Dissections of Cervical Arteries – Clinical Presentation, Course, and Therapy in 71 Consecutive Patients of a Single University Centre

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Abstract: Dissections of the cervical arteries are among the most frequent causes of juvenile strokes. The etiology and pathogenesis of spontaneous dissections remain elusive. Best treatment remains to be defined. Here, we analyzed 71 consecutive patients from the Department of Neurology, University Hospital of Jena. We asked if immediate anticoagulation or alternative treatment with ASA would affect outcome. Patients treated initially with i.v. ASA tended to have a better outcome than patients who were anticoagulated ($r=0.3$; $p<0.05$). In heparin treated patients, an initial i.v. bolus shortened the interval before the target PTT was reached by 1.3 days ($p<0.05$), yet did not affect neurological outcome. Low NIHSS (*National Institute of Health Stroke Scale)* ($r=-0.71$; $p<0.01$) and high Barthel scores ($r=0,77$; $p<0.01$) at presentation predicted a good outcome. In 14 of 52 patients, low TSH (*thyroid- stimulating hormone*) indicated hyperthyreosis, while no patient was hypothyreotic. In 33 of 64 patients CRP (*C-reactive protein*) was elevated. These findings merit validation in larger trials.

Keywords: Dissection, vertebral artery (VA), internal carotid artery (ICA), stroke, anticoagulation, platelet aggregation inhibition.

INTRODUCTION

Dissections of the cervical arteries, i.e. vertebral arteries (VA) and internal carotid arteries (ICA) are among the most frequent causes of juvenile strokes. While the incidence of dissections is estimated to be 1–3/100.000 per year, they account for 15–25% of ischemic strokes in patients aged 50 or younger [1-3]. Early diagnosis and consequent secondary prophylaxis are essential.

PATIENTS AND METHODS

71 consecutive patients from the Department of Neurology at the University Hospital of Jena, Germany, were included in this retrospective analysis [4]. To this end, the clinical files of all patients treated in the department between 01/1997 and 12/2005 were searched for the following terms: *dissection, vertebral artery, carotid artery, dissection of cervical arteries, dissection of brain supplying arteries*. Dissections classified as either *traumatic* or *spontaneous* were included (see below). The files were recovered from the archives and checked for the following inclusion criteria: dissection of cervical arteries verified by magnetic resonance tomography/magnetic resonance angiography (MRT/MRA) or by digital subtraction angiography (DSA). A further inclusion criterion was primary clinical treatment at the centre including admission within 24 hours after symptom onset. 71 patients were identified (46 male [64.8%] and 25 female [35.2%]) aged 24 to 78 years (mean: 47 years) and analysed. Diagnosis was confirmed using MRT with MRA according to GAIN-criteria [5], that was usually accomplished by extracranial, contrast enhanced MR-angiography (n = 66) or DSA (n = 5). Patients were excluded if diagnosis was not unequivocal or if they were referred to the centre more than 24 hours after symptom onset. The files were systematically searched for predefined criteria: past and present medical history, vascular risk profile, clinical presentation, diagnostic tests, clinical course, therapy and outcome. Two clinical scores were routinely used: National Institute of Health Stroke scale (NIHSS) at admission [6]; early rehabilitation Barthel-Index (ER-BI) at discharge or at the time of referral to a rehabilitation hospital. At the end of rehabilitation treatment or at clinical controls, the Barthel Index (BI) was defined [7]. We analysed if there was a correlation between the onset of intravenous anticoagulation with heparin (1–4 days after admission) and the difference between the Barthel-Index at the end of rehabilitation treatment and the Barthel-Index defined in the early hospital phase. In addition, possible correlations between an initial i.v. bolus-injection of 5.000 IE Heparin, and the partial thrombine time (PTT), NIHSS and improvement in BI were examined. In patients treated with ASA rather than anticoagulation, a possible correlation between early treatment with 500 mg ASA and ensuing differences in the BI was examined. The patients were divided into 2 subgroups. Patients in the first group (n = 39) scored an ER-BI of 100 points, and therefore had no relevant impairment. For these patients, there was no chance for statistically measurable clinical improvement. All of these

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patients remained stable without clinical fluctuations or deterioration, and were not considered for further analysis. The second group (n = 32) comprised all patients with an early rehabilitation BI of -100 to 99 points.

Statistical Analysis

The program SPSS was used for data acquisition and statistical analysis. A two-taled error of 5% ($p < 0.05$) was considered significant and an error of 1% ($p < 0.01$) was considered highly significant. The following statistical tests were used: linear correlation analysis, odds ratio, Levene-Test, t-test in case of equal variations and Welch-test in case of different variations.

