anatomy of internal carotid and vertebral arteries and pathology of CCAD

The arterial wall is composed of three coats: intima (an internal or endothelial coat), media (a middle or muscular coat), and adventitia (an external or connective-tissue coat). The intima consists of a layer of pavement endothelium, a subendothelial layer, and an internal elastic membrane. The thickness of the arterial wall is mainly due to the media, which consists of elastic fibers alternating with layers of muscular fibers. The adventitia consists mainly of collagen fibers, but also contains elastic fibers, i.e. there is an external elastic membrane between the adventitia and the media. Arteries situated in the cavity of the cranium and the vertebral canal have extremely thin walls relative to their size, the difference being due to the thinness of the external and middle coats. Thin fibro-areolar investments form the sheaths of the arteries and usually enclose the accompanying veins, sometimes also a nerve. The arteries in the cranium are not included in sheaths. All larger arteries are supplied by nutrient blood vessels called the vasa vasorum. Arteries are also supplied by nerves, which are derived from the sympathetic system, but may pass through the cerebrospinal nerves. They form intricate plexuses upon the surfaces of the larger trunks. (Williams et al. 1989.)

Dissection occurs when the intima or media of the arterial wall disrupts, causing an intramural hematoma to develop in the subintimal, medial, or subadventitial layers (Hart & Easton 1983, de Bray et al. 1994, Lal et al. 1994, Provenzale et al. 1995). Whether a primary intimal tear allows blood to pass from the lumen into the arterial wall or whether a primary intramedial hematoma secondarily ruptures into the true lumen is unclear. Most probably, the two mechanisms co-occur. Histological examinations of CCAD are usually done postmortem, and reports are thus rare (Jenzer 1954, Petro et al. 1986, Bogousslavsky et al. 1987, Steinke et al. 1996, Hamada et al. 2001). Intimal tear has not been visible in all cases.

The internal carotid artery (ICA) supplies the anterior part of the brain, the eye and its appendages, and sends branches to the forehead and nose. It may be divided into four portions. The cervical portion begins at the bifurcation of the common carotid artery and
runs almost vertically in front of the transverse processes of the upper three cervical vertebrae to the carotid canal at the base of the skull. It is closely related to the glossopharyngeal (IX), vagus (X), accessory (XI), and hypoglossal (XII) nerves, the superior cervical ganglion of the sympathetic trunk, the superior laryngeal nerve, the internal jugular vein, the pharynx, and the ascending pharyngeal artery. In the petrous portion, ICA enters the canal in the petrous portion of the temporal bone, ascends a short distance, then turns forward and medially, and again ascends as it leaves the canal to enter the cavity of the skull between the lingula and the petrosal process of the sphenoid. A prolongation of the dura mater separates the artery from the bony wall of the carotid canal. The petrous portion of ICA is surrounded by a number of small veins and by filaments of the carotid plexus, derived from the ascending branch of the superior cervical ganglion of the sympathetic trunk. In the cavernous portion, ICA is situated between the layers of the dura mater, forming the cavernous sinus, and in the upper part it perforates the dura mater, forming the roof of the sinus. It is surrounded by filaments of the sympathetic nerve, and it is in a close topographical relationship with the oculomotor (III), trochlear (IV), and abducent (VI) nerves and the ophthalmic and maxillary divisions of the trigeminal nerve (V). In the cerebral portion, having perforated the dura mater, the ICA passes between the optic (II) and oculomotor (III) nerves to the anterior perforated substance at the medial extremity of the lateral cerebral fissure, where it gives off its terminal or cerebral branches. The cervical portion of the internal carotid gives off no branches, but the main branches arising from the cerebral portion are the middle cerebral artery (MCA) and the anterior cerebral artery (ACA). (Williams et al. 1989, Uflacker 1997.)

Extracranial ICAD may be caused by a sudden stretching of the ICA over the transverse processes of the upper cervical vertebrae in hyperextension and flexion or rotation of the neck (Stringer & Kelly 1980). The most usual localization of extracranial ICAD is the cranial part of the bulbus up to the skull base, i.e. foramen lacerum (Mokri et al. 1986, Ast et al. 1993, Klufas et al. 1995).

The vertebral artery (VA) is the first branch of the subclavian artery. It can be divided into four parts. The first part, often referred to as V1, is the part from the origin to the entry into the foramen transversarium of a cervical vertebra, usually C6. Behind it are the transverse process of the seventh cervical vertebra, the sympathetic trunk, and its inferior cervical ganglion. The second part, V2, courses cranially through the foramina in the transverse processes of the C6-C2. It is in close contact with the trunks of the cervical nerves and surrounded by branches from the inferior cervical sympathetic ganglion and by a plexus of veins. The third part, V3, is the part from the C2 foramen transversarium to the dura mater. V3 issues from the latter foramen and curves backward behind the superior articular process of the atlas. The anterior ramus of the first cervical nerve is on its medial side. V3 runs in the groove on the upper surface of the posterior arch of the atlas, and enters the vertebral canal by passing beneath the posterior atlanto-occipital membrane. The first cervical or suboccipital nerve lies between the artery and the posterior arch of the atlas. The fourth part, V4, is the intradural segment of the vertebral artery. It is placed between the hypoglossal nerve (XII) and the anterior root of the first cervical nerve. At the lower border of the pons, it joins the vessel on the opposite side to form the basilar artery. (Williams et al. 1989, Uflacker 1997.)
Vertebral artery dissection (VAD) may be caused by stretching and compression of the VA over the lateral masses of the C1 and CII vertebral bodies (Sherman et al. 1981, Sheth et al. 2001) in hyperextension and flexion or rotation of the neck. The most frequently affected level was C1-C6 in one study (Chiras et al. 1985), the C1-C2 level in one (Mokri et al. 1988a), and the Th1-C2 level in one (Bartels & Flügel 1996), while one study (Provenzale et al. 1996) failed to establish any predominant site of extracranial VAD. Extracranial dissections most often involve the medial layer or occur subadventitially and expand either outward, causing an increase in the vessel diameter, or inward, causing narrowing or occlusion of the lumen (Petro et al. 1986, Sturzenegger & Huber 1993, de Bray et al. 1994, Klufas et al. 1995).

Intracranial dissections usually involve the intimal and medial layers, and the most common location of intramural hematoma is between the internal elastic lamina and the medial layer (Hart & Easton 1983, Berger & Wilson 1984, O’Connell et al. 1985, Rawat et al. 1992). Intracranial dissections tend to extend inward, causing narrowing or occlusion of the vessel lumen (Luken et al. 1979, Hart & Easton 1983, Sturzenegger & Huber 1993). Pseudoaneurysms develop when the dissection proceeds through the media to the subadventitial layer and causes dilatation of the outer vessel wall (Luken et al. 1979, Hart & Easton 1983, Petro et al. 1986, Lepojärvi et al. 1988, Mokri et al. 1988a). Intracranial dissections may rupture through the adventitia and cause subarachnoid hemorrhage (SAH) (Mokri et al. 1988a, Klufas et al. 1995). Histological studies have shown that intracranial arteries lack an external elastic membrane and have a thinner adventitia, fewer elastic fibers in the media, and generally a thicker internal elastic lamina than extracranial arteries (Wilkinson 1972, Berger & Wilson 1984). The most usual localization of dissection in anterior circulation is the supraclinoidal part of ICA (Rawat et al. 1992, Schievink et al. 1994b). Dissections of the anterior (Ohkuma et al. 2003a) and middle cerebral arteries (Ohkuma et al. 2003b) are less common. In the posterior circulation, the most usual localization of intracranial dissection is the intracranial part of the VA at or near the origin of the posterior inferior cerebellar artery (PICA) (Saver & Easton 1998, Ihara et al. 2002). Dissections of the basilar artery (Leibowitz et al. 2003), PICA (Tikkakoski et al. 1997), posterior cerebral artery (PCA) (Lazinski et al. 2000), and anterior inferior cerebellar artery (AICA) (Hancock & Millar 2000) are rare.

### 2.2 Epidemiology of CCAD

Cerebrovascular diseases were the third leading cause of death in Finland in the year 2000 after heart disease and cancer (Statistics Finland 2002). The annual incidence of stroke in two Finnish studies was 235 (Sivenius 1982) and 236 (Rissanen 1992) per 100,000 population, including the first and recurrent strokes in all age groups. Spontaneous CCAD may explain up to 22–32% of strokes in young patients under 40 years of age (Norrving et al. 1986, Bogousslavsky & Regli 1987) and about 1–2% of all instances of cerebral ischemia (Saver & Easton 1998). There are, however, no reliable epidemiologic reports on the occurrence of CCAD. In a community-based population study carried out in Rochester, Minnesota, the average annual incidence of the most common spontaneous CCAD, ICAD, for all age groups was 2.6 per 100,000 and that for
persons aged 20 years or older 3.5 per 100,000 (Schievink et al. 1993). CCAD occurs predominantly in the mid-40s, but the mean age for intracranial dissections tends to be slightly lower, in the 30s (Saver & Easton 1998). There is no sex predilection.

2.3 Pathogenesis of CCAD

Blunt or penetrating trauma to the neck may cause traumatic CCAD. Spontaneous CCAD is more common, and it is reported to be associated with several genetic and environmental factors. In most cases, however, the pathogenesis remains unclear, and even patients with no apparent risk factors may have CCAD. An arterial dissection is probably the endpoint of a complex and possibly heterogeneous group of vasculopathies developing under the influence of various genetic and environmental factors (Brandt & Grond-Ginsbach 2002).

2.3.1 Genetic

Patients with spontaneous CCAD are thought to have an underlying structural defect of the arterial wall, although the exact type of arteriopathy remains elusive in most cases. FMD, cystic medial necrosis, Marfan’s syndrome, and Ehlers-Danlos syndrome type IV are reported in 14–16% of patients with CCAD (Houser et al. 1984, Chiras et al. 1985, Mokri et al. 1986, Ast et al. 1993, Schievink et al. 1996). FMD shows a female preponderance. Approximately 5% of patients with CCAD have a family history of arterial dissection, which also increases the risk of recurrent dissection (Schievink et al. 1996). Internal carotid artery redundancies – coils, kinks, and loops – are reported to be possible predisposing factors in dissection (Sturzenegger & Huber 1993, Ozodoba et al. 1996). Ultrastructural abnormalities of dermal connective-tissue components have been detected in up to two thirds of patients with spontaneous CCAD (Brandt et al. 1998, Brandt et al. 2001).

2.3.2 Environmental

Because of the anatomic conditions of ICA and VA mentioned in 2.1, sudden severe stretching, compression, or both or prolonged extension, flexion, or rotation of the neck may cause extracranial dissections. The precipitating events reported include motor vehicle accidents, all varieties of sports activity, cervical manipulation, painting a ceiling, anesthesia administration, head turning while reversing a car, and even coughing, vomiting, and sneezing (Schellhas et al. 1980, Stringer & Kelly 1980, Sherman et al. 1981, Zelenock et al. 1982, Chiras et al. 1985, Mokri et al. 1988b, Hoffmann et al. 1993, Leys et al. 1995).
Common vascular risk factors considered to be associated with CCAD are hypertension, smoking, diabetes mellitus, hyperlipidemia, and use of oral contraceptives (Chiras et al. 1985, Mokri et al. 1986, Mokri et al. 1988a, Eljamel et al. 1990, Ast et al. 1993, Bioussé et al. 1994, Sturzenegger 1994, Provenzale et al. 1996). In a recent study, mild hyperhomocyst(e)inemia was also found to be a possible risk factor (Gallai et al. 2001). A recent history of infection is a risk factor for CCAD (Grau et al. 1999, Guillón et al. 2003), and seasonal variation in the incidence of spontaneous CCAD was noted in one study, which reported a peak incidence in the fall (Schievink et al. 1998). Migraine was shown to have a significant positive association with non-traumatic CCAD independently of type and treatment regimen (D’Anglejan-Chatillon et al. 1989).

2.4 Clinical manifestations in CCAD

CCAD has a wide spectrum of symptoms and signs. CCAD may occur as clinically silent, cause minor symptoms, or result in a major stroke leading to severe permanent disability or even death. Some clinical features differentiate ICAD from VAD and intracranial dissections from extracranial dissections.

2.4.1 Extracranial internal carotid artery dissection

The classic triad of symptoms of extracranial ICAD is head or neck pain and Horner’s syndrome followed by focal motor or sensory deficits appearing hours or days later (Houser et al. 1984, Mokri et al. 1986, Schulze et al. 1992, Bioussé et al. 1994). The presence of any two elements of this triad should strongly suggest the diagnosis.

Pain is the most common, and often the initial, manifestation of ICAD, being present in more than 70% of patients. It is considered to be due to distension of the artery, which stimulates pain-sensitive receptors in the vessel wall. Typical pain is an ipsilateral headache in the frontotemporal area, occasionally in the entire hemicranium or the occipital area. In approximately 10% of cases pain manifests as isolated local neck pain, sometimes as isolated facial or orbital pain, but usually there is simultaneous headache. The median duration of pain in CCAD is 5 days. (Bioussé et al. 1994, Silbert et al. 1995.)

Ipsilateral oculosympathetic palsy, called Horner’s syndrome, usually consisting of ptosis, pupillary miosis, and facial anhidrosis, is found in one third of ICAD patients. It is considered to be due to compression of the sympathetic fibers of the internal carotid plexus running along the distended vessel wall. (Saver & Easton 1998.)

