AHA/ASA Scientific Statement

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Cervical Arterial Dissections And Association with Cervical Manipulative Therapy

A Statement for Healthcare Professionals from the American Heart Association/American Stroke Association

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On behalf of the American Heart Association Stroke Council

AHA/ASA STROKE COUNCIL

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Glossary of terms seen in the Presentation

- CD= Cervical dissection
- VA= Vertebral Artery
- ICA= Internal Carotid Artery
- CMT= Cervical Manipulative therapy
- mRS= Modified Rankin Scale. A scale that measures functional disability where 0-2 minimal or no disability and 3-5 moderate to severe disability, 6 is death
- IS – Ischemic Stroke

Objectives

- To understand the presentation of cervical dissection(CD) including Carotid and Vertebral Artery Dissection
- To understand the current management of CD and its prognosis
- Association of Cervical Manipulative Therapy (CMT) where a low or high velocity low amplitude thrust is applied to the neck and cervical spine with CD

Methodology

The writers used the following sources to develop these guidelines

- Systematic literature reviews
- Published clinical and epidemiology studies and Morbidity and mortality reports
- Clinical and public health guidelines
- Personal files
- Expert opinion to summarize existing evidence, and indicate gaps in current knowledge.

Prevalence

- CD accounts for less than 2% if all ischemic strokes
- But common cause of stroke in the young <45 years, accounting for 8-25% of all cases
- Overall prevalence underestimated since a large number may remain asymptomatic
- Slight male preponderance
- Reported rates tend to be higher in countries where access to health care professionals is higher

Underlying Defects

- **Ultrastructural aberrations** of dermal collagen fibrils and elastic fibers have been reported in approximately 50% of patients with spontaneous CDs in whom there was no prior diagnosis of a connective tissue disorder suggesting a molecular defect in the biosynthesis of the extracellular matrix.
- **Seasonal variability,** particularly increased CD occurring more often in autumn or winter than in the spring or summer, has also been demonstrated and believed due to increased occurrence of infection or weather-related changes in blood pressure.
- Possible association between an elevated C-reactive protein and dissection that was not present in patients with cryptogenic or large artery strokes. The evidence is weakly supported by single study but does suggest that inflammation may play a role
- Traditional risk factors are less commonly associated with CD compared to other ischemic stroke (hypercholesterolemia, obesity, and increased body mass index (BMI)

Associations with CD

- Major and minor cervical trauma
- Arterial hypertension
- Young age
- Current use of oral contraceptives
- Migraine
- Fibromuscular dysplasia (FMD)
- Ultrastructural connective tissue abnormalities
- Vascular subtype of Ehlers-Danlos syndrome
- Marfan syndrome
- Turner syndrome
- Williams syndrome
- Familial cases
- Hereditary hemochromatosis
- Osteogenesis imperfecta type 1
- α 1 antitrypsin deficiency
- 677T genotype MTHFR
- Hyperhomocysteinemia
- Cystic medial necrosis
- Styloid process length
- ICAM-1 E4690 K gene polymorphism
- Autosonal dominant polycystic kidney disease
- Infections
- Moyamoya disease
- Lentiginosis
- Vessel redundancies (coils, kinks, loops) especially if bilateral

Role of Traumatic Injuries in CD

- Mechanical trauma plays a role
- Blunt Injuries 1-2%. The percentage risk increases with the severity of the trauma especially penetrating injuries to the thorax and neck as well as whiplash injuries.
- Minor cervical injuries are seen in 12-34% of CD

Cervical Manipulative Therapy (CMT)

- A low or high velocity, low amplitude force applied to the spine
- According to 2007 US statistics on alternative medicine, 38% adults and 12% children have undergone CMT (ref: US Statistics on Alternate Medicine 2007) including chiropractic, and osteopathic manipulations – mainly for back, neck or joint pain.
- Association between CD and CMT is largely based on four large case control studies (next slide for details)
- Associated mostly with posterior circulation stroke
- This association is suggestive but not conclusive of causation

Authors	Methodology	Population	Time frames, number of visits of CMT	Increased Risk of Stroke
Rothwell et al (2001)	Population based nested case control design	All Ontario cases of posterior circulation stroke(1993-98)	Posterior circulation stroke 1)Within 1 week of Chiropractic visit 2)>3 visits in a month	**<45 years** **1)X 5** **2) X 5** >45 years 1) < 1 2) X1.6
Smith et al (2003)	Nested Case Control Study	Combined databases of 2 academic stroke centers	CMT with preceding I month	6 times increased risk vs control
Cassidy et al (2008)	Population based case control – crossover study	All residents of Ontario over 9 years	Posterior circulation stroke 1)DC 2)PCP	**< 45 years** **2.5 -3 times** **Of cervical DC visit** **3-20 times**
Engelter et al 2013	Multicenter case control cervical dissection and ischemic stroke	Case Control Comparing CD vs non CD -IS	Any trauma CMT	**7.6 times** **12 times**