RESULTS

Clinical Parameters

The 72 patients included were aged 47 ± 13.7 years (24–78 years), female patients were on average 1.9 years younger than male patients. There were more males (64,8%) than females (35,2%). The ICA was affected in 29 cases (40.8%), the VA in 43 cases (60.6%). In 4 cases (5.1%) more than one vessel was affected (both ICA, ICA and VA or both VA).

Putative Causes for Cervical Arterial Dissections

In 19.7% a traumatic event was identified that appeared to be adequate as a possible cause of traumatic dissection (e.g., whiplash injury, gunshot injury, chiropractic manoeuvre [8]), and in 14.1% a minor trauma (fall, head bang) was identified as possible cause. In the remaining 66.2% a spontaneous dissection appeared likely. Obviously, it is difficult to correctly estimate the putative impact of a possible trauma (e.g., service in tennis, golf, rapid turning movement of the head) and its relevance with respect to the possible cause of a dissection. According to our own experience, repeated interviewing of the same patient increased the frequency of reporting possible dramatic causes. However, the relevance of such events often remains elusive in individual patients [9,10].

Cardiovascular Risk Factors

In 75% of the patients cardiovascular risk factors such as arterial hypertension (n = 25), diabetes mellitus (n = 13) and cigarette smoking (n = 13) were present. This proportion appears rather high considering that cervical arterial dissections often affect relatively young patients without typical vascular risk profile [11,12]. Diabetes (24% *vs* 15.2%) and hypercholesterolemia (60.0% *vs* 39.1%) were more frequent in women, while arterial hypertension (50.9% *vs* 28.0%) and alcohol abuse (26.1% *vs* 12.0%) prevailed in male patients. Cigarette smoking was similarly frequent in both sexes (males 17.4% *vs* females 20.0%). No correlation was found between any of the risk factors and patient age at clinical manifestation. No consistent family histories were available.

Symptoms and Clinical Presentation

In 59 patients (83.1%) the dissection presented clinically with ischemic infarction (89.7% of the ICA- and 76.7% of VA-dissections). In 12 cases no ischemia was detected, even with cerebral MRI. Accordingly, severity of clinical symptoms was highly variable. In some patients, headache was the only symptom, while others were severely ill, requiring intensive care unit treatment in the initial phase. Table **1** shows the clinical findings at admission. In 62 patients (transient) clinical symptoms were present in the immediate pre hospital phase. The most frequent first symptoms were headache (40.3%) and vertigo (16.1%). In these patients, the time lag between symptom onset and reporting/admission to the hospital was astonishingly long (latency with headache as presenting symptom: 10.9 days; vertigo, 4.2 days). Systemic complications such as pneumonia and severely impaired circulation parameters including hypertensive crisis and hypotension occurred in 52.1%.

Table 1. Clinical Findings

Findings at Admission	Number of Patients	n/71 [%]
aphasia	17	23.9
dysarthria	13	18.3
headache	35	49.3
paresis	26	36.6
vertigo	31	43.7
sensory impairment	25	35.2
impaired level of consciousness	7	9.9
visual impairment	10	14.1

Diagnostic Tests

Diagnosis of cervical artery dissection was accomplished in 50 cases (70.4%) using immediate MRI, in 16 cases (22.5%) using colour duplex ultrasound sonography, and in 5 cases (7.0%) using digital substraction angiography (DSA). Colour duplex sonography of the cervical vessels suggested diagnosis of a dissection of brain supplying vessels in 24 patients (33.8%). In 17 (23.9%) of these patients, arteriosclerotic vessel alterations were present.

Acute Treatment

In the acute phase, the patients were treated on a certified neurological stroke unit at a single university centre, according to defined procedures. In 6 patients, systemic thrombolytic treatment using rt-PA was completed before diagnosis of the dissection was established. Another 7 patients received a bolus injection of ASA (500 mg i.v.), again before diagnosis of a dissection was established. Another 11 patients were initially treated with an i.v. Heparin bolus in order to rapidly achieve therapeutic anticoagulation.

Secondary Prophylaxis

68 patients (95.8%) were treated with PTT-controlled anticoagulation using continous i.v. heparin infusion, started within the first four days after symptom onset (Fig. **1**). It took 1–8 days before sufficient anticoagulation (PTT > 50 s) was reached. Two patients were excluded from i.v. anticoagulation for osteoclastic trepanation to prevent malignant brain oedema. In one case, pre-existing oral anticoagulation using a vitamin K-antagonist was continued.