Reportedly, 49–86% of extracranial ICAD patients suffer from symptoms of cerebral or retinal ischemia (de Bray et al. 1994, Bioussé et al. 1995, Silbert et al. 1995, Engelter et al. 2000, Baumgartner et al. 2001). Approximately one third of them have transient ischemic attacks, while the rest have stroke (Bioussé et al. 1995). Retinal infarctions are rare (Baumgartner et al. 2001). In almost 90% of cases, stroke occurs within the first 7 days following the onset of the symptoms (Bioussé et al. 1995).
Cranial nerve deficits occur in more than 10% of extracranial ICAD patients, and they are due to ischemia or compression caused by dilatation of the dissected vessel (Sturzenegger & Huber 1993, Klossek et al. 1994, Gobert et al. 1996, Mokri et al. 1996). The most common affected nerve is the XII nerve, such deficits being present in 5% of ICAD patients (Mokri et al. 1996), followed by other lower cranial nerves (IX, X, XI) and the V nerve.

Pulsatile tinnitus is almost always due to the sound of nonlaminar blood flow that is transmitted to the inner ear. Extracranial ICAD may cause local disorders anatomically close to or within the petrous bone and alteration of the hemodynamics leading to pulsatile tinnitus. In a review of 140 extracranial ICADs from 1974–1983, pulsatile tinnitus was the only symptom in 4% and an associated symptom in 35% of patients (Hart & Easton 1983). Ast et al. (1993) reported subjective tinnitus as a symptom in 7.5% (5/68) of ICAD patients. In another study, subjective or objective pulsatile tinnitus was reported in 50% (18/36) of patients with ICAD (Mokri et al. 1986). Steinke et al. (1994) reported pulsatile tinnitus in 12% of 48 patients. In two previous studies, the frequency of pulsatile tinnitus was 16% (Baumgartner et al. 2001) and 27% (Silbert et al. 1995) out of 181 and 161 patients, respectively. Pulsatile tinnitus was an associated symptom in all cases.

### 2.4.2 Intracranial carotid system dissection

Some clinical features differentiate intracranial carotid system dissections from extracranial ICADs. Headache is usually more severe in the former group. Almost all patients have symptoms of cerebral or retinal ischemia, often a major stroke developing over several days. In one fifth of cases, dissection presents as SAH. Intracranial dissections do not cause Horner’s syndrome, cranial nerve palsies, or pulsatile tinnitus. (Saver & Easton 1998.)

### 2.4.3 Extracranial vertebral artery dissection

The most typical symptoms of VAD are sudden occipital headache or posterior neck ache on the same side as the dissected vessel and symptoms typical of a vertebrobasilar TIA or infarction. Headache, present in up to 88% of VAD patients (Sturzenegger 1994, Saeed et al. 2000), may also be located temporally, retroorbitally, or bilaterally. Ischemic symptoms of vertebrobasilar circulation, present in about two thirds of patients (Provenzale et al. 1996), include vertigo, nausea, vomiting, more or less complete Wallenberg syndrome, the locked-in syndrome, cerebellar syndrome, vestibular syndrome, transient amnesia, blurred vision, and hemianopia. TIA is less common in VAD than in ICAD. Uncommon manifestations of VAD are isolated spinal manifestations and spinal epidural hematomas (Crum et al. 2000).

Horner’s syndrome has been reported in 36% of VAD patients (Sturzenegger 1994). Rarely, VAD presents with pulsatile tinnitus: in two studies VAD was never the cause of
pulsatile tinnitus (Silbert et al. 1995, Baumgartner et al. 2001), while in a third study only one patient out of 25 with VAD presented with pulsatile tinnitus (Mokri et al. 1988a). Cranial nerve palsies of the nerves V, VII, VIII, IX, X, XII have been reported (Sturzenegger 1994).

2.4.4 Intracranial vertebrobasilar system dissection

The main clinical feature distinguishing intracranial VAD from extracranial is the quite frequent occurrence of SAH. Hosoya et al. (1999) found SAH in 3 of 31 patients with intracranial VAD, while in another study more than half of patients (4/7) with intracranial VAD had SAH (Provenzale et al. 1996). Intracranial VADs do not cause Horner’s syndrome or cranial nerve palsies.

2.5 Vascular imaging of CCAD

2.5.1 Digital subtraction angiography

Angiography has long been the gold standard in diagnosing CCAD, but being an invasive method, it carries a potential, though minimal, risk of severe complications. Digital subtraction angiography (DSA) requires the use of intravascular, usually iodine-based contrast agents, but their use is limited or contraindicated in patients with renal insufficiency or a history of reaction to iodinated contrast media. Angiography shows the arterial lumen but does not enable assessment of the arterial wall. Signs of CCAD are indirect, but often typical and diagnostic. Pathognomonic signs are rare. Angiographic findings depend on the degree of luminal stenosis and the depth at which the false lumen is situated in the vessel wall. When dissection occurs in the subadventitial layer without relevant narrowing of the arterial lumen, or when an aneurysm is thrombosed, angiography does not yield the diagnosis (Sturzenegger & Huber 1993). Technical developments in non-invasive modalities (magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), ultrasound, and computed tomography (CT) angiography) are replacing angiography in many centers.

2.5.1.1 Imaging technique

In the past decades, DSA techniques have replaced conventional angiography in cerebrovascular imaging. In DSA, an initial image acquired before the introduction of contrast agent is a mask that is subtracted from the subsequent images with contrast agent. This results in a subtracted image of contrast only. This technique has certain
advantages, such as instant acquisition, real-time information, increased contrast sensitivity, and the possibility to electronically manipulate images. A 1024 x 1024 matrix size is required for sufficient resolution (Katzen 1995). Usually, transfemoral bilateral carotid and bilateral vertebral artery angiography in at least two orthogonal directions is performed, sometimes with aortic arch injections in postero-anterior and left and right oblique projections. In recently introduced rotational three-dimensional (3D) angiography, two multidirectional C-arms in a single system allow simultaneous projection from two directions. The 3D capability provides added visual depth perception for more precise images and reduction of radiation exposure.

2.5.1.2 Findings

Double lumen develops when an intramural hematoma ruptures back into the real lumen, allowing blood to flow through both lumens. Intimal flap is a floating membrane in the lumen near the proximal margin of dissection. These angiographic signs are considered pathognomonic of dissection as seen also in the case of aortic dissection, but they are rare and present in less than 10% of CCAD patients. (Houser et al. 1984.)

Indirect, nonspecific signs of CCAD in angiography are most common, and absence of atheroma is typical of CCAD patients. Subintimal hematoma tends to expand inward, causing narrowing or occlusion of the lumen. The most common sign of extracranial ICAD is irregular stenosis, visible as a “wavy ribbon” or a “string sign”. It is found in 58–75% of extracranial ICAD patients (Houser et al. 1984, Ast et al. 1993). Usually, stenosis begins 2–3 cm distal to the carotid bulb, extending over a variable distance. Dissection terminates, in all but exceptional cases, before the entry of ICA into the petrous part of the temporal bone, where mechanical support seems to limit further expansion and where the lumen is abruptly reconstituted. (Hart & Easton 1983, Houser et al. 1984, Mokri et al. 1986, Mokri 1990, Ast et al. 1993, Saver & Easton 1998.) Gradually tapering occlusion of ICA is less specific. It is found in 17–35% of extracranial ICAD patients (Mokri et al. 1986, Ast et al. 1993, Saver & Easton 1998). In the acute phase, a flame-like occlusion at least 2 cm above carotid bifurcation is characteristic of dissection. Dissecting aneurysms, i.e. pseudoaneurysms, develop when the dissection proceeds through the media to the subadventitial layer and causes dilatation of the outer vessel wall. They are usually located near the base of the skull and may be present in up to 37% of extracranial ICAD patients. Irregular dilatation is rare. Embolic occlusions of distal branches may be present in 11% (Mokri et al. 1986). In a canine model, morphologic changes in angiography after experimental carotid dissection were closely related to the size of the intimal entry zone; small entry zones resulted in spontaneous healing and large ones in stenotic lesions, but medium entry zones (4–6 mm) potentially induced aneurysm formation (Okamoto et al. 2002).

Extracranial VAD is less common than extracranial ICAD. It has the same set of patterns in angiography as extracranial ICAD, but the findings are less specific. Irregular stenosis is the most common finding present in about 80% (Mokri et al. 1988a, Saver & Easton 1998). The previous reports on the most typical location of VAD are controversial. The most frequently affected level was C1-C6 in one study (Chiras et al. 1985), the
C1-C2 level in one (Mokri et al. 1988a), and the Th1-C2 level in one (Bartels & Flügel 1996), while one study (Provenzale et al. 1996) failed to establish any predominant site of extracranial VAD. VA enters the skull through the foramen magnum, which explains why up to 20% of VAD may extend intracranially (Mokri et al. 1988a).

Intracranial CCAD is rare. Most intracranial dissections occur in the posterior circulation in the distal VA or basilar artery (Mokri et al. 1988a, Kitanaka et al. 1994, Hosoya et al. 1999). Dissections of PICA (Berger & Wilson 1984, Tikkakoski et al. 1997) and PCA are rare (Lazinski et al. 2000). Intracranial carotid system dissection is usually located in the supraclinoid part of ICA (Rawat et al. 1992, Schievink et al. 1994b) or MCA (Ohkuma et al. 2003b), sometimes ACA (Ohkuma et al. 2003a). Findings in angiography are usually nonspecific, typically irregular stenosis with or without dissecting aneurysm or total occlusion following tapering stenosis. Double lumen and intimal flap are rare but specific. Intracranial dissections may rupture through the adventitia and cause SAH (Mokri et al. 1988a, Klufas et al. 1995, Lazinski et al. 2000, Ohkuma et al. 2003a, Ohkuma et al. 2003b).

Multivessel dissections are quite common, being found in 16–28% of CCAD patients (Schievink et al. 1994a, Mokri et al. 1996, Ozodoba et al. 1996). FMD is seen in angiography as an additional finding in about 25% of CCAD patients (Mascalchi et al. 1997). String of beads is a characteristic finding.


### 2.5.2 Magnetic resonance imaging

The major advantage of MRI is that it can demonstrate the intramural crescentic hematoma itself. The resolution of MRA is now approaching that of angiography, and nonspecific changes in the calibre of the vessel can be seen. MRI and MRA are non-/mini-invasive and free of radiation, but not readily available in all centers. (Levy et al. 1994, Ozodoba et al. 1996, Mascalchi et al. 1997, Lecrerc et al. 1999.)

#### 2.5.2.1 Imaging technique

The sequences used in MRI (0.5–1.5 Tesla (T) system) of cervicocephalic arteries usually include T1, T2, and proton density (PD)-weighted images of the neck in an axial plane. Caudal spatial presaturation pulse is often used to suppress arterial inflow. Fat saturation techniques are used in T1-weighted images to differentiate hyperintense intramural hematoma from the surrounding tissues. Section thickness of 4 mm is recommended for good spatial resolution. (Levy et al. 1994, Ozodoba et al. 1996, Mascalchi et al. 1997, Lecrerc et al. 1999.)
Two types of MRA techniques are used routinely in neurovascular imaging. Flow-based techniques utilize the fact that flowing blood moves through the vessels during the measurement. Such techniques include time-of-flight (TOF) and phase contrast (PC) imaging techniques, which can be run in most magnetic resonance (MR) scanners. In the contrast-enhanced technique, intravenously injected contrast agents shorten the T1 of blood, and scanning is done during their passage through the vessels. This technique requires a state-of-the-art system with high slew rates and dedicated tools for accurate timing of acquisition during the first pass of the contrast bolus. (Bosmans et al. 2001.)

In the time-of-flight technique, stationary tissues are suppressed by subjecting their spins to the complete series of radio frequency (RF) pulses in an imaging sequence. With a short time of repetition (TR), the signal intensity in stationary tissue during a series of RF pulses decreases, resulting in a low signal. Flowing spins in the blood, however, experience only few RF pulses, with blood continuously entering and leaving the imaging plane. Therefore, the hypointense steady-state value is never reached in blood, while positive contrast with the surrounding tissues is obtained. The usability of TOF depends on the velocity of blood in the vessel, the length of the vessel in the imaging slab, the flow pattern, and the sequence parameter setting. Two-dimensional (2D) and 3D applications are available, 3D TOF being mostly recommended for the diagnosis of CCAD. (Bosmans et al. 2001.) However, the field of view is limited in 3D TOF and also dependent on the flow direction. For example, in the case of subclavian steel VA cannot be seen.

Phase contrast imaging is based on the fact that there is a direct relationship between the velocity of the spins and the phases they acquire when moving along a magnetic field. In the PC imaging technique, bipolar pulses are used to achieve flow-induced calculable phase in spins that move along the direction of the gradients, while pulses have no effect on stationary spins. Minimally, two measurements are made, a flow-compensated (TOF) acquisition and a second acquisition with bipolar pulses in a particular direction. Complete flow data can be obtained for bipolar pulses in all of the three dimensions. Measurement in PC imaging takes quite long, and in order to get optimal vessel contrast, velocity encoding (VENC) must be done. 2D PC imaging with different VENC is more practical than 3D PC, which takes even longer and should be done with the optimal VENC. In practice, PC imaging is used most commonly in the visualization of venous pathologies, but it can also be used, for example, to show possible absence of flow in MCA in acute ischemic stroke, providing complementary information to diffusion and perfusion-weighted imaging in predicting the outcome of acute stroke patients (Liu et al. in press). It also gives information about flow dynamics, such as velocities. (Bosmans et al. 2001.)

In MRA, contrast agents, usually gadolinium-based contrast agents, are used to achieve higher signal intensity in blood than in other tissues in T1-weighted images, as the T1 of blood is shortened. Contrast enhancement helps to overcome the saturation effect in TOF techniques in the case of slow or turbulent flow, as in aneurysms. Contrast-enhanced MRA is not dependent on the direction of flow. Recently, new ultrafast acquisitions have been introduced. They enable the use of stronger gradients in a shorter time, giving rise to 3D techniques with very short TR. Ultrafast MRA must be performed during the first pass of the contrast bolus. Techniques used to attain accurate timing include test bolus acquisition, semiautomatic or automatic bolus tracking,
acquirement of series of ultrashort acquisitions, and use of multiple boluses and dedicated post-processing tools. (Bosmans *et al.* 2001, Wilms *et al.* 2001.) The coverage in contrast-enhanced MRA is better than that in flow-based MRA techniques, allowing, for example, good overall imaging of the aortocervical vessels.