Explanation of the Studies

- The association of CD with any trauma and with CMT is largely confined to younger patients less than 45 years
- In this population the risk is largely for VA dissection
- Across the 4 studies trauma is associated with a 3-5 times higher association with CD
- CMT has a greater association with CD ranging from 5-12 times across various large studies and seem to be temporally linked with CMT
- It remains unclear why the association is lower in older patients

Biomechanics of the Cervical Spine

The cervical spine is made up of seven vertebral bodies and is divided into four anatomical sections: the atlas, the axis, the root (C2-3 junction), and the column (C3-C7).

Movements of the cervical spine, including flexion, extension, rotation, and lateral flexion, is dependent on the orientation of the joint facets and is further restricted by muscles and ligaments surrounding the cervical vertebrae.

At the atlanto-occipital junction, the only movement allowed is nodding (flexion/extension) due to the shape of the superior articular sockets which receive the condyles of the occiput.

The atlanto-axial junction allows for axial rotation as the arch of the atlas pivots around the odontoid process of the axis, with a normal reported range of motion of 50° to each side. The lateral atlanto-axial joints, biconcave in shape, subsequently glide over one another, causing a small degree of lateral flexion and extension, which is coupled with the rotation. The C2-C3 junction, known as the root, secures the cervical column to the upper cervical spine.

Due to the unique shape of the joint articulations between C2-C7, any degree of rotation is always coupled with some lateral flexion and vice versa.

Biomechanics and Susceptibility

- V3 segment of the VA is most often suspected of being injured during CMT, but any segment of the VAs can be involved.
- Rotation and extension of the neck predispose the VA to dissection by stretching the vessel against either the atlas or posterior atlanto-occipital membrane, which the VA penetrates as it courses superiorly into the skull.
- Similarly, stretching narrows the vascular lumen, thereby possibly promoting the development of intra-arterial thrombus.
- Typical movements for cervical manipulation can be rotation, lateral flexion, flexion, extension or a combination of those.
- The presence of high cervical osteophytic disease or other anatomic variations may predispose or increase the likelihood of VA injury during extension and rotation of the head.

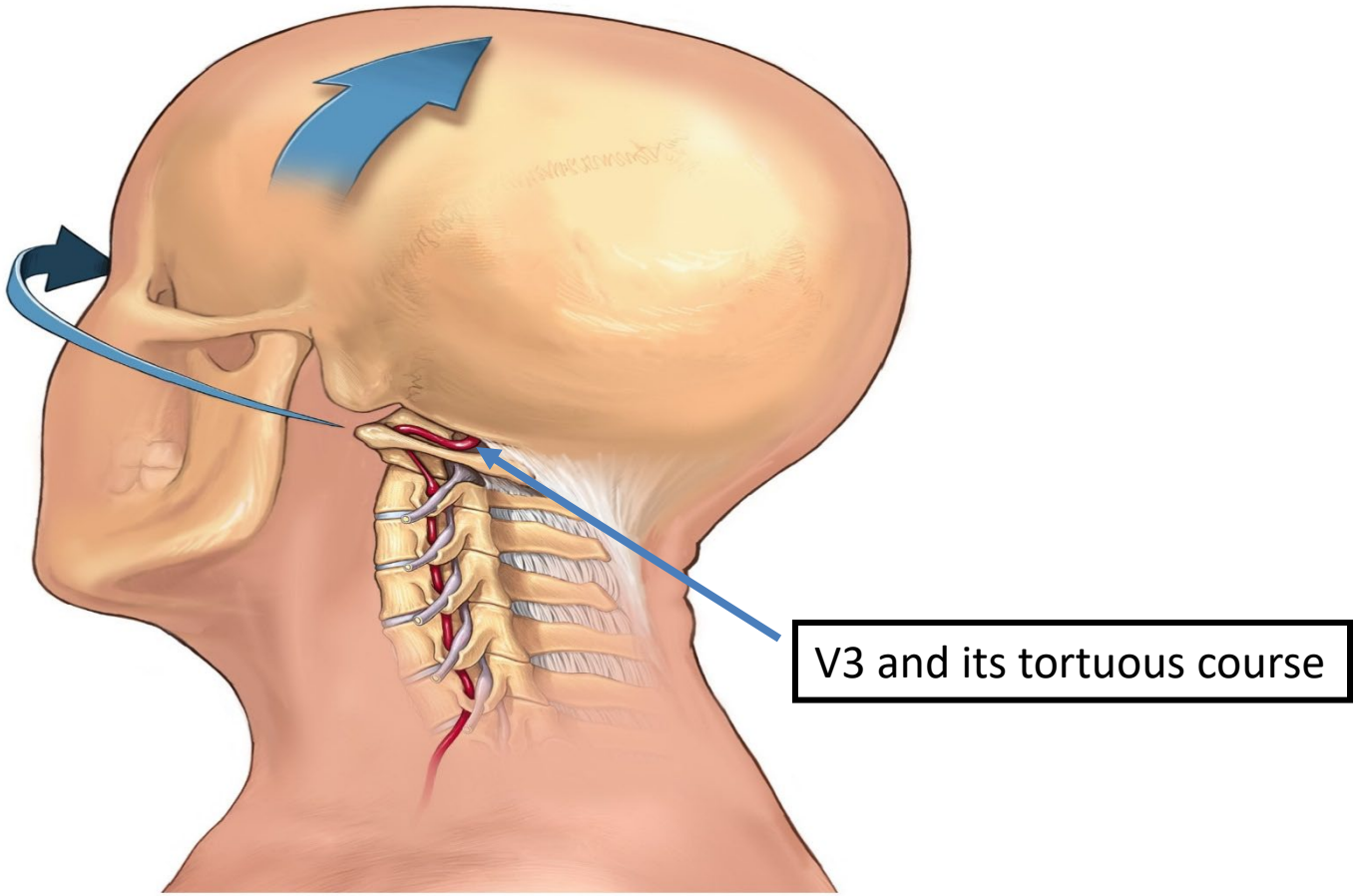
Biomechanics and Susceptibility Continued