Clinical Course and Prognosis

In most cases, the clinical course and outcome was good and (at least partial) clinical improvement of neurological functions was common (Table **2**). One female patient aged 39 years died 28 days after discharge from recurrent cerebral infarction. This patient was comatose already at admission with an NIHSS score of 23 and had not experienced clinical improvement at any time point during hospital treatment. AT III deficiency was present. Statistically, age, sex, onset of heparin treatment, i.v. heparin bolus at onset of anticoagulation and the duration of i.v. heparin treatment all did not influence prognosis. An i.v. heparin bolus significantly shortened the interval before therapeutic PTT values were reached by 1.3 days ($p < 0.05$). None of the patients treated with heparin suffered from bleeding complications. Heparin bolus injections did not affect outcome (Fig. **2**). In contrast, patients who initially received an ASA bolus injection had a significantly better outcome

Table 2. Clinical Scores

Score	Minimum	Maximum	Mean	± SD
ER-BI	-100	100	68.0	± 52.7
BI	30	100	91.5	± 17.3
Difference BI/ER-BI	0	170	20.6	± 38.8

SD = Standard deviation.

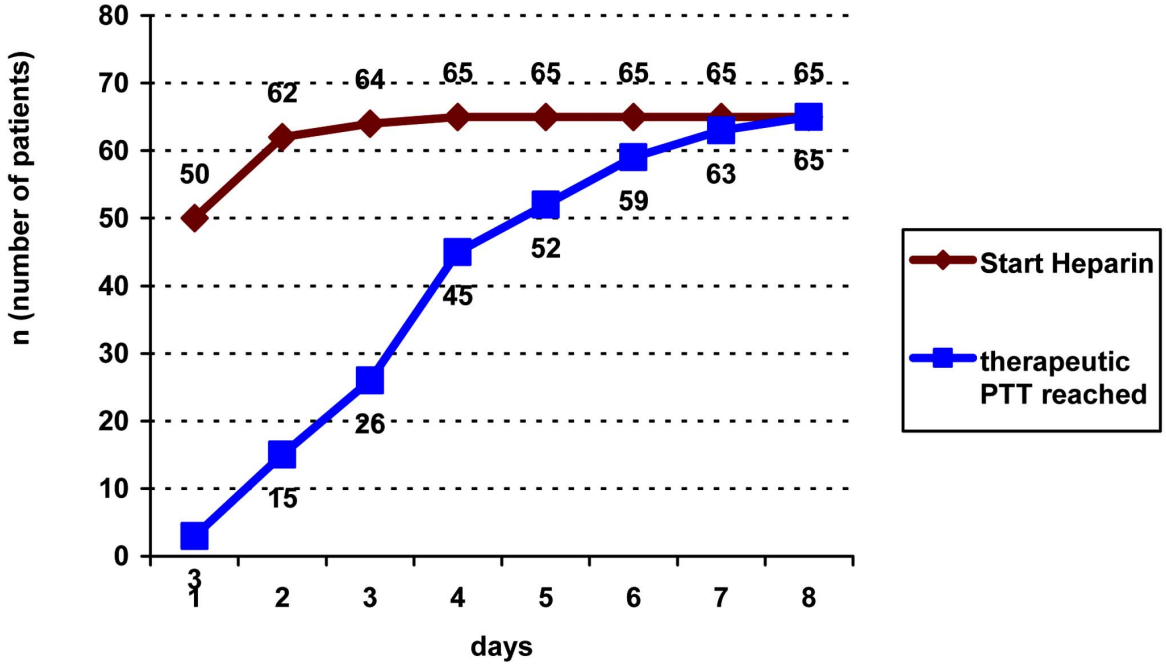

Fig. (1). Heparin treatment and PTT values.