Both flow-based MRA techniques tend to overestimate stenosis both in diameter and in length, and severe stenosis may stimulate occlusion due to the slow or turbulent flow. For the same reason, aneurysms may be invisible in MRA. Contrast agents help to overcome these effects. The most widely recommended technique of MRA in CCAD is 3D TOF and contrast-enhanced ultrafast MRA, when available. The hyperintense intramural hematoma can mimic flowing blood on a maximum intensity projection (MIP), and correlation with the spin echo MR images is necessary. (Levy *et al.* 1994, Ozodoba *et al.* 1996, Mascalchi *et al.* 1997, Lecrerc *et al.* 1999, Bosmans *et al.* 2001, Wilms *et al.* 2001.)

### 2.5.2.2 Findings

A pathognomonic sign of CCAD in MRI is an eccentrically narrowed lumen with an adjacent crescent-shaped increased signal, representing the intramural hematoma, i.e. the extravasated blood in the vessel wall. It is best demonstrated in T1-weighted fat-suppressed MR images with caudal spatial presaturation, where the high-intensity intramural hematoma can be distinguished from the surrounding fat and cerebrospinal fluid (CSF). (Provenzale *et al.* 1995, Ozodoba *et al.* 1996, Mascalchi *et al.* 1997, Saver & Easton 1998.) In the first few days, the intramural hematoma is intermediate on T1-weighted images and high on PD and T2-weighted images. After that, the signal is high on T1, PD, and T2-weighted images, before the changes gradually resolve. A hyperacute intramural hematoma would have a low signal on T2-weighted MR images due to susceptibility effects of deoxyhemoglobin, but no such cases have been reported. (Mascalchi *et al.* 1997.)

Less specific signs of dissection in MRI are increased signal or poor or absent visualization of the entire vessel, marked narrowing of the vessel lumen by adjoining tissue with abnormally increased signal intensity, and an enlarged vessel diameter, which, in the early stage, may be the only indicator of dissection (Ozodoba *et al.* 1996, Saver & Easton 1998). MRI is superior to DSA and MRA in cases of nonspecific occlusion and dissection without associated luminal abnormalities.

The sensitivity of MRI in ICAD is 84% and specificity 99%, but in VAD its sensitivity is only 60% and specificity 98% (Levy *et al.* 1994). The detectability of the VA intramural hematoma on MRI depends on the segment involved. The surrounding tissues have different signal characteristics at different levels. On T1-weighted images, the intermediate or high-signal intramural hematoma is best visualized in V4 (intradural segment), where VA is surrounded by low-signal CSF. In V3 (from C2 foramen transversarium to the duramater) and V2 (C6 to C2 level), the intermediate to high-signal perivascular structures and the slow flow proximal and distal to the intramural hematoma make the intramural hematoma more difficult to detect. On PD images, intramural hematoma can be easily detected only in V4. In T2-weighted images, CSF in V4 and
perivascular structures in V2 and V3 have a similar high signal as intramural hematoma. (Mascalchi et al. 1997.) Additionally, VA is more sensitive than ICA to the technical artefacts of MR due to the smaller and variable diameter.

Intracranial arteries are small and sensitive to artefacts, but the crescent-shaped high-signal change representing the intramural hematoma may sometimes be seen. In the study of Hosoya et al. (1999), the positive rate of intramural hematomas in intracranial vertebrobasilar artery dissection was 32%.

MRA shows changes in the calibre of the vessel, which are indirect and nonspecific signs of dissection. The most common findings in dissection are irregular stenosis and absence of the arterial signal. An abnormal signal indicating intramural hematoma adjacent to the dissection may be seen. The sensitivity of MRA in ICAD is 95% and specificity 99%. In VAD, the corresponding figures are 20% and 100% (Levy et al. 1994). In another study, MRA detected signal abnormalities within the dissected extracranial vertebral artery in 94% (16/17), and MRI was specific for dissection in 29% (5/17) in the acute and subacute stages, but specificity (true negative rate in subjects free of disease) was not considered in this study because all patients had vertebral artery dissection (Auer et al. 1998). Better results in VAD can be achieved by using contrast agent, which allows acquisition of a large volume in a short scan time without major artefacts (Leclerc et al. 1999). Contrast agents shorten the T1 relaxation time of blood, giving a high signal and reducing in-plane saturation.

Due to the artifacts that can mimic the MR appearance of FMD and thus decrease the sensitivity and specificity of MRA in its detection, MRA is inadequate, similarly to MRI, for the demonstration of FMD and aneurysms associated with dissection (Heiserman et al. 1992, Levy et al. 1994). MRA is suitable for the detection of FMD when the characteristic pattern is combined with moderate stenosis of the vessel, but DSA remains the standard of reference (Link et al. 1996). Angiography is also needed in the detection of filiform stenosis with very slow blood flow and FMD changes and other irregularities of the vessel wall (Schulze et al. 1992). MRI and MRA are good in the follow-up of CCAD (Kasner et al. 1997, Leclerc et al. 1999).

2.5.3 Computed tomography angiography

CT angiography is minimally invasive and, with the improved technology, able to provide high-resolution images of the arterial lumen as well as the vessel wall. However, similarly to DSA, CT angiography requires the use of intravascular iodine-based contrast agents, and their use is limited or contraindicated in patients with renal insufficiency or a history of reaction to iodinated contrast agent. The experience of carotid and vertebral as well as cerebral CT angiography is so far limited.
2.5.3.1 Imaging technique

Helical CT angiography was introduced in the late 1980s. It combines continuous gantry rotation with simultaneous displacement of the examination table throughout the acquisition, providing a registered volume data set with thinner images and more rapid acquisition compared to pre-helical scanners. Multirow / multidetector CT (MDCT) was introduced in 1998. MDCT systems with 4, 8 or 16 channels have improved both the coverage speed and the z-axis resolution of CT angiography and increased the range of clinical applications. (Leclerc et al. 1996, Foley & Karcaaltincaba 2003.)

The three aims of CT angiography are 1) to achieve an adequate level of arterial contrast enhancement during acquisition, 2) to provide cephalocaudad coverage of the targeted anatomy during the first circulation of the injected bolus and during an easily sustainable breath hold interval, and 3) to time the onset of CT acquisition after a peripheral contrast injection in such a way that the first circulation enhancement is obtained from the beginning to the end of the acquisition. Timing of circulation can be achieved using a preliminary mini-test bolus or online bolus tracking. (Foley & Karcaaltincaba 2003.) The thickness of the arterial wall and the size of the opacified lumen are usually evaluated on the axial CT images, but axial scan data can also be reformatted in various paraxial and oblique planes.

2.5.3.2 Findings

Helical CT is a reliable method for evaluating extracranial ICAD. The most sensitive and specific sign of dissection is a narrowed eccentric lumen in the upper portion of ICA. Mural thickening, occlusion, and aneurysms can be evaluated well with CT angiography, but are not specific to dissection. The target picture is a rare and less reliable sign. (Leclerc et al. 1996.) Helical CT can be used in the follow-up of extracranial ICAD (Leclerc et al. 1998) and in the diagnosis of extracranial VAD with similar findings as in ICAD (Soper et al. 1995, Kurokawa et al. 2000).

2.5.4 Ultrasound

Being a non-invasive and readily available procedure, ultrasound is often the first screening method in suspected carotid or vertebral artery obstructive disease. The result of the ultrasound examination strongly depends on the diligence and experience of the examiner.
2.5.4.1 Imaging technique

Before the introduction of the duplex technology, continuous-wave Doppler and high-resolution gray-scale (B-mode) imaging were the ultrasound techniques used to examine carotid and vertebral arteries. Nowadays, color duplex ultrasound allows simultaneous visualization of vascular lesions in the gray-scale image (plaques, stenosis, occlusion) and the associated abnormalities in flow in the color-encoded image (intrastenotic velocity increase, poststenotic flow disturbances, lack of flow signal due to occlusion). Hemodynamic quantification of the pathology is achieved by analysis of Doppler spectral wave forms. Examinations should be done in both transverse and sagittal planes, using linear transducers (5–7.5 MHz). Power Doppler and the use of ultrasound contrast agents are helpful in differentiating high-grade stenosis from occlusion. (Landwehr et al. 2001.) Transcranial Doppler ultrasound (TCD) can show intracranial collateral blood flow (Steinke et al. 1994) and distal microemboli (Srinivasan et al. 1996).

2.5.4.2 Findings

The signs considered specific to dissection in high-resolution gray-scale (B-mode) and color duplex ultrasound are intramural hematoma and intimal flap, which, however, are seen rarely, in less than one fifth of patients with extracranial ICAD (de Bray et al. 1994, Steinke et al. 1994, Bartels & Flügel 1996). Intramural hematoma is seen as an echolucent matrix causing an increase of the arterial diameter. Intimal flap is seen as a moving, thin, echogenic intravascular structure. Suggestive but not specific signs of extracranial ICAD or VAD are tapering stenosis, tubular vessel, segmental ectasis, occlusion without atheroma, double lumen, and pseudoaneurysm (de Bray et al. 1994, Steinke et al. 1994, Bartels & Flügel 1996).

In Doppler ultrasound, a high-resistance flow pattern with bidirectional signal components and absent diastolic flow is characteristic of dissection. Steinke et al. (1994) found it in 68 % of angiographically confirmed extracranial ICAD patients (n=48). In statistical analysis, sensitivity was 68%, specificity 99%, positive predictive value 94% and negative predictive value 99% based on over 3000 carotid artery angiograms and corresponding duplex Doppler examinations. Bakke et al. (1996), however, found it in only one of twelve extracranial ICAD patients. Suggestive indirect signs of more distal extra- or intracranial CCAD are markedly reduced systolic and diastolic blood flow velocities, absence of any Doppler signal, retrograde ophthalmic blood flow (in ICAD), spectral broadening, and retrograde flow (in VAD). (Rawat et al. 1992, de Bray et al. 1994, Steinke et al. 1994, Bakke et al. 1996, Bartels & Flügel 1996.)

Transcranial Doppler ultrasound rarely shows stenosis suggestive of dissection, but collateral blood flow via the anterior and posterior communicating arteries is seen more often (Steinke et al. 1994, Srinivasan et al. 1996). TCD is useful in the detection and follow-up of microemboli in the MCA distal to the ICAD (Srinivasan et al. 1996).

Ultrasound has several limitations in the diagnosis of CCAD. The distal and intracranial parts of the arteries cannot be seen satisfactorily or at all. The intramural
hematoma is hypoechoic and difficult to analyze. Severe stenosis may mimic occlusion. VA may be hypoplastic or have changes in lumen diameter mimicking pathologies. VA is also partly hidden behind the transverse processes of the C6-C2 vertebrae. The abnormalities are usually indirect and not specific. In the follow-up of known CCAD, however, ultrasound is useful.

2.6 Imaging of brain manifestations in CCAD

The main purpose of brain imaging in CCAD is to assess the presence of an infarction and, in intracranial CCAD, also the presence of SAH and to exclude other diseases mimicking ischemia (tumor, intracerebral hemorrhage, subdural hematoma, vascular malformation). Brain imaging plays a vital role in the management of stroke.

2.6.1 Computed tomography

Cerebral CT is still the first method in the differential diagnosis of acute stroke. It is widely available, quick, cheaper than MRI, and sensitive in excluding hemorrhage. Cerebral CT is usually done without intravenous contrast agent in transverse sections with a slice thickness of 4–5mm infratentorially and 8–10 mm supratentorially (Dippel et al. 2000, Urbach et al. 2000). Intravenous contrast agent can be used to help in differential diagnosis, but it has not been demonstrated to increase the detectability of ischemic lesions within the first 24 hours and it may even hide hemorrhage or infarction by enhancing it to the same Hounsfield Unit (HU) level as the surrounding brain. Cerebral CT is often normal during the first few hours after acute ischemic stroke (Dippel et al. 2000). The early CT signs of brain infarction are subtle, but a slight decrease in the density of gray matter, leading to a loss of precise delineation between gray and white matter, or sulcal effacement may be seen. These findings are typical early CT signs of infarction, and they are due to an increase in the brain tissue water content and cerebral edema. In the middle cerebral artery territory, the reported early CT signs of infarction are attenuation of the lentiform nucleus, loss of the insular ribbon, and the hyperdense middle cerebral artery sign (Tomura et al. 1988, Truwit et al. 1990, Moulin et al. 1996). The decrease in the density of the infarction area becomes prominent over time, and increasing edema may also cause a mass effect. About half of CCAD patients have signs of infarction in brain imaging (Saver et al. 1992, Steinke et al. 1996), but other findings, such as hyperdense artery, hemorrhage, and SAH, are rare.

Disturbances in cerebral capillary perfusion can be quantitatively evaluated with perfusion CT, using an iodine-based contrast agent. Perfusion CT helps in the early differential diagnosis of acute ischemic stroke. Dynamic scanning is performed about 5 seconds after the initiation of rapid contrast agent infusion. Cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time, and time to peak are perfusion parameters that can be calculated and presented in images or maps, allowing assessment of the type and extent of cerebral perfusion disturbances. Perfusion CT can also be done
with the subtraction technique, in which the initial images acquired before the introduction of contrast agent are subtracted from the subsequent images with contrast agent, leaving only the change in the attenuation values, i.e. perfusion data. (Hamberg et al. 1996, Hunter et al. 1998, Aksoy & Lev 2000, Wityk & Beauchamp 2000.) A 4-row CT scanner enables the acquisition of sections about 2cm thick and a 16-row CT scanner sections about 3cm thick, but whole brain perfusion studies are not yet possible (Tomandl et al. 2003). Multi-row CT allows the combined use of three imaging modalities, nonenhanced CT, perfusion CT, and CT angiography, to rapidly obtain comprehensive information regarding the extent of ischemic damage in acute stroke patients (Tomandl et al. 2003). A less frequently used technique is xenon-CT, in which the patient breathes xenon gas (Jungreis et al. 1999). The gas then dissolves into blood and passes into the brain, where it readily diffuses through the blood brain barrier. Its distribution in the brain is measured with CT based on changes in attenuation.