- Dissection of the VA can propagate rostrally to involve the intracranial (V4) segment and the basilar artery.
- Isolated injuries to the V4 segment are likely the result of torsion of the vessel as it pierces the dura mater.
- Dissecting aneurysms of this arterial segment can produce SAH, although this has not been associated with CMT.[,]
- The ICA may potentially be injured during cervical manipulation.
- With extension and lateral flexion of the head, the artery becomes fixed in place abutting the upper cervical vertebrae.

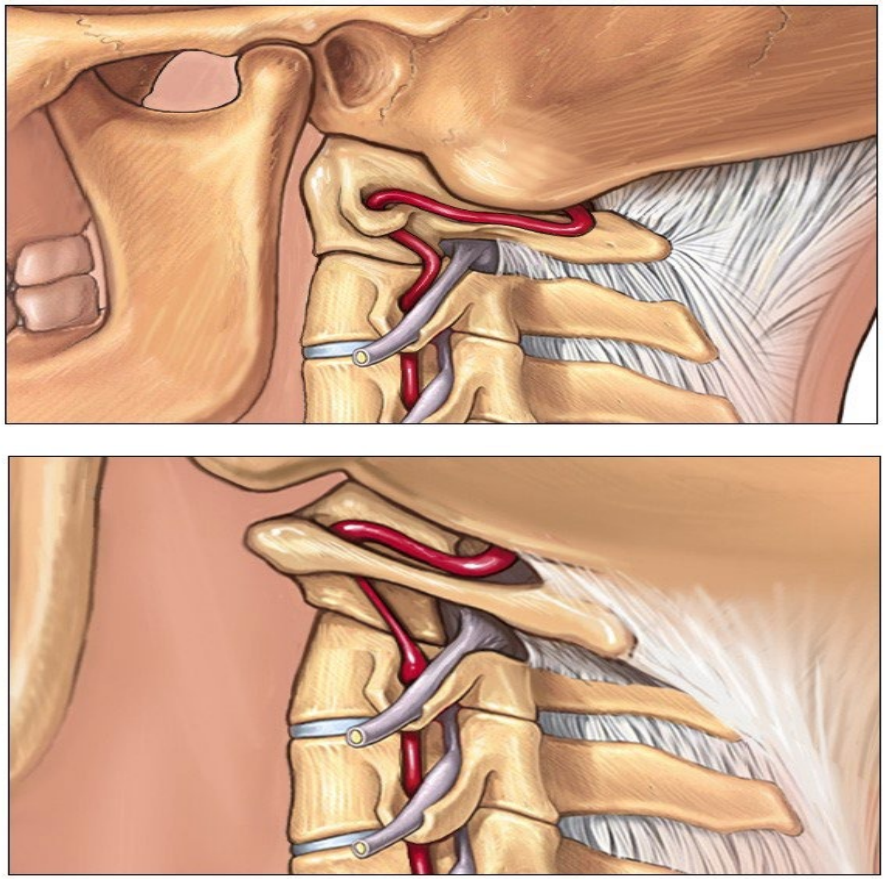
Why Do Vertebral Arteries Show Greater Vulnerability