### 2.6.2 Magnetic resonance imaging

When infarction is suspected, conventional MRI of brain usually includes T1-weighted images in the sagittal plane and T1, PD, and T2-weighted images in the axial plane. Section thickness of 5mm with a 1mm gap is commonly used (Mullins et al. 2002). Conventional MRI has been reported to be more sensitive than CT in acute ischemic changes (Bryan et al. 1991), but due to the facts that MRI is expensive and not readily available, that the scanning takes a relatively long time, and that the sensitivity of detecting hemorrhage with routine MRI sequences is lower than in CT, it has not been widely used as the first imaging modality in acute stroke. Gadolinium-based contrast agent may help in differential diagnosis and also improve the detection of brain infarction in T1-weighted images. Transverse fluid-attenuated inversion recovery (FLAIR) images visualize edema (Mullins et al. 2002). MRI may also show an abnormal arterial flow void or the presence of an intramural hematoma indicating intracranial dissection. In the past decade, new techniques allowing the evaluation of functional parameters have been introduced. Such techniques include MR diffusion-weighted imaging (DWI) and MR perfusion-weighted imaging (PWI). DWI exploits the transitional mobility of water molecules to obtain information of the microscopic behavior of tissues, e.g. the changes in intracellular vs. extracellular water balance in acute stroke. PWI makes use of endogenous and exogenous tracers in monitoring regional hemodynamic quantities, such as cerebral blood volume, cerebral blood flow, and mean transit time. (Luypaert et al. 2001.) DWI and PWI are superior to CT and conventional MRI in the diagnosis of acute stroke during the first 12 hours after presentation (Mullins et al. 2002), but these techniques are not readily available in all centers.
2.6.3 Magnetic resonance spectroscopy, single photon emission computed tomography, and positron emission tomography

Magnetic resonance spectroscopy utilizes the fact that different chemicals vibrate at different frequencies when stimulated by a magnet. The signals are detected with MRI, and a "signature" is produced to show what chemicals and in what amounts are present. Magnetic resonance spectroscopy can be used to evaluate the metabolic abnormalities associated with focal brain ischemia by specific biochemical measurements. The level of N-acetylaspartate drops and the lactate level rises in infarction during the first few hours of ischemia already. (Saunders 2000, Liu et al. 2003.)

In single photon emission computed tomography (SPECT), a radioisotope, such as technitium-99m (99mTc), is added to a delivery compound that passes through the blood brain barrier after an intravenous injection and is metabolized by neuronal and glial cells. Its uptake in brain is proportional to CBF at the moment of passage. Imaging with a 2-headed or 3-headed SPECT imaging system can be performed within a few hours after the injection. SPECT is a relatively low-resolution method for imaging cerebral perfusion, without the inherently high spatial resolution of CT or MRI. (Holman & Devous 1992.)

Positron emission tomography is a technique for measuring the concentrations of positron-emitting radioisotopes within the tissues of living subjects. It enables measurement of the function of cerebral tissue, which depends critically on the use of oxygen, and impairment in its rate of consumption often constitutes a pathological condition. Using $^{15}$O$_2$ and H$_2$$^{15}$O with positron emission tomography, oxygen consumption and cerebral perfusion can be quantitatively measured in ischaemic stroke. However, its availability and practicality in acute clinical settings are limited. (Heiss 2000.)

2.6.4 Topography and etiology of cerebral infarction in CCAD

Using the current pathogenetic concepts of the topography of cerebral infarction, the etiology can be considered either hemodynamic or embolic (Ghika et al. 1989, Bogousslavsky 1991, Fisher 1991). Territorial infarctions (involving the cerebral cortex of one or more major cerebral artery territories), subcortical infarctions (affecting the territory of deep perforating branches originating from the distal ICA or the MCA, involving the basal ganglia, thalamus, internal capsule, or centrum ovale), and territorial infarctions with fragmentation (representing a lesion similar to territorial infarction with additional smaller lesion(s) in cortical regions) are considered embolic, whereas watershed infarctions (located between two arterial territories in regions considered to constitute a hemodynamic risk zone) are considered hemodynamic. Most infarctions in ICAD patients are considered embolic, as only about 5% of all infarctions are located in hemodynamic risk zones (Steinke et al. 1996, Lucas et al. 1998, Baumgartner et al. 2001, Milhaud et al. 2002). Weiller et al. (1991) reported a nearly 50% frequency of hemodynamic infarctions in their study of fifteen patients with eleven infarctions.
2.7 Treatment of CCAD

There are no randomized trials of the different treatment regimens in CCAD, and treatment hence remains controversial. The natural course of dissection is favorable, and in some centers, CCAD patients, especially those without ischemic symptoms, are treated with antiplatelets only. Dissection-related strokes usually occur in the first few days after the onset of the symptoms, but may occur up to one month later (Biousse et al. 1995). Early diagnosis and treatment are therefore essential. While a great majority of dissection-related infarctions are considered thromboembolic (Steinke et al. 1996, Lucas et al. 1998, Baumgartner et al. 2001), and while there is a high frequency of intracranial microemboli detectable with transcranial Doppler (Srinivasan et al. 1996), treatment aims at the prevention of further cerebral embolism. The most frequently used empiric therapy is parenteral anticoagulation for about a week followed by warfarin for 3–6 months (Srinivasan et al. 1996), often followed by acetylsalicylic acid (ASA). Koch et al. (2001) demonstrated a decline of microembolic signals in transcranial Doppler with heparin anticoagulation in the case of ICAD. Many dissections recanalize / normalize during the first three months, but whenever there is persistent abnormality in follow-up angiography or MRI + MRA, anticoagulation is often continued for three more months. Recurrence of symptoms is rare after 6 months, and despite possible abnormalities in follow-up angiography or MRI + MRA, warfarin is usually discontinued and replaced by antiplatelet therapy, generally aspirin. (Schievink 2000.) Anticoagulation is contraindicated when there is a large infarction involving more than one third of the middle cerebral artery territory (Adams et al. 1996) with an associated mass effect, hemorrhagic transformation of the infarcted area, an intracranial aneurysm, or intracranial dissection with SAH. Intravenous and intraarterial thrombolysis with urokinase or recombinant tissue plasminogen activator have been used with promising results in the treatment of patients with ICAD or VAD-related acute stroke and no contraindications for thrombolysis (Derex et al. 2000, Arnold et al. 2002, Restrepo et al. 2003). Both anticoagulation and thrombolysis, however, entail a minor risk of intracranial hemorrhage, but the risk of the extension of intramural hematoma during treatment is mainly theoretical (Mokri et al. 1986, Arnold et al. 2002).

Endovascular treatment should be considered in patients who remain symptomatic (thromboembolic events or progression) despite therapeutic anticoagulation, in cases of persistent pseudoaneurysms, and when anticoagulation is contraindicated (Liu et al. 1999, Simionato et al. 1999, Saito et al. 2000, Schievink 2000). The most commonly used technique in the case of persistent, hemodynamically significant stenosis is percutaneous balloon angioplasty followed by placement of one or more balloon-expandable or, preferably, self-expanding metallic stents. It has been successfully applied and reported in extracranial ICA (Liu et al. 1999, Simionato et al. 1999, Malek et al. 2000, Albuquerque et al. 2002). Dissecting aneurysms may require coil embolization or placement of a covered stent (Manninen et al. 1997). Vanninen et al. (2003) reported successful treatment of an intrasellar iatrogenic ICA pseudoaneurysm with a polytetrafluoroethylene-covered stent. Dissecting aneurysm, especially in a vertebral artery and in cases of SAH, can be treated with endovascular occlusion of the parent artery at or just proximal to the dissection site (Halbach et al. 1993, Iihara et al. 2002, Leibowitz et al. 2003). Therapeutic intervention should be performed as soon as possible
because of the high risk of rebleeding. Internal trapping of the dissected site is preferable to proximal occlusion, while proximal occlusion does not completely eliminate the risk of rebleeding (Kitanaka et al. 1992, Iihara et al. 2002). When the dissection of VA involves PICA, proximal endovascular occlusion performed during the acute stage followed by internal trapping of the dissected site, if possible, based on the results of a balloon test occlusion of the distal VA segment of the dissected site, may be the treatment of choice (Iihara et al. 2002). All endovascular treatments carry a potential risk of thrombosis and consequent ischemic complications, and the long-term results of stenting are unknown, which is why endovascular treatment should be used in selected cases only.

Surgical treatment of CCAD is rarely needed and should be considered only in patients with persistent symptoms despite maximal medical therapy and who are not candidates for endovascular treatment. The techniques used include arterial ligation, an in situ interposition graft, extracranial to intracranial bypass, and rarely, surgical clipping of the dissecting aneurysm (Schievink 2000).

2.8 Prognosis of CCAD

Prognosis in extracranial CCAD is mainly related to the possible presence of cerebral ischemic complications, while local manifestations rarely significantly disable patients. The reports on outcomes in extracranial ICAD are controversial. Many authors have reported excellent or good recovery in 71–85% of extracranial ICAD patients (Mokri et al. 1986, Leys et al. 1995, Saver & Easton 1998, Engelter et al. 2000). Poor outcomes have been reported in about half of patients with occlusive dissection of extracranial ICAD and acute stroke (Bobousslavsky et al. 1987, Ast et al. 1993). Pozzati et al. (1990) reported high mortality (23%) and poor outcome (37%) in patients with cerebral infarction due to occlusive dissection of ICA, while the rate of early death due to brain infarction was 2–5 % in other reports (Schievink et al. 1994a, Leys et al. 1995, Saver & Easton 1998). Milhaud et al. (2002) reported worse outcome in stroke patients with occlusion of ICA due to dissection than in stroke patients with occlusion of ICAD due to atherothrombosis. Traumatic dissection of ICA may have a worse prognosis than spontaneous ICAD (Mokri 1990).

Extracranial VAD is considered to have good prognosis, with excellent or good recovery in 67–87 % of the patients (Chiras et al. 1985, Mokri et al. 1988a, de Bray et al. 1994, Leys et al. 1995, Saver & Easton 1998, Saeed et al. 2000, Czechowsky & Hill 2002). Mortality rate is estimated to be about 6 % (Saver & Easton 1998).

The prognosis of intracranial dissection is related to ischemic complications and bleeding. Worse outcomes in intracranial compared to extracranial ICAD, with mortality rates up to 75 % (Hart & Easton 1983, Schievink et al. 1994b), have been reported. In intracranial VAD, prognosis is controversial. de Bray et al. (1997) reported poor outcome in 44 % of patients with intracranial VAD, while others have reported 84–88 % of patients to have good or excellent recovery (Mokri et al. 1988a, Hosoya et al. 1999, Nakagawa et al. 2000). Reports on outcomes in rare intracranial dissections of basilar artery, ACA, MCA, and PCA are scant. Anterior cerebral artery dissection (ACAD) seems to have good prognosis, with 78 % of patients recovering well (Ohkuma et al. 2003a). In a report
of 13 middle cerebral artery dissection (MCAD) patients (cerebral ischemia in 4 and SAH in 9), good recovery was only seen in 3 patients, while 5 had severe disability, 1 remained in vegetative state, and 4 died (Ohkuma et al. 2003b). In the same study, about 50% of patients with SAH suffered from rebleeding, which impaired their prognosis. There are no large reports on long-term outcomes in posterior cerebral artery dissection (PCAD), but in a review by Berger & Wilson (1984), one patient with isolated PCAD had a good outcome, as did three patients in another review (Pozzati et al. 1994).

No correlation between the clinical outcome of patients and angiographic outcome of the dissected artery has been reported (Steinke et al. 1994, Provenzale et al. 1996, de Bray et al. 1997). Occlusion of extracranial ICAD at the initial angiography seems to be associated with poor outcome (Bogousslavsky et al. 1987, Milhaud et al. 2002). Touze et al. (2001) reported a very small risk of ischemic events or other complications under antiplatelet treatment inaneurysmal forms of ICAD and VAD. Guillon et al. (1999) described a benign clinical course in extracranial ICAD with dissecting aneurysm.

The risk of recurrent dissection in an initially unaffected artery is about 2% during the first month and about 1% per year (Schievink et al. 1994a). In a large series, recurrent events in other vessels were found in 8%, and a family history of arterial dissections was found to be the only factor increasing the risk (Schievink et al. 1996). However, recurrence of dissection in the same vessel is extremely rare (Ast et al. 1993, Schievink et al. 1996).
3 Purpose of the study

The purpose of the present study was:

1. to investigate the angiographic spectrum and course of cervicocephalic artery dissection. (I, II)
2. to evaluate pulsatile tinnitus as a symptom of cervicocephalic artery dissection. (III)
3. to assess the frequency of brain infarctions and subarachnoid hemorrhage detectable by CT/MRI in cervicocephalic artery dissection patients, to evaluate the correlation between initial vessel wall findings and brain infarctions, and to explore the patterns of cerebral infarctions in order to find out if they are of embolic or hemodynamic origin. (IV)
4. to examine the long-term clinical outcome of cervicocephalic artery dissection patients, to find out if there are differences in outcome between extra- and intracranial CCAD patients, and to examine the predictive clinical value of the angiographic finding of the dissected vessel at the time of diagnosis. (I, V)
4 Patients and methods

4.1 Patients

The total number of patients included in these studies was 136 (42 women). They were consecutive patients diagnosed with CCAD at Oulu University Hospital between August 1982 and March 2002. Diagnosis was based on clinical presentation, angiographic (124 patients) or MRI and MRA (12 patients) findings, and exclusion of other specific arterial wall pathologies, e.g. atherosclerosis and arteritis. The mean age of the patients was 42.9 years, range 1–72 years. Potential precipitating events, vascular risk factors, and concomitant diseases are listed in Table 1.

Table 1. Potential precipitating events, vascular risk factors, and concomitant diseases in the 136 patients participating in the present study with cervicocephalic artery dissection.

<table>
<thead>
<tr>
<th>Precipitating event</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activities involving physical strain</td>
<td>35</td>
</tr>
<tr>
<td>Head or neck trauma</td>
<td>17</td>
</tr>
<tr>
<td>Forced head turning</td>
<td>4</td>
</tr>
<tr>
<td>Iatrogenic, complication of angiography</td>
<td>2</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>1</td>
</tr>
<tr>
<td>Caldwell-Luc operation</td>
<td>1</td>
</tr>
<tr>
<td>Sneezing</td>
<td>1</td>
</tr>
<tr>
<td>Vascular risk factors or diseases¹</td>
<td>n</td>
</tr>
<tr>
<td>Arterial hypertension²</td>
<td>60</td>
</tr>
<tr>
<td>Elevated serum cholesterol levels</td>
<td>40</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>9</td>
</tr>
<tr>
<td>Fibromuscular dysplasia</td>
<td>9</td>
</tr>
<tr>
<td>Family history of cerebral infarction or intracranial hemorrhage</td>
<td>9</td>
</tr>
<tr>
<td>Family history of aortic or cervicocephalic artery dissection</td>
<td>2</td>
</tr>
<tr>
<td>Arteritis</td>
<td>1</td>
</tr>
<tr>
<td>Klinefelter syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Essential thrombocytopenia</td>
<td>1</td>
</tr>
</tbody>
</table>

¹ patients may have more than one vascular risk factor or disease, ² 24 patients had medication at the time of the index event
The 136 patients had a total of 165 CCADs. Of them, 139 dissections (found in 114 patients) were extracranial and 26 dissections (found in 22 patients) intracranial (Table 2).

Table 2. Dissected vessels in 136 consecutive CCAD patients.

<table>
<thead>
<tr>
<th>Dissected vessel</th>
<th>Extracranial dissections</th>
<th>Intracranial dissections</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unilat</td>
<td>Bilat</td>
</tr>
<tr>
<td>ICA</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>VA</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>ICA + VA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ICA + bilateral VA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bilateral ICA + bilateral VA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ICA + MCA</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>PCA</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>basilar artery</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Unilat = unilateral, Bilat = bilateral, n = number of patients

Paper I describes the first nine consecutive patients (two women) diagnosed to have ten angiographically proved intracranial cervicocephalic artery dissections. The numbers of patients covered in the original papers are presented in Table 3. The patients were aged from 5 to 49 years (mean 29 years). Five dissections were in ICA (in one case the extracranial part of ICA was also affected), four in VA (in one case the extracranial part of VA was also affected), and one in the posterior inferior cerebellar artery.

Table 3. Numbers of patients in the original papers.

<table>
<thead>
<tr>
<th>Paper</th>
<th>Number of patients</th>
<th>Period of data collection</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Intracranial dissections</td>
<td>9</td>
<td>August 1982 – September 1996</td>
</tr>
<tr>
<td>II Extracranial dissections</td>
<td>93</td>
<td>August 1982 – August 1999</td>
</tr>
<tr>
<td>III Pulsatile tinnitus</td>
<td>16 (^1)</td>
<td>August 1982 – March 2002</td>
</tr>
<tr>
<td>IV Brain manifestations</td>
<td>131 (^2)</td>
<td>August 1982 – March 2002</td>
</tr>
<tr>
<td>V Clinical outcome</td>
<td>136 (^3)</td>
<td>August 1982 – March 2002</td>
</tr>
</tbody>
</table>

\(^1\) A subgroup of patients with pulsatile tinnitus derived from the total number of 136 patients in paper V.

\(^2\) Five patients without brain imaging were excluded from the total number of 136 patients in paper V.

\(^3\) The patients covered in the papers I–IV are included.

Paper II covered the first 93 consecutive patients (32 women) with 111 angiographically (one MRA) proved extracranial internal carotid and vertebral artery dissections and one concomitant intracranial vertebral artery dissection. The patients’ ages ranged from 3 to 72 years (mean 45.2 years). There were 55 unilateral ICADs, 22 unilateral VADs, 9 bilateral ICADs, 5 bilateral VADs, 1 unilateral ICAD + bilateral VAD, and 1 bilateral ICAD + bilateral VAD.

Paper III deals with 16 of the 136 CCAD patients (9 women, mean age 43.8 years, range 33–55 years), who had pulsatile tinnitus as a presenting symptom. They had 11
unilateral ICADs, 2 bilateral ICADs, 2 unilateral VADs, and 1 bilateral ICAD + bilateral VAD, all dissections being extracranial.

Of the 136 patients described in paper V, 5 patients with extracranial dissections (3 unilateral ICADs, 1 bilateral ICAD, and one unilateral VAD) were excluded from paper IV, because they had no brain imaging. The remaining 131 patients (42 women, mean age 42.7 years, range 1–62 years) had a total of 159 CCADs. One hundred and nine patients had extracranial dissections and 22 intracranial dissections.

4.2 Methods

4.2.1 Clinical information

Information on the 136 patients was gathered from the medical records of our hospital and reviewed retrospectively by a radiologist (O.P.). The patients’ symptoms and signs, their treatment, and their clinical outcome were analyzed. All patients had undergone a clinical examination by a staff neurologist. The symptoms and signs listed were cerebral infarction, cerebellar infarction, carotid TIA, vertebrobasilar TIA, head or neck pain, Horner’s syndrome, pulsatile tinnitus, cranial nerve palsy, dizziness / disturbance of equilibrium, seizure / loss of consciousness, amaurosis fugax, diplopia, dysphagia, disorientation, visual field defect, loss of hearing, and no symptoms. Pulsatile tinnitus was analyzed in more detail in paper III, where it was evaluated as the presenting or sole symptom of CCAD, and its duration was assessed to be days, weeks, months, years, or persistent. The follow-up time ranged from five days in a patient who died in the acute phase up to 11 years and 7 months, median 11 months. In paper III, follow-up data of 13 patients were also collected by telephone interviews (O.P.) in November 2002, and one of these patients was followed up for 14 years and 3 months. Two methods used to assess long-term clinical outcome are presented in Table 4. Based on the neurological defects and symptoms, the clinical outcome was classified into five categories by a radiologist (O.P.) and a neurologist (K.S.). The categories ranged from 1 (no neurological defects, no symptoms) to 5 (death). Outcomes were considered good in the categories 1–3. This classification takes into account functional outcome, but also symptoms and disabilities, such as visual defects, neuropsychological defects, and problems in the cognitive domain. Functional outcome was assessed by using the universally known modified Rankin Scale (mRS), with scores ranging from 0 (no symptoms) to 6 (dead) (Wade 1992). A good outcome was defined as mRS 0–2. The differences in outcome between extra- and intracranial CCAD patients were evaluated, and the predictive clinical value of the dissection-related vessel finding at angiography at the time of diagnosis was assessed using Fisher’s exact test. p-values of less than 0.05 were considered significant.
Table 4. The two methods used to assess long-term clinical outcome in 136 patients with cervicocephalic artery dissection.

<table>
<thead>
<tr>
<th>Five-category classification based on neurological defects and symptoms</th>
<th>modified Rankin Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 = No neurological defects, no symptoms.</td>
<td>0 = No symptoms at all.</td>
</tr>
<tr>
<td>2 = No neurological defects, symptoms present.</td>
<td>1 = No significant disability despite symptoms; able to carry out all usual duties and activities.</td>
</tr>
<tr>
<td>3 = Persistent neurological defects, no or mild disability.</td>
<td>2 = Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.</td>
</tr>
<tr>
<td>4 = Persistent neurological defects, moderate or severe disability.</td>
<td>3 = Moderate disability; requiring some help, but able to walk without assistance.</td>
</tr>
<tr>
<td>5 = Death.</td>
<td>4 = Moderately severe disability; unable to walk without assistance, and unable to attend to own bodily needs without assistance.</td>
</tr>
<tr>
<td></td>
<td>5 = Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.</td>
</tr>
<tr>
<td></td>
<td>6 = Death.</td>
</tr>
</tbody>
</table>

4.2.2 Vascular imaging

4.2.2.1 Initial angiography

Intra-arterial DSA with transfemoral catheterization was performed initially on 125 patients (until 1989 a 512 x 512 matrix, Angiotron, thereafter a 1024 x 1024 matrix, Polytom, Siemens, Erlangen, Germany). One hundred and five patients underwent aortic arch injections in postero-anterior and left and right oblique projections. Seventy-one of them and further 20 patients had selective common carotid or vertebral injections in at least two orthogonal directions. Angiography confirmed the diagnosis in 124/125 patients, but in one case, in which dissection did not cause any luminal abnormalities, angiography was negative. All the initial angiograms were analyzed retrospectively from films by a radiologist (O.P.) and another radiologist (S.L.) or a neuroradiologist (T.T.). The findings were classified as irregular stenosis, occlusion, pseudoaneurysm, fusiform aneurysm, intimal flap, irregular dilatation, double lumen, and irregularity of vessel wall. In each dissected vessel, one major finding was considered to be the main finding, while the other findings were considered additional. A detailed overall analysis of the initial angiographic (one MRA) findings of the 121 dissected cervicocephalic arteries from the studies I and II and the levels of VADs was done (I,II).
4.2.2.2 Initial MRI + MRA

The dissection was diagnosed with MRI + MRA in ten patients, including the one with a previous negative angiography. In two further patients, MRI without MRA was sufficient to confirm the diagnosis. MRI and MRA were performed by using a 1.5 T scanner (Signa Echospeed 1.5 T, General Electric, USA). In all of the twelve patients, MRI of the head included spin echo T1-weighted sagittal and/or coronal images and T2 and/or PD-weighted axial images. Slice thickness was 4–5 mm. Contrast-enhanced T1, T2*, EPI FLAIR, FLAIR, and T1 fat sat images were acquired from only a few/single patients. In two cases, DWI was done in the axial plane. MRA was performed initially in ten cases, 3D TOF in three, 3D TOF and 2D PC in two, 2D TOF and 2D PC in two, and 3D TOF, 2D TOF, and i.v. bolus angiography in three. MRA confirmed the diagnosis in all of the ten patients. All the MRI and MRA images were reviewed retrospectively by a radiologist (O.P.) and a neuroradiologist (T.T. or J.P.). A narrowed lumen with an adjacent crescent-shaped increased signal in T1-weighted images representing an intramural hematoma was considered pathognomonic. The other findings were occlusion seen as an increased signal or absent visualization of the entire vessel, marked narrowing of the vessel, and enlarged vessel diameter. MRI and MRA findings of the dissected vessels were needed when the correlation between the initial vessel wall findings and the brain infarctions as well as the long-term clinical outcome was assessed.

4.2.2.3 Follow-up angiography

In paper I, follow-up angiograms were obtained 1–6 months (mean 3.2 months) after the initial angiography and were available for review in all of the nine cases. One patient had a new dissection 7 months after the first dissection, but this was not followed up with angiography. In paper II, follow-up angiograms performed within 6 days to 19 months (mean 4.0 months) after the initial angiography were available for review in 77/93 cases (83%). The follow-up findings of the dissected vessels were classified as total or partial normalization / recanalization, slight improvement, occlusion of an initially stenosed artery, no change, growth of a pseudoaneurysm, and other occasional findings.

4.2.3 Cerebral CT and MRI

All but five of the 136 patients underwent either cerebral CT (127) (Somatom Plus, Siemens, Germany, Highspeed, General Electric, USA or Aquilion, Toshiba, Japan) or MRI (4) (Magnetom 1 T, Siemens, Erlagen Germany or Signa Echospeed 1.5 T, General Electric, USA) a mean of 2.1 days after the onset or distinct aggravation of symptoms (range 0–20 days). Conventional spin-echo T2-weighted and T1-weighted images in the axial, sagittal, and coronal planes were included. Follow-up brain imaging was done on 73 patients (51 CT, 22 MRI) a mean of 13.2 days after the onset or aggravation of
symptoms (range 0–120), and a third imaging was done on 29 patients (21 CT, 8 MRI), a fourth imaging on 14 (9 CT, 5 MRI), and a fifth imaging on 6 (1 CT, 5 MRI). All of the CT and MRI scans were analyzed by a radiologist (O.P.) and a neuroradiologist (J.P. or T.T.) to evaluate the presence and topography of cerebral ischemic and/or hemorrhagic lesions. Of the 74 infarctions detected in CT / MRI, the films of 70 were available for detailed analysis.

Infarctions involving the anterior circulation were differentiated into four patterns according to Szabo et al. (2001). Territorial infarction involves the cerebral cortex of one or more major cerebral artery territories. Subcortical infarction affects the territory of deep perforating branches originating from the distal ICA or the MCA, involving the basal ganglia, thalamus, internal capsule, or centrum ovale. Territorial infarction with fragmentation represents a lesion similar to territorial infarction with additional smaller lesion(s) in cortical regions. Watershed infarctions are located between two arterial territories in regions considered to constitute a hemodynamic risk zone.

Of the posterior circulation infarctions, only the side of the infarction and the presence of hemorrhagic lesions were determined.