- The VA run through the transverse foramina of C1-C6 and occasionally through C7.
- Four segments are recognized: the prevertebral segment (V1), cervical segment (V2), atlantal segment (V3), and intracranial segment (V4).
- The V3 segment takes a tortuous course between C2 to the suboccipital triangle between the atlas and the occiput, where it is covered by the atlanto-occipital membrane.
- The V3 segment, runs horizontally in a groove on the superior aspect of the posterior arch of the atlas, adjacent to the atlanto-axial junction (C1-C2) where most rotation occurs, is most susceptible to injury.

Vertebral artery as it passes through the transverse foramina of C6 through C2 and then enters the skull base through the foramen magnum (not shown here). Arrows indicate head movement during lateral rotation and lateral flexion. Flexion, extension and traction may also affect the artery (not shown here). Reprinted with permission.

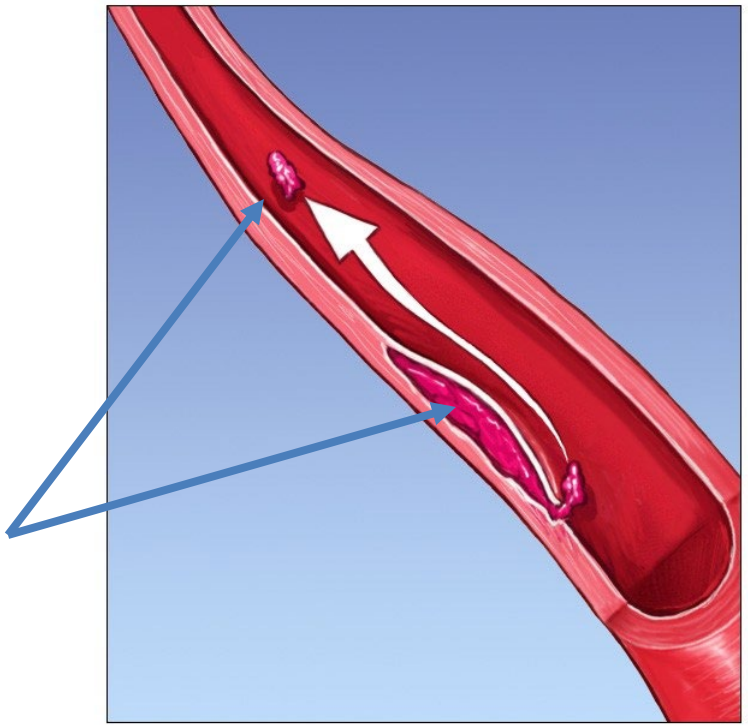


Schematic diagram illustrating the neutral anatomic alignment of the vertebral artery and stretching of the V3 segment during lateral rotation and lateral flexion (bottom). Reprinted with permission



Thrombus from a non-occlusive dissection becoming dislodged and embolizing downstream. Reprinted with permission.

Cervical Dissection, associated false lumen and arterial embolism



Diagnosis

- Diagnosis of CD should be suspected in patients with an appropriate clinical syndrome especially when patients are young and without conventional cerebrovascular risk factors
- Diagnosis of CD is supported by *absence* of radiological findings typical for other cerebral arteriopathies (e.g. atherosclerotic cerebrovascular disease)
- No single test must be viewed as a gold standard
- Imaging of the arterial wall is advisable
- Repeat imaging studies over time are often required

Clinical Presentation

- Asymptomatic
- Ischemic stroke in isolation or associated with one or more of the following symptoms/signs
  - Neck pain
  - Dizziness/Vertigo
  - Pulsatile tinnitus
  - Gait unsteadiness
  - Slurred speech
  - Double vision
  - Horner's syndrome
  - Associated cranial nerve involvement not explained by the stroke that may include lower cranial nerve palsies
- CD can present without a stroke and can be asymptomatic or associated with the signs/symptoms listed above