4.2.4 Statistical analysis

The data in the present study were analyzed using cross-tabulation. In study V, Fisher’s exact test was used in statistical evaluations, and p-values of less than 0.05 were considered significant.
5 Results

5.1 Angiographic spectrum and course of CCAD (I,II)

The main initial and follow-up angiographic findings of the 121 dissected vessels from the studies I and II are presented in Table 5. There were 10 intracranial dissections (nine in study I and one in study II) and 111 extracranial dissections (study II). Recurrent dissections were detected in follow-up in five previously unaffected arteries (in four of the 102 patients, 4%), but they are not included in the table.

Table 5. Main initial and follow-up angiographic findings in 10 intracranial and 111 extracranial cervicocephalic artery dissections (I,II).

<table>
<thead>
<tr>
<th>Initial angiography</th>
<th>Follow-up angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of dissected arteries</td>
</tr>
<tr>
<td>Irregular stenosis</td>
<td>61</td>
</tr>
<tr>
<td>Occlusion</td>
<td>40</td>
</tr>
<tr>
<td>Pseudoaneurysm</td>
<td>14</td>
</tr>
<tr>
<td>Irregular dilatation</td>
<td>5</td>
</tr>
<tr>
<td>Double lumen</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>121</td>
</tr>
</tbody>
</table>

*Further thrombosis of the artery, **artery ligated, ***irregular dilatation normalized, new intimal flap

The most common finding in initial angiography (one MRA) was irregular stenosis, which was seen in 50% (6/10 of the affected intracranial and 55/111 of the affected extracranial arteries). In follow-up, 81% of the stenoses showed total or partial normalization. Occlusion was the second most common main finding, being detected in 33% (2/10 and 38/111). Occlusion was persistent in follow-up in 66%, showing even further thrombosis of the artery in one case, while 34% showed total or partial recanalization. Pseudoaneurysm was the main initial angiographic finding in 12% (1/10
and 13 /111). No change was seen in follow-up in 62%, and growth was seen in only one case. Irregular dilatation (5/121) and double lumen (1/121) were rare findings.

Additional findings were detected in initial angiography in two intracranial (1 ICA, 1 VA) and 19 extracranial (18 ICA, 1 VA) vessels: an intimal flap (10), a pseudoaneurysm (10), irregular stenosis (2), and irregular dilatation (2).

Among the 39 VADs in the studies I and II, the most often and almost equally frequently affected levels of VAD were the C6-Th1 and C1-C2 levels (Table 6). Of the four intracranial VADs, three were in the post-PICA segment.

Table 6. Levels of 39 vertebral artery dissections (I, II).

<table>
<thead>
<tr>
<th>Level</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td>4</td>
</tr>
<tr>
<td>Skull base - intracranial</td>
<td>2</td>
</tr>
<tr>
<td>skull base - C1</td>
<td>6</td>
</tr>
<tr>
<td>skull base - Th1</td>
<td>1</td>
</tr>
<tr>
<td>C1 - C2</td>
<td>13</td>
</tr>
<tr>
<td>C5 - C6</td>
<td>1</td>
</tr>
<tr>
<td>C4 - Th1</td>
<td>1</td>
</tr>
<tr>
<td>C6 - Th1</td>
<td>11</td>
</tr>
</tbody>
</table>

C = cervical vertebrae, Th = thoracal vertebrae.

5.2 Pulsatile tinnitus as a symptom of CCAD (III)

Pulsatile tinnitus was a presenting symptom in 12% of the CCAD patients (16/136). On admission, ten patients presented with subjective tinnitus and five with objective tinnitus. One ICAD patient had objective tinnitus as the only presenting symptom, while the others had concomitant head or neck pain, ischemic brain symptoms, Horner’s syndrome, or cranial nerve palsies. In the remaining one case, subjective tinnitus appeared three months after the first symptoms of bilateral ICAD, although contralateral cervical bruit was evident on admission. Unilateral ICAD was the cause of pulsatile tinnitus in eleven patients, unilateral VAD in two, bilateral ICAD in two, and bilateral ICAD+bilateral VAD in one patient. All patients with objective tinnitus had ICAD. All dissections were extracranial, and the most common finding was irregular stenosis in eight patients. Two patients had irregular stenosis and pseudoaneurysm, two pseudoaneurysm and intimal flap, two pseudoaneurysm, one double lumen, and one occlusion. According to telephone interviews, pulsatile tinnitus lasted for five minutes in one patient, for 1–7 days in three, for 1–8 weeks in 7, and for six months in two. Three patients could not be reached by telephone, and the duration of pulsatile tinnitus could not be defined based on medical records.
5.3 Cerebral CT and MRI findings in CCAD (IV)

Of the 131 patients who underwent brain imaging, 73 (56%) had signs of altogether 74 cerebral or cerebellar infarctions. Infarction was already seen in the first scan performed a mean of 2.1 days, range 0–20 days, after the onset or distinct aggravation of the symptoms in 55 patients. In one case cerebral CT was performed at 10 months, and in two cases the onset or aggravation of symptoms could not be defined. A repeated scan (51 CT and 22 MRI) (0–120 days, mean 13.2 days, after the onset or aggravation of symptoms) showed 17 new infarctions, and in one case a fourth scan showed the first signs of infarction. Based on a correlation with the dissected vessels, 47% of the dissected vessels caused a detectable brain infarction in a relevant territory, while 53% of the dissected vessels did not cause signs of infarction (Table 7). Occlusion of the dissected vessel was accompanied by infarction in 76%, irregular stenosis in 40%, and other findings, such as pseudoaneurysm, fusiform aneurysm, irregular dilatation, double lumen, and irregularity of the vessel wall, only rarely (Table 7). Not all clinically evident infarctions could be detected in brain imaging: 88 patients (67%) had symptoms of cerebral (57) or cerebellar (31) infarction, but brain imaging showed signs of infarction in 46 and 17 of them. Thirteen of the 88 patients had no signs of infarction in brain imaging done at least three days after the onset of the symptoms.

Table 7. Frequency of infarctions in brain imaging correlated with vessel findings in 156 dissected cervicocephalic arteries (in three cases with simultaneous ICAD + MCAD on the same side, the number of vessels is counted as one).

<table>
<thead>
<tr>
<th>Vessel finding</th>
<th>Infarction at CT / MRI (n)</th>
<th>No infarction (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular stenosis</td>
<td>40% (32)</td>
<td>60% (48)</td>
</tr>
<tr>
<td>Occlusion</td>
<td>76% (39)</td>
<td>24% (12)</td>
</tr>
<tr>
<td>Other *</td>
<td>12% (3)</td>
<td>88% (22)</td>
</tr>
<tr>
<td>Total</td>
<td>47% (74)</td>
<td>53% (82)</td>
</tr>
</tbody>
</table>

* pseudoaneurysm, fusiform aneurysm, irregular dilatation, double lumen, or irregularity of the vessel wall

Fourty-four of the 74 detected infarctions were in the anterior and 30 in the posterior circulation. Of the 30 posterior circulation infarctions, 17 were related to occlusion, 12 to irregular stenosis, and one to another nonocclusive finding of the dissected vessel. Intracranial posterior circulation dissection was associated with cerebral infarction rarely (in 1/11 of the dissected vessels), whereas intracranial anterior circulation dissections were accompanied by infarctions more commonly (in 9/12 of the dissected vessels). The stroke patterns of 41 anterior circulation infarctions were analyzed, and the results are presented in Table 8.
Table 8. Stroke patterns of 41 infarctions in anterior circulation compared to angiographic or MRA findings of the dissected vessels.

<table>
<thead>
<tr>
<th></th>
<th>Territorial infarction (n)</th>
<th>Subcortical infarction (n)</th>
<th>Territorial infarction with fragmentation (n)</th>
<th>Watershed infarction (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irregular stenosis</td>
<td>37 % (7)</td>
<td>32 % (6)</td>
<td>26 % (5)</td>
<td>5 % (1)</td>
</tr>
<tr>
<td>Occlusion</td>
<td>35 % (7)</td>
<td>20 % (2)</td>
<td>50 % (10)</td>
<td>5 % (1)</td>
</tr>
<tr>
<td>Other *</td>
<td>–</td>
<td>50 % (1)</td>
<td>50 % (1)</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>34 % (14)</td>
<td>22 % (9)</td>
<td>39 % (16)</td>
<td>5 % (2)</td>
</tr>
</tbody>
</table>

* pseudoaneurysm, fusiform aneurysm, irregular dilatation, double lumen, and irregularity of the vessel wall

Since territorial and subcortical infarctions and territorial infarctions with fragmentation are considered embolic, 95% (39/41) of the cerebral infarctions in the present study were of embolic origin. Hemodynamic etiology was indicated in only two cases (5%) with watershed infarctions. The stroke patterns did not correlate with the angiographic findings, and only territorial infarctions with fragmentation occurred slightly more often in cases of occlusion (10/20) than in cases of stenosis (5/19) (Table 8).

Subarachnoid hemorrhage was found in CT in 5 of the 22 patients (23%) with intracranial dissection, all the dissections being in the posterior circulation vessels (two VADs, one PCAD, one posterior inferior cerebellar artery dissection (PICAD), and one dissection of the basilar artery). One of them also involved signs of infarction. Hemorrhagic transformation of cerebral infarction was present in 5/131 patients at the initial or follow-up brain imaging, and the dense middle cerebral artery sign in CT in six.

5.4 Long-term clinical outcome in CCAD and the correlation between outcome and initial angiographic or MRA finding (I,V)

The clinical manifestations of the 136 CCAD patients are listed in Table 9.
One hundred and eleven patients were treated with anticoagulants (heparin and/or warfarin). The mean duration of oral anticoagulation was 5.7 months. Seventy-three patients had acetylsalicylic acid (ASA) after warfarin. Eight patients were treated with acetylsalicylic acid only, 7 with surgery or endovascular treatment, and 10 with no specific treatment.

Nine patients died during follow-up, four due to massive infarction within 9 days after the onset of symptoms, one due to status epilepticus at 3 years, and four due to causes unrelated to dissection (two myocardial infarctions, one pulmonary embolism after hip fracture, and one death at over three years from an unknown cause).

When outcomes were classified into five categories based on neurological defects and symptoms, 60% (82/136) of all CCAD patients in the present study recovered well, having no or mild disability (Table 10). When dissection affected only one cervicocephalic artery and did not cause vessel occlusion, the prognosis was good; 79% of the patients recovered with no or mild disability. When non-occlusive dissection affected two or more arteries, the outcome was poorer; 50% of the patients had at least moderate disability. In cases of occlusive dissection in one or more arteries, the outcome was even less advantageous, with only about 35% of the patients recovering enough to have no or mild disability. There was a statistically highly significant difference (p<0.0001) in outcome between the patients with non-occlusive dissection in one or more arteries and those with non-occlusive dissection in two or more arteries.
arteries and those with occlusive dissection in one or more arteries; 75% of the former but only 35% of the latter recovered well, having no or mild disability.

Table 10. Initial angiographic vessel findings and long-term clinical outcome based on the neurological defects and symptoms in 136 patients with cervicocephalic artery dissection.

<table>
<thead>
<tr>
<th>Number of dissected vessels and angiographic finding</th>
<th>Clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No neurol. defects, no symptoms (%)</td>
</tr>
<tr>
<td>1 vessel, no occlusion</td>
<td>30.1% (22)</td>
</tr>
<tr>
<td>1 vessel, occlusion</td>
<td>13.5% (5)</td>
</tr>
<tr>
<td>≥2 vessels, no occlusion</td>
<td>28.6% (4)</td>
</tr>
<tr>
<td>≥2 vessels, occlusion</td>
<td>8.3% (1)</td>
</tr>
<tr>
<td>Total</td>
<td>23.5% (32)</td>
</tr>
</tbody>
</table>

When mRS was used to assess outcome, the results were better. Good recovery, defined as mRS 0–2, was found in about 79% of all the patients and in 89% of the patients with non-occlusive dissection of one cervicocephalic artery. In case of non-occlusive dissection of two or more arteries 86% and in case of occlusive dissection of one or more arteries 61% of the patients recovered well. Also, when mRS was used, there was a statistically highly significant difference (p=0.0004) in outcome between the patients with non-occlusive dissection in one or more arteries and those with occlusive dissection in one or more arteries; 89% of the former but only 61% of the latter recovered well, scoring 0–2 on mRS.

No significant differences in recovery between intra- and extracranial dissections were seen in either of the two outcome classifications (p=0.481 / p=0.785). Outcomes were also similar in the patients with anterior and posterior circulation dissections, except that all the four patients who died due to large dissection-related infarctions had dissection in the anterior circulation.

All the five patients with SAH recovered well: three patients had persistent defects but only mild or no disability, and the remaining two cases had no defects or symptoms. The hyperattenuating middle cerebral artery sign in CT seen in six patients predicted a poor outcome; two died within a week, and the remaining four had persistent neurological defects and disability.
6 Discussion

In the present study, the angiographic spectrum and the course of cervicocephalic artery dissection were studied. Initial and follow-up angiograms were retrospectively analyzed, and the initial and follow-up vessel findings were categorized. Clinical manifestations, especially pulsatile tinnitus as a presenting symptom, were evaluated. In addition, the current pathogenetic concepts of topography of cerebral infarction were used as indicators of hemodynamic versus embolic etiology. Anterior circulation infarctions were analyzed, and territorial, subcortical, and territorial infarctions with fragmentation were considered embolic. Comparisons were made between the different vessel findings, the frequencies and patterns of brain infarction, and the long-term clinical outcome.

Irregular stenosis, which normalized in 81%, was the most frequent finding, being present in half of the patients in the studies I and II. Occlusion, which recanalized in about 34%, was found initially in one third of the patients. The symptoms showed a wide range of variation, and pulsatile tinnitus was the presenting symptom, sometimes the only symptom, in more than one out of ten patients with CCAD (III). Ninety-five per cent of the analyzed anterior circulation infarctions were considered embolic (IV). Occlusion was accompanied by infarction more often than other vessel findings (IV), and in long-term clinical follow-up, the prognosis was worse in occlusive dissection of one or two cervicocephalic arteries (V).

The 136 patients in the present study were consecutive patients diagnosed with CCAD at Oulu University Hospital between August 1982 and March 2002. Diagnosis was based on clinical presentation, angiographic (124 patients) or MRI and MRA (12 patients) findings, and exclusion of other specific arterial wall pathologies, e.g. atherosclerosis and arteritis. Both intra- and extracranial dissections of ICA and VA were included together with fewer dissections in intracerebral arteries. There may have been some selection bias in the sense that the patients with mild symptoms may not have consulted the hospital or undergone extensive investigations, such as angiography, to confirm the diagnosis. Furthermore, some dissections, especially intracranial dissections, have probably gone undiagnosed, especially when angiography without selective injections with a 512x512 matrix was used. Patients with unspecific occlusion in angiography showing no recanalization on follow-up angiography were excluded from the present study, and some of these occlusions are likely to have been caused by dissection. However, awareness of
this medical condition has increased and imaging modalities have improved during the 20-year period of data collection, and most missed cases are from the early years. The present study population is relatively large compared to previous reports. To my knowledge, the biggest series from a single institution was gathered at the Mayo Clinic between 1970 and 1990. That series consisted of 200 patients with spontaneous ICAD. The reports on that series focused on recurrent dissections. (Schievink et al. 1994a, Schievink et al. 1996). Silbert et al. (1995) reported characteristics of headaches in 161 symptomatic patients with spontaneous dissections of ICA or VA, and they also belonged to the series gathered at the Mayo Clinic between 1970 and 1990. Baumgartner et al. (2001) reported on 181 consecutive patients with spontaneous ICAD, but the patients were from two different hospitals, as was also the case in another report on the follow-up of 105 consecutive patients with ICAD or VAD (Leys et al. 1995). The populations reported in other studies do not exceed one hundred, are often selected, and sometimes come from many, up to 46 institutions (Ohkuma et al. 2003b).

6.1 Imaging findings in dissected vessels

Angiography has long been the golden standard in diagnosing cervicocephalic artery dissection, as in the present study. First conventional angiography and thereafter digital subtraction angiography have confirmed the diagnosis by showing indirect signs of dissection in the vessel lumen. Angiography is available in most centers. It is still the best imaging modality that can show filiform stenosis with very slow blood flow, FMD changes, and other irregularities of the vessel wall (Schulze et al. 1992, Link et al. 1996). In addition, contrary to MRI and MRA, only angiography enables dural arteriovenous fistulas to be excluded in a patient with pulsatile tinnitus and normal otoscopy (Shah et al. 1999). Angiography can be, and nowadays usually is, done with selective injections, giving better images and real-time information of flow dynamics. The relatively high incidence of multivessel dissections, 19 % (26/136) in the present study and 16–28 % in previous reports (Schievink et al. 1994a, Mokri et al. 1996, Ozodoba et al. 1996), emphasizes the importance of four-vessel imaging. In endovascular treatments, angiography is the only universally used guiding method.

There are, however, many disadvantages in the angiographic imaging of CCAD, which have led to the development and increasing use of other imaging modalities, such as MRI and MRA, CT angiography, and Duplex ultrasound. Firstly, angiography is invasive, being associated with a 1% overall incidence of neurologic deficits and a 0.5% incidence of persistent deficits (Warnock et al. 1993, Heiserman et al. 1994). In the present study and, to my knowledge, in other studies on CCAD, no complications were encountered after angiography. However, two recent studies reported clinically silent embolism and ischemic lesions after angiography (Bendszus et al. 1996, Kato et al. 2003). Secondly, angiography can only show indirect signs of dissection in the vessel lumen, and when the dissection occurs in the subadventitial layer without relevant narrowing of the arterial lumen or when the aneurysm is thrombosed, conventional angiography does not yield the diagnosis (Sturzenegger & Huber 1993). One of the patients in the present study had left-sided Horner’s syndrome and retroorbital pain, but
no abnormalities in DSA. MRI and 3D TOF MRA done seven days later showed a typical hyperintense crescent-shaped intramural hematoma in the extracranial part of the left ICA with only minimal irregularity of the lumen. It is possible that some other cases in the present study may have gone undiagnosed in normal initial angiography. When CCAD is clinically strongly suggested but angiography is normal, or when there is an unspecific occlusion in angiography, MRI and MRA should be performed to improve diagnostic accuracy. There are also differential diagnostic problems in angiography. Atherosclerotic disease, arteritis, arterial spasm, and partially recanalized emboli may cause similar arterial narrowing and irregularity as dissection (Hoffman et al. 1993, Lazinski et al. 2000). Follow-up angiography approximately three months later may help in differential diagnosis by showing changes in the vessel finding, e.g. recanalization / normalization or development of a dissecting aneurysm, and thus confirming the diagnosis of CCAD. In follow-up angiography of CCAD, irregular stenosis is often normalized, while that never happens when atherosclerotic changes are involved. Clinical presentation may give more information of the etiology. Mini-invasive imaging modalities, i.e. MRI, MRA, and CT angiography, may also resolve some of the aforementioned problems in initial angiography, but may also be negative in CCAD. Helical CT has higher resolution than MRI and no flow-related artifacts, but near the skull base, artifacts from bone impair image quality (Leclerc et al. 1998), and the use of this method may be limited by the requirements for intravenous contrast and ionizing radiation (Kasner et al. 1997). MRI with MRA (3D TOF) is sensitive in diagnosing ICAD (Levy et al. 1994, Bakke et al. 1996, Ozodoba et al. 1996), but its sensitivity to VAD is only 20% (Levy et al. 1994), and it is not readily available in all hospitals.

Angiographic findings depend on the degree of luminal stenosis and the depth at which the false lumen is situated in the vessel wall. Furthermore, dissection is a dynamic process, and the degree of luminal stenosis may change within a short time; stenosis may progress to occlusion, or contrariwise, occlusion may recanalize. Compared to previous reports, no significant differences in initial vessel findings were found in the present study. The most common main initial finding, which was present in 50% of the present patients was irregular stenosis. This is in line with two previous reports, where stenosis was found in 55–58% of cases (Ast et al. 1993, de Bray et al. 1994). Some authors have reported figures of 70–80%, especially in VAD (Houser et al. 1984, Mokri et al. 1986, Mokri et al. 1988a, Levy et al. 1994, Schievink et al. 1994b). The size of the population varies in different studies, which may influence the incidence of stenosis, but all studies have established stenosis as the most common vessel finding. Occlusion, found in 33% of the present cases, has been reported in 11–35% previously (Hart & Easton 1983, Houser et al. 1984, Mokri et al. 1986, Mokri et al. 1988a, Ast et al. 1993, de Bray et al. 1994, Levy et al. 1994, Schievink et al. 1994b). Pseudoaneurysm was the main initial finding in the present study in 12%, but when additional findings were included, it was found in 20%, as in previous studies (Mokri et al. 1988a, Ast et al. 1993, de Bray et al. 1994, Levy et al. 1994). Irregular dilatations and double lumens are rare. Despite the fact that there are differences in the vessel wall structure between intra- and extracranial arteries, no significant differences in the distribution of different vessel findings were found between them in the present study.

All nine patients in study I and 77/93 patients in study II underwent follow-up angiography. The total follow-up rate was thus 84%, which is clearly higher than the 38–
64% in previous studies (Houser et al. 1984, Mokri et al. 1986, Mokri et al. 1988a, Mokri 1990, Steinke et al. 1994). Stenoses have been reported to normalize totally or partially in 77–85% (Houser et al. 1984, Mokri et al. 1986, Mokri et al. 1988a, Mokri 1990), which was also the case in the present study, where a 81% normalization rate was seen. More of the occlusions than previously reported recanalized totally or partially, namely 34%. In the study of Mokri (1990), only one (8%) of the initially occluded twelve ICAs recanalized during follow-up, and the result was similar in dissected VAs, while 1/13 (8%) recanalized (Mokri et al. 1988a). Houser et al. (1984) found recanalization in 14% of the occluded arteries, but only 29/57 of all arteries were followed up.

Pseudoaneurysms rarely increase in size during follow-up, but this may happen, as was the case in one of the present patients described in more detail in the study of Tikkakoski et al. (1997). More than half of the pseudoaneurysms resolve or decrease in size (Houser et al. 1984, Mokri et al. 1986, Mokri et al. 1988a, Touzé et al. 2001). In the present study, no change was seen in follow-up in 62% of the pseudoaneurysms, while in the study of Touzé et al. (2001), 46% of the aneurysms persisted.

Previous reports claim that there is no correlation between the angiographic outcome of the dissected artery and the clinical outcome the patient (Steinke et al. 1994, Provenzale et al. 1996). Furthermore, disabling infarctions usually occur within the first few days after the onset of symptoms (Bioussé et al. 1995). Why, then, should we control the vessel finding? Follow-up angiography may confirm the diagnosis of dissection. Infarctions may occur as much as one month later (Bioussé et al. 1995), and persistent changes in follow-up angiography increase the risk of further ischemic complications. Therefore, follow-up angiographic findings often affect therapeutic decisions. The risk of recurrent stroke under antithrombotic medication (ASA or warfarin) remains low in both stenotic or occlusive dissections (Leys et al. 1995, Kremer et al. 2003) and in aneurysmal forms (Touzé et al. 2001). Pseudoaneurysms cannot be seen in initial angiography if they are thrombosed, and they may only be visible in follow-up angiography. Pseudoaneurysm may also increase in size and require endovascular treatment to prevent ischemic complications or bleeding when intracranial. Recurrent dissections are rare, but a new dissection in another vessel may be found in follow-up, especially in patients with a family history of arterial dissections (Schievink et al. 1996) or in patients with new symptoms. Mini-invasive imaging modalities, i.e. MRI, MRA, and CT angiography, can also be used in follow-up.

6.2 Pulsatile tinnitus as a presenting symptom in CCAD

Tinnitus is defined as pulsatile when the patient describes a sound synchronous with heart beat. It is classified as subjective when heard only by the patient and as objective when the sound is also audible by auscultation. Pulsatile tinnitus is almost always due to the sound of nonlaminar blood flow transmitted to the inner ear. This may occur in systemic disease causing general alteration of the hemodynamics or in local disorders that are anatomically close to or within the petrous bone. In a review of 140 extracranial ICADs from 1975–1983, pulsatile tinnitus was the only symptom in 4% and an associated symptom in 35% of patients (Hart & Easton 1983). Ast et al. (1993) reported subjective
tinnitus as a symptom in 7.5% (5/68) of ICAD patients. In another study, subjective or objective pulsatile tinnitus was reported in 50% (18/36) of patients with ICAD (Mokri et al. 1986). Steinke et al. (1994) reported pulsatile tinnitus in 12% of 48 ICAD patients. In two studies, the frequency of pulsatile tinnitus was 16% (Baumgartner et al. 2001) and 27% (Silbert et al. 1995), out of 181 ICAD and 161 ICAD or VAD patients, respectively. Pulsatile tinnitus was an associated symptom in all. VAD has been thought to be a very rare cause of pulsatile tinnitus: in two studies VAD was never the cause of pulsatile tinnitus (Silbert et al. 1995, Baumgartner et al. 2001), while in a third study only one patient out of 25 with VAD presented with pulsatile tinnitus (Mokri et al. 1988a). In the present study, nearly 12% of the patients (16/136) had pulsatile tinnitus. In all of the 16 cases, dissection was extracranial and located in ICA in 13 cases, in VA in 2 cases, and in both ICA and VA in one case. Thus, of the present extracranial CCAD patients, 14% had pulsatile tinnitus. Contrary to previous works (Hart & Easton 1983, Ast et al. 1993, Baumgartner et al. 2001), the present patient series was collected in a single centre and represented consecutive angiographically confirmed dissections. The present result is best comparable with the results reported by Silbert et al. (1995), who had 161 symptomatic patients with spontaneous dissections of ICA or VA at the Mayo Clinic between 1970 and 1990. The overall incidence of pulsatile tinnitus in the present study was lower, but contrary to Silbert et al. (1995), three of the present VAD patients had pulsatile tinnitus. Compared to the 12% frequency of pulsatile tinnitus in 48 consecutive extracranial ICAD patients from a single hospital in the report of Steinke et al. (1994), slightly more (19%, 14/75) of the extracranial ICAD patients in the present study had pulsatile tinnitus. The majority of the present patients with pulsatile tinnitus had concomitant head or neck pain, ischaemic brain symptoms, Horner’s syndrome, or cranial neuropathies, and only one had it as the only presenting symptom. Although pulsatile tinnitus overall is an uncommon otologic symptom and mostly subsided in less than two months in the present study, it is found quite frequently, and should arouse active suspicion of CCAD or other serious and potentially life-threatening pathology, such as dural arteriovenous fistula, carotid-cavernous fistula, extracranial and intracranial arteriovenous malformations, atherosclerotic carotid stenosis, cerebral aneurysms, fibromuscular dysplasia, or paraganglioma.

### 6.3 Cerebral CT and MRI findings

CT or MRI signs of cerebral infarction have been reported in 48–55% of CCAD patients (Saver et al. 1992, Steinke et al. 1996). In agreement with previous reports, the frequency of cerebral and cerebellar infarctions in the present study was 54% (73/136). Due to its retrospective quality, no consistent imaging protocol was used in the present study. However, all but five patients underwent at least one CT (127 patients) or MR (4 patients) imaging, and follow-up brain imaging was done on 73 patients (51 CT, 22 MRI). Due to the fact that CT was the modality used in most cases, some infarctions in the acute phase have not been detected, and the use of MRI, or preferably diffusion-weighted MRI, would have improved accuracy. CT is known to be less sensitive than diffusion-weighted MRI in detecting signs of infarction during the first 12 hours after stroke (Mullins et al. 2002).
and also in posterior circulation territories (Sturzenegger 1994). Some clinically evident infarctions could not be detected in brain imaging in the present study. Eighty-eight patients (65%) had symptoms of cerebral (57) or cerebellar (31) infarction, but brain imaging showed signs of infarction in 63 (46 and 17) of them. However, in 13 of them, brain imaging was done at least three days after the onset of the symptoms, and no signs of infarction were present even then.