Imaging Modalities

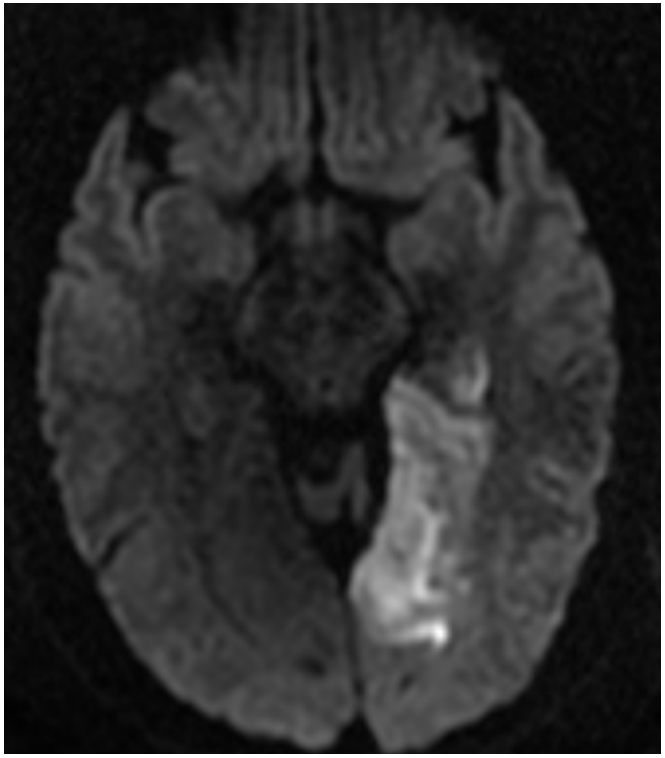
- MRI and MR Angiography
- CT and CT Angiography
- Carotid Doppler (poor sensitivity in CD and mild stenosis)
- Digital Subtraction Angiogram carries a small <1% risk of serious complications(stroke)

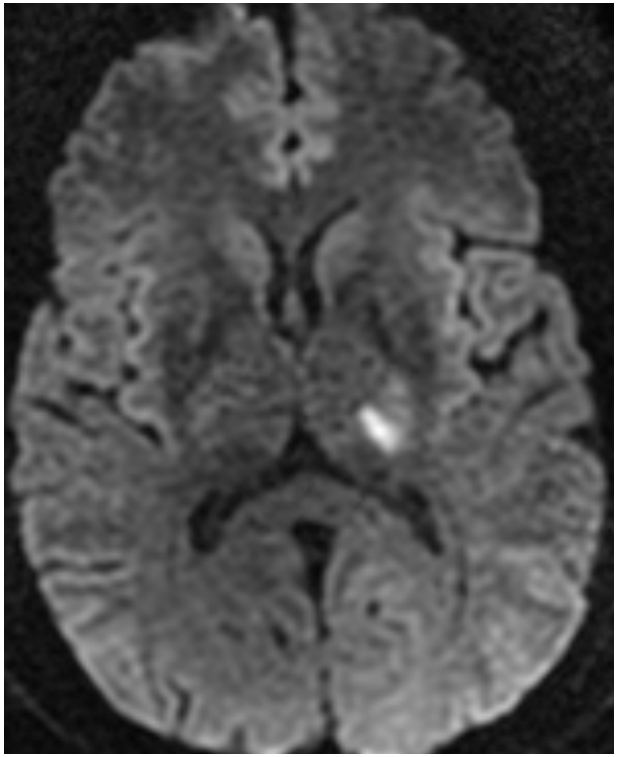
MR studies have the advantage of demonstrating the dissection, false lumen thrombus as well as the IS not usually seen early on the CT

Radiological Signs

- Intimal Flap (separating the false and true lumen
- Double lumen
- Blood in the false lumen (MRI T1 Fat Suppressed Images)
- Smooth tapering stenosis/occlusion especially in the absence of any other evidence of atherosclerotic disease

37 year-old with left occipital temporal and left thalamic infarcts due to a left V2-V3 junction dissection. MRA shows healing of the dissection.



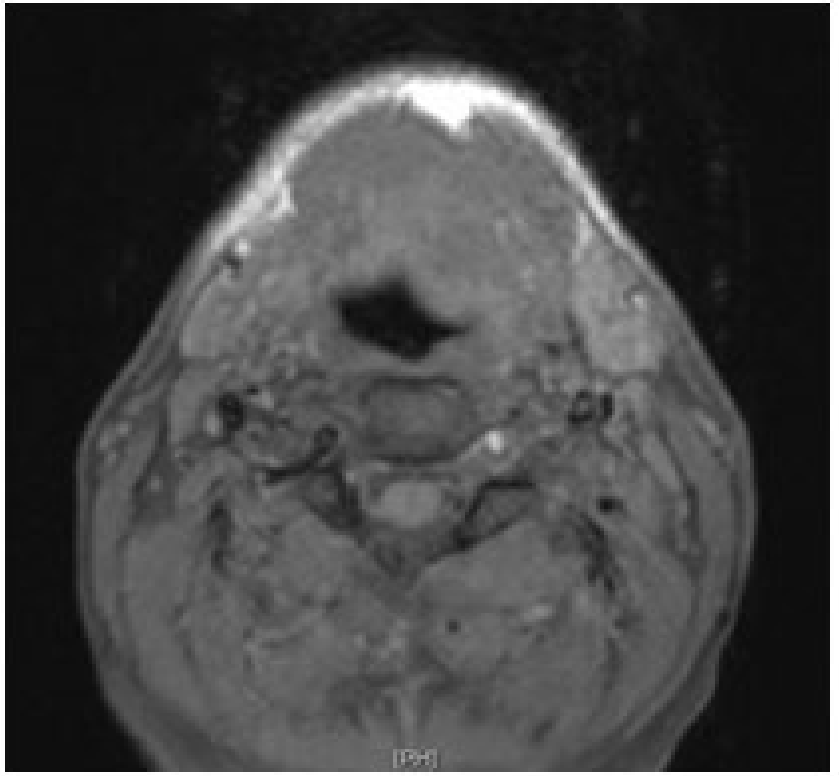


Cerebellar Infarction due to VA dissection

Large are of hypodensity in the posterior medial left cerebellar hemisphere.

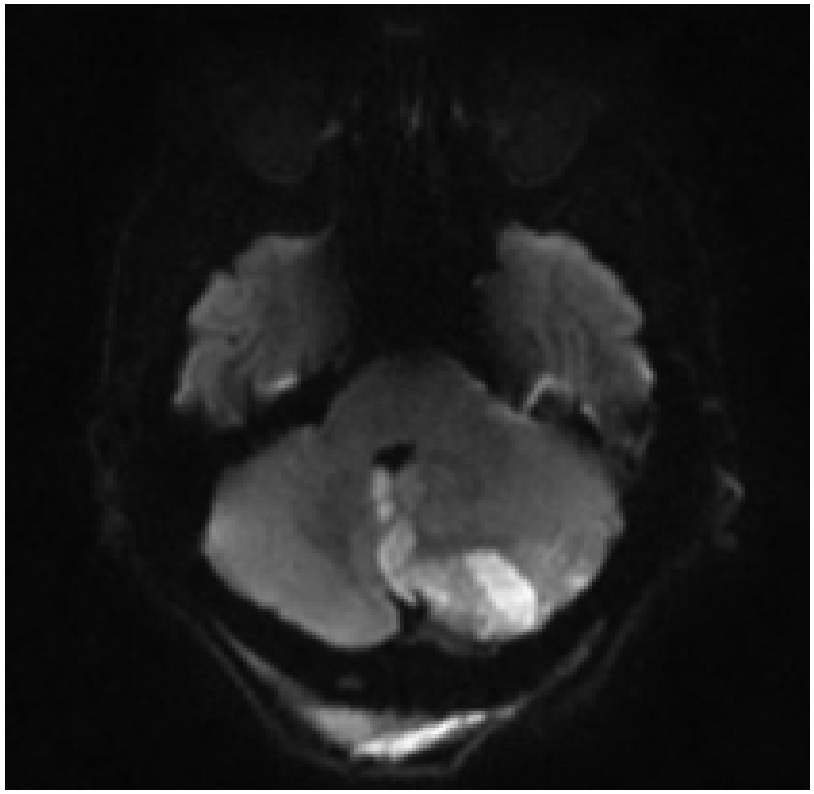
Radiographic Images of Posterior Circulation with concern for left VA dissection

The left VA tapers to the level of C2 where there is no visualized flow until just proximal to the basilar artery, concerning for left VA dissection. On the fat saturated T1 axial images, there is high signal intensity in the region of the left VA, which again is concerning for dissection. The right VA is well visualized and unremarkable.



Left Cerebellar

Large area of restricted diffusion and surrounding edema predominately in the left cerebellar hemisphere; postoperative changes of suboccipital craniectomy.