The patterns of anterior circulation infarctions in ICAD patients were explored in order to find out if the etiology of infarction is embolic or hemodynamic. Of the 44 infarctions in anterior circulation, films of 41 were available for detailed analysis. The current pathogenetic concepts of the topography of cerebral infarction were used as an indicator of hemodynamic versus embolic etiology (Ghika et al. 1989, Fisher 1991, Bogousslavsky 1991). Territorial, subcortical, and territorial infarctions with fragmentation were considered embolic, whereas watershed infarctions were considered hemodynamic. The results of the present study strongly suggest that most infarctions in ICAD patients are of embolic origin; only 5% of the infarctions (2/41) were in hemodynamic risk zones, which is in agreement with the corresponding 5% rate in three previous studies (Steinke et al. 1996, Lucas et al. 1998, Baumgartner et al. 2001). Weiller et al. (1991) reported a nearly 50% frequency of hemodynamic infarctions in their study of fifteen patients with eleven infarctions. Embolic etiology is also supported by reports of microembolic signs in transcranial Doppler in CCAD patients (Srinivasan et al. 1996, Kimura et al. 2001) and by histologic reports on thrombus formation in the lumen of the dissected vessel (Bogousslavsky et al. 1987, Steinke et al. 1996). The etiology of brain infarction in ICAD may, however, be a more complicated issue. The collateral blood supply and the territories of the major cerebral arteries may vary. Furthermore, the CCAD itself is a dynamic process. The degree of luminal stenosis may change within a short time, stenosis may progress to occlusion, or contrariwise, occlusion may recanalize. Distal embolism may be associated with all kinds of vessel wall abnormalities or develop without them. One limitation of this technique is the lack of direct embolus detection, which could be achieved to some extent by using transcranial Doppler ultrasound with or without diffusion-weighted MRI (Srinivasan et al. 1996, Kimura et al. 2001).

The patterns of cerebral infarctions in the present study did not correlate with the angiographic findings, which is in agreement with Steinke et al. (1996) and Lucas et al. (1998). Only territorial infarctions with fragmentation were found slightly more often in cases of occlusion (10/20) than in cases of stenosis (5/19) in the present study. However, contrary to the results of Biousse et al. (1995) and Steinke et al. (1996), the present vessel occlusions correlated well with the presence of infarction. Infarction was found in more than 70% of the cases with occlusion, but in only about 40% of the cases with irregular arterial stenosis and in about 10% of the cases with other, non-occlusive angiographic findings. The present results are in line with a recent study, where, however, stenosis of 80% or more was not differentiated from total occlusion (Baumgartner et al. 2001). Occlusion of the dissected vessel is most probably due not only to the intramural hematoma but also to the intraluminal thrombosis, which may cause distal embolism and infarctions.

Intracranial arteries have fewer elastic fibres in the media, thinner adventitia, and no external elastic membrane compared to extracranial arteries (Wilkinson 1972, Berger & Wilson 1984). These characteristics increase the risk of rupture through the adventitia and
SAH (Mokri et al. 1988a, Klufas et al. 1995, Iihara et al. 2002). Also, mucoid degeneration of the intima in a ruptured dissecting aneurysm leading to SAH has been reported (Hamada et al. 2001). In the present study, SAH was found in CT in 5 of the 22 patients (23%) with intracranial dissection, all the dissections being in the posterior circulation vessels. Ruptured dissecting aneurysms have a high risk of rebleeding, and therapeutic interventions in carefully selected cases should be performed as soon as possible. Internal trapping of the dissected site is preferable, while proximal occlusion does not completely eliminate the risk of rebleeding (Kitanaka et al. 1992, Iihara et al. 2002).

Hemorrhagic transformation occurs rarely in brain infarctions caused by CCAD. Steink e et al. (1996) reported it in 5.4% of their ICAD patients, which is in agreement with the present figure of 6.8%. The overall incidence of hemorrhagic transformation in acute ischemic stroke has been reported to be of the order of 40% (Larrue et al. 1997). Okada et al. (1989) studied the incidence of hemorrhagic transformation after acute cerebral embolism and found it to be 40.6% (65/160). In both studies, advanced age, large size of the infarction, and the presence of atrial fibrillation were associated with an increased risk of hemorrhagic transformation. The lower prevalence of hemorrhagic transformations associated with CCAD may be due to the smaller infarction size and the lower age of the patients.

6.4 Long-term clinical outcome

Nearly 82% of the patients in the present study were treated with anticoagulants, followed by acetylsalisylic acid in most cases. The treatment was acetylsalisylic acid only in 6%, surgery or endovascular treatment in 5%, and no specific treatment in 7%. The present study does not therefore allow any comparisons between different treatments and outcomes. It is notable that, with the exception of four patients who died within about one week after the onset of the symptoms due to massive cerebral infarctions, no further patients had any progression of symptoms regardless of the treatment regimen. Furthermore, with the exception of one peripheral bleeding complication related to anticoagulation treatment, no other complications were encountered.

Local manifestations of CCAD, such as Horner’s syndrome and cranial nerve palsies, seldom significantly disable patients, and the prognosis of CCAD is mainly related to the cerebral ischemic complications, which usually occur within the first few days after the onset of symptoms (Biousse et al. 1995). In assessing long-term clinical outcome, two methods measuring slightly different aspects were used in the present study. One was based on the neurological defects and symptoms, and the clinical outcome was classified into five categories: 1) no neurological defects, no symptoms, 2) no neurological defects, symptoms present, 3) persistent neurological defects, no or mild disability, 4) persistent neurological defects, moderate or severe disability, and 5) death. The outcomes in the groups 1–3 were considered good. The advantage of this classification, though it is not universally known, is that it also takes into account symptoms and disabilities, such as visual defects, neuropsychological defects, and problems in the cognitive domain, that may have a major influence on the patients’ long-term outcome. The other classification
used in the present study was the universally known modified Rankin Scale (Wade 1992), which assesses functional outcome. Good outcome was defined as mRS 0–2, while mRS 6 refers to death. The limitation of the present study is that it was retrospective and outcome classification was based on information gathered from medical records. A new clinical examination by a neurologist along with a patient interview would have given additional, more accurate information on outcome. Moreover, quality of life, which is an important patient-centered outcome measure (Chechowsky & Hill 2002), cannot be assessed from medical records. The median follow-up time of 11 months (range 5 days to 11 years 7 months) seemed sufficient, however.

Long-term clinical outcomes assessed using the modified Rankin Scale were excellent in the present study. Good functional recovery was shown by about 79% of all patients. There was a major difference in outcome between non-occlusive and occlusive dissections (p=0.0004). In non-occlusive dissection of one or more cervicocephalic arteries, good recovery defined as mRS 0–2 was seen in 89%, but in the case of occlusive dissection of one or more arteries, only 61% of the patients recovered well. When outcome was assessed using classification into categories based on the neurological defects and symptoms, approximately 60% of all patients in the present study recovered well. This is slightly less than in some previous reports with favorable outcomes in 70–90% of CCAD patients (Mokri et al. 1986, Mokri et al. 1990, Engelter et al. 2000, Saeed et al. 2000). In one further study on 105 CCAD patients, 73% of those discharged alive after CCAD remained fully independent, but patients with early death were thus excluded (Leys et al. 1995). Comparison between different studies is difficult because of the heterogeneous definitions of outcome, the small and often selected populations, and the variable imaging reference standards and follow-up times. Furthermore, only the study of Saeed et al. (2000) also included intracranial CCADs, but on the other hand, excluded ICADs. The difference in long-term clinical outcome between non-occlusive and occlusive CCADs in the present study was even more evident when a classification into five categories was used. Only 35% of the patients with occlusive CCAD of one or more arteries recovered well, while 75% of the patients with non-occlusive dissection of one or more arteries recovered well, having no or only mild disability (p<0.0001). The present findings support the reports of some other authors, in which occlusive CCAD has been found to have worse outcome than previously suggested. Ast et al. (1993) reported poor outcome in about half of the patients with occlusive dissection of extracranial ICAD. Half of the patients with occlusive extracranial ICAD also had poor outcome in the study of Bogousslavsky et al. (1987), but all patients had acute stroke, and traumatic dissections were presumably excluded.

In the present study, both intra- and extracranial dissections of anterior and posterior circulation arteries were included, regardless of etiology, and this gives better information of the clinical outcome in CCAD in general. No differences between intra- and extracranial or anterior and posterior circulation dissections were found in the present study contrary to some other reports with poor outcomes in up to 75% of the patients with intracranial CCAD (Hart & Easton 1983, Schievink et al. 1994b). The reports on outcome in intracranial VAD are controversial. de Bray et al. (1997) reported poor outcomes in 44% of their patients with intracranial VAD, while other reports have shown 84–88% of the patients to have good or excellent recovery (Mokri et al. 1988a, Hosoya et al. 1999,
Nakagawa et al. 2000). The patients with SAH also recovered well in the present study, and no rebleeding was encountered.

The initial vessel finding has not been reported to correlate either with the patterns of brain infarction or with the frequency of infarctions in CCAD patients (Biousse et al. 1995, Steinke et al. 1996, Lucas et al. 1998). In the present study, however, occlusions correlated well with the presence of infarction but not with the stroke patterns. Therefore, the more severe hemodynamic compromise in occlusive dissections does not seem to explain the worse outcome. More likely, the overall higher frequency of infarctions in occlusive dissection seems to be the main reason for the worse outcome. In multivessel dissections, the extent of collateral circulation may be compromised. Moreover, compared to patients with atherothrombotic infarctions, CCAD patients have been hypothesized to have poorer functioning and mobilization of the secondary collateral leptomeningeal pathways (Milhaud et al. 2002).

6.5 Future prospects

Radiologic imaging of vessels is shifting more and more from imaging of the vessel lumen toward direct imaging of the pathologic vessel wall. Reports concentrate on atherosclerosis, but new techniques might also be feasible in imaging CCAD. Intravascular ultrasound (IVUS) has already been shown to be feasible in carotid arteries with mild atherosclerosis, often revealing intimal thickenings and concentric plaques in angiographically normal segments (Manninen et al. 1998). Imaging of arterial calcium is possible using CT, whereas MRI has the potential to visualize the lipid and fibrous components of plaque acquisition and 3-dimensional slice registration (Rumberger 2001). Recently, a new intravascular magnetic resonance device for in vivo high-resolution imaging (Worthley et al. 2003) and spectroscopy of atherosclerotic plaques has been developed. One of the most promising new technologies is optical coherence tomography, which is basically similar to IVUS, but measures back-reflected infrared light rather than sound. It has an extremely high axial resolution, 10–15 μm in standard-resolution imaging and up to 1–2 μm in ultrahigh-resolution imaging (Fujimoto 2003).

MRI and MRA will displace, and in many centers already have displaced, angiography in the diagnostic imaging of CCAD. Due to the radiation, the use of CT angiography will remain limited. In order to reach the diagnosis of CCAD before disabling ischemic complications develop, early imaging is mandatory. Along with the mini-invasive imaging techniques, patients with mild symptoms should also be investigated thoroughly with multiple methods, including imaging. In a modern hospital, neuroradiologic imaging could be done with MRI (diffusion and perfusion) of the head and MRI and contrast-enhanced MRA of the cervicocephalic arteries. If a double lumen or an intramural hematoma with stenosis or aneurysmal dilatation is detected, DSA can be omitted. If the MRI/MRA findings do not correlate with the clinical findings or are unspecific, selective DSA should be done to improve diagnostic accuracy, especially in VAD and intracranial dissections. Early treatment will decrease further ischemic complications, but also improve prognosis in patients who already suffer from brain infarction. Perfusion CT helps to detect early ischemic signs, and perfusion-
diffusion-weighted MRI can be used to select candidates for aggressive stroke therapy (Restrepo et al. 2003). Angiography will, at least for now, maintain its position in endovascular treatments, which will, however, require more investigations to define their indications and long-term outcome.
7 Conclusions

1. In cervicocephalic artery dissection, irregular stenosis is the most common angiographic finding, and 81% of these stenoses normalize. Occlusion is the second most common finding, and 33% of the occlusions recanalize. Pseudoaneurysms, intimal flaps, double lumens, and irregular dilatations are rare findings and often remain unchanged in follow-up.

2. Over 10% of the patients with cervicocephalic artery dissection present with pulsatile tinnitus, which may even be the only symptom, although the majority of patients also have concomittant head or neck pain, ischemic brain symptoms, Horner’s syndrome, or cranial neuropathies.

3. More than half of CCAD patients have cerebral or cerebellar infarction at CT or conventional MRI. Initial occlusion of the dissected vessel is accompanied by infarction more often than other vessel wall abnormalities. Most cerebral infarctions caused by arterial dissections are of embolic origin. Intracranial dissections cause subarachnoid hemorrhage in more than 20% of patients.

4. In the case of dissection of one or more cervicocephalic arteries without occlusion, 75% of patients recover well, having no or mild disability, and when good recovery is defined as mRS 0–2, 89% of patients recover. Contrary to that, only 35% of patients with occlusive dissection of one or more arteries recover well, having no or mild disability, and 61% of the patients score 0–2 on mRS. There seem to be no significant differences in recovery after intra- and extracranial dissections.
References


References