Radiological Studies Should be Repeated

- It is recommended that radiological vascular non-invasive studies should be repeated as occluded CD often recanalize while those related to atherosclerosis rarely do making the diagnosis more obvious, especially in the absence of diffuse atherosclerotic disease

Radiological Outcomes on Follow-up

- Recanalization
  - Recanalization rate about 80%
  - Higher rates in spontaneous CD, resulting stenosis vs occlusion, VA>ICA and female gender
- Extracranial dissecting aneurysms
  - 10-50% of cases
  - Low risk of IS or SAH
  - No association with CMT related CD

Acute Therapy

- ***Endovascular treatment***
  - There are no randomized trials with endovascular treatment in patients with CD.
    - Several case reports document the success of endovascular intervention to reestablish blood flow in patients with severe stenosis or occlusion at the site of the CD.
    - In one recent systematic review of stenting failure of medical management and contraindication to anticoagulation use were the most common indications for endovascular treatment.
    - Procedural complications and recurrent strokes were uncommon.
  - No evidence to suggest it improves outcomes over other treatments
- ***Thrombolysis***
  - **Thrombolysis with tPA appears to be safe in patients with acute ischemic stroke secondary to CD**
  - A recent meta-analysis of 180 patients with CD and acute stroke did not show any increase in complications, including intracranial hemorrhage (ICH), when outcome in thrombolyzed patients was compared to controls from the Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombosis Register (SITS-ISTR).
  - In another study of thrombolysis in 488 patients with acute stroke secondary to CD in the United States between 2005 to 2008, there was no increase in the risk of ICH when compared to patients without arterial dissection.[210] Patients where CMT was associated with the CD were not reviewed separately in either report.

Preventing Recurrence

- Anticoagulation or Antiplatelet therapy
- Large meta-analysis of studies have not revealed a difference in outcomes between the 2 treatments
- Choice of treatment is largely empirical
- Large IS associated with CD are preferably treated with Aspirin
- Severe arterial stenosis associated with CD, presence of thrombus in the false lumen or pseudoaneurysms are preferably treated with anticoagulants
- A randomized controlled study (CERVICAL ARTERY DISSECTION in STROKE STUDY) an ongoing trial may answer the question of choice of therapy

Management Conclusions for Extracranial CD

- Thrombolysis with IV tPA is reasonably safe in the treatment of patients with acute ischemic stroke caused by CD within 4.5 hrs.
- For patients with TIA or IS resulting from CD, antiplatelets or anticoagulant therapy for 3-6 months is reasonable.
- Endovascular therapy may be considered for patients with CD who experience definite recurrent cerebral ischemic events while on appropriate antithrombotic therapy.

Duration of Preventive Therapy

- Anticoagulation is usually done for 3-6 months as arteries recanalize/remodel within that time period .
- Antiplatelet therapy can also be stopped within 3-6 months unless there is collagen diseases, recurred CD or a family history of CD where treatment should be prolonged possibly indefinite
- Secondary preventive measures such as optimal control of hypertension, hyperlipidemia, discontinuing hormone replacement therapy (HRT) or oral contraceptive pills (OCP) should be considered as for any IS

Outcomes

- Good outcomes with Modified Rankin Scale (mRS) of 0-2 (minimal or no disability) are seen in 70-92% cases
- Predictors of favorable outcome
  - Recanalization
  - Lesser initial stroke severity
- Predictors of poor outcome
  - Bilateral VA dissection
  - Persistent arterial occlusion
  - ICA dissection
  - Older age

Stroke Specific Quality of Life Scale (SS-QOL)

- Usually mRS correlates well with SS-QOL
- However a large study from Berlin revealed a discord in 30% of patients with a mRS = 0-1 with SS-QOL suggesting that mRS may underestimate disability
- Predictors of poor SS-QOL
  - Older Age
  - Initial high NIHSS scores

Outcomes after Cervical Dissection

- Good or favorable outcome is most commonly defined as follow-up mRS scores of either 1 or 1 (little or no disability) or 0 to 2 (includes slight disability).
- In general the majority of patients with strokes caused by CDs have good outcomes, with rates that vary from 70%-92%.
- In one series, when considering the main intracranial arterial collaterals, (ophthalmic, anterior communicating, posterior communicating), patients with $\geq$ 2 such collaterals present had lower initial NIHSS and only 5% had mRS scores > 1 at 90 days compared with 77% with mRS scores > 1 among those with < collateral.

Outcomes of CD and Associated CMT

- Limited Data
- 12-15% with moderate disability after 6 months follow-up from 2 different case series from Arizona, United States and Berlin , Germany
- The Canadian Stroke Consortium included 116 CD cases. 17% were associated with CMT. However CMT was not a predictor of outcome
- Data specific to CD and CMT related outcomes is not conclusive but in terms of numbers the outcomes do not seem as good as those without CMT

Is There a Link to CMT?

- Case control and observational studies have found a link to preceding CMT and subsequent CD
- Is this casual?
  - Not enough studies to pool for causation but enough to prove an association

CMT and Where We Stand

- Vertebral Artery dissections are more closely linked with CMT based on the current evidence
- Carotid Artery dissection is less commonly associated with CMT
- Both antiplatelet therapy and anticoagulation are acceptable
- Anticoagulation may not be the right therapy in intradural VA dissections because of the risk of SAH

Risk of Recurrent Dissection

Lead Author, year	Method	Population	Recurrence Risk Comments
Bassetti 1996 [233]	Single center prospective cohort	81 consecutive patients with CD	All surviving patients had repeat clinical and ultrasound examinations; 3/74 (4%) patients had recurrent ICAD over about 3 years.
Guillon 1999[231]	Single center retrospective cohort	16 patients with 20 ICA dissecting aneurysms	No aneurysm worsening, and no recurrent strokes over mean of 37 months.
Touze 2001[65]	Single center prospective cohort	35 patients with ICA or VA dissecting aneurysms	No aneurysm worsening, and no recurrent strokes over mean of 42 months.
Dziewas 2003 [98]	Single center retrospective cohort	126 consecutive patients with CD	Recurrent CD in 4 patients (3.2%) in first month, and an additional 2 patients (1.6%) from 1 month to one year
Kremer 2003 [225]	Two center prospective nested case-control study	92 patients with either persistent (cases) or transient (controls) severe ICA stenosis or occlusion due to dissection (at a 1 year follow-up ultrasound examinations)	Risk of subsequent stroke was 1.4%/year for cases (average follow up 6.2 years) and 0.6%/year for controls (average follow-up 7.2 years).
Beletsky 2003 [218]	Multicenter, prospective cohort	116 patients with CD	Recurrent events occurred in 9 of 105 followed for a rate of 10.4%/year; most of these events occurred in the first two weeks after CD.
Touze 2003 [234]	Multicenter retrospective cohort	459 patients with CD	During a mean follow-up of 31 months, 4 patients had ischemic stroke and 4 had recurrent CD for rates of 0.3%/year.
Lee 2006 [8]	Population based retrospective cohort	48 patients with CD	No recurrent CD occurred with mean follow-up of 7.8 years.
Arauz 2006 [223]	Single center retrospective cohort	130 patients with CD	6 (4.8%) had recurrent non-fatal ischemic stroke in the first 2 weeks after diagnosis; overall recurrence rate was 0.15% per year. Average follow-up was 19 months.
de Bray 2007 [219]	Single center prospective cohort	103 patients with CD	Annual recurrence rates of stroke of 0.4% and CD 2% with an average follow-up of 4 years.
Georgiadis 2009 [235]	Two center retrospective cohort	355 patients with ICA dissection	One ischemic stroke (0.3%) occurred during 3 months of follow- up for each patient.
Metso 2009 [160]	Single center retrospective cohort	301 patients with 322 CD	6 (2%) new CDs over 4 years (all in different arteries) and 1 stroke from a new CD
Schwartz 2009 [2]	Single center retrospective cohort	177 patients with CD	15 cases (8.5%) of recurrent ischemic events over a median of 7 months (about half of these events were in the first 2 weeks). Two patients (1.1%) had recurrent CD.
Debette 2011 [222]	Multicenter, prospective cohort	982 patients with CD	19 (2.1%) patients had recurrent CDs and 18 (2%) had a stroke within 3 months of diagnosis.

Recurrent Cervical Dissection

- Mayo clinic series:
  - 2% at 30 days
  - 3.7% 2 years
  - 5% over 5 years
  - 11.9% at 10 years
- Recurrences were symptomatic, in vessels unrelated to the initial CD and more frequent in younger patients and unassociated with CMT

Predictors of Recurrence

- Family history
- FMD
- Multiple CDs at initial presentation

Conclusions

- Cervical dissection is an important cause of ischemic stroke in the young and middle aged patients
- Cervical dissection is more prevalent in the upper cervical spine probably related to the biomechanics of that region
- Vertebral arteries are more frequently effected compared to internal carotid arteries.
- A statistical association exists between cervical manipulative therapy (CMT) and cervical dissection.
- CMT has not been shown to be a factor associated with outcome of a subsequent, resultant stroke
- Patients should be informed of the association of CD and CMT before undergoing manipulations of the cervical spine