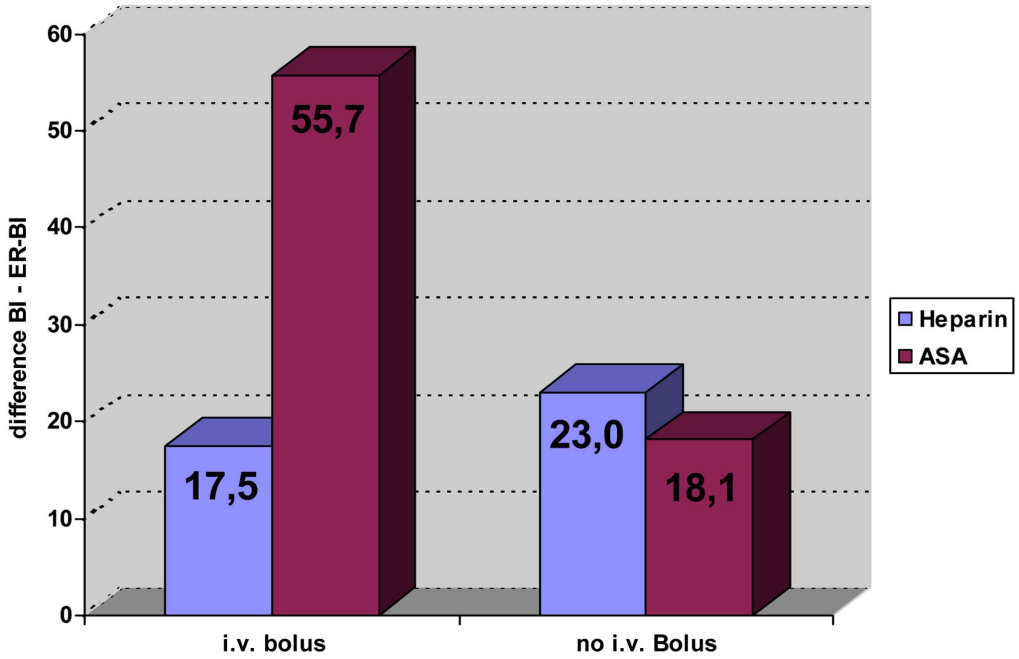

Fig. (2). Effect of treatment on the Barthel Index. BI: Barthel Index; ER-BI: Early rehabilitation Barthel Index.

(as measured as the difference between BI at admission and ER-BI; $r = 0.3$; $p < 0.05$) compared to the patients who were primarily treated with heparin. ASA treatment was safe and did not result in bleeding complications. Patients with anatomical variants of basal brain supplying arteries (most commonly, incomplete circle of Willis; n = 22 [=31%]) had a 2.1 times higher risk to experience ischemic stroke. Indicators for a poor outcome were an initially high NIHSS and a low ER-BI.

Recurrences

All patients identified and included in this study had a first clinical event and diagnosis. No recurrent cervical artery dissections were noted. Also, during the study period, no patient reported with a second dissection event.

Laboratory Parameters

Increased plasma homocysteine, considered a risk factor for cervical artery dissection, was found in 4 patients. 33 patients showed increased CRP (C-reactive protein) levels (> 5 mg/l; mean value 25.3 ± 30.2 mg/L), putatively indicating inflammation and increased risk for both arteriosclerosis and dissections. 14 out of 52 patients had hyperthyreosis as indicated by decreased levels of thyroid stimulating hormone (TSH < 0.35 mU/L; mean value 0.21 ± 0.11 mU/L). Hypothyreosis was not present in any of the patients (Table **3**).

DISCUSSION

This study investigated a cohort of 71 consecutive patients of a single neurological university centre with proven cervical artery dissections. All patients received MRI imaging [13] within 4 days after admission and were initially treated in a neurological stroke unit or neurological intensive care unit.

Epidemiology

In this series, age and sex distribution corresponded to earlier published series [1-3,14]. However, there were differences with respect to the vessels affected. In published series of cervical artery dissection, the ICA has often been described at the most commonly affected vessel [3]. More recent papers described more or less equal frequencies for affection of the ICA and VA [15]. In contrast, in our cohort, the VA was affected more frequently. The course of the VA in the lateral vertebral process may account for a preference to dissections [16-18]. Thorough MRI and MRA investigations in all patients in the acute phase may be a reason for a high proportion of VA-dissections (n = 43) in the present cohort. In many series, dissections were only investigated if unequivocally classified as "spontaneous", while this study included all dissections, independent of (putative) aetiology. This appears reasonable, since a clear-cut distinction is often difficult to achieve (see below).

Aetiology and Pathogenesis

The pathological mechanism of vessel dissections includes tears in the arterial wall with ensuing intramural haematoma. Many questions regarding aetiology and pathogenesis of dissections of brain supplying arteries remain unanswered. With respect to possible aetiological factors, dissections are usually classified as spontaneous (without adequate trauma) or traumatic. In this series, a possibly causing trauma (e.g., car accident, parachute jumping, angiography) was identified in 33.8% of all patients. 25% of dissections classified as traumatic in origin were preceded by chiropractic manoeuvres [18,19]. However, differentiation between spontaneous and traumatic dissection may be difficult in some cases, as it is hard to define which traumata should be considered "adequate" [20]. Moreover, in single cases putatively adequate traumata were reported only after repeated history taking, and with some latency to the index event [4]. Therefore, this concept has been challenged. The aetiology of "spontaneous" dissections remains elusive. In at least part of the cases traumatic structural defects in the arterial wall appear to play a role that increase vulnerability of the vessel wall. Decreased connective tissue resistance can increase vulnerability even to minor trauma, e.g. with sudden head extension or upper airway infections [12].

Connective tissue disorders such as Ehlers-Danlos-Syndrome increase the risk for vessel dissections [21]. Electron microscopical investigations found changes in collagen fibres. Chromosomal aberrations (e.g. 15q24) as well as polymorphisms (e.g. E 469 in ICAM-1) and further gene aberrations have been found [2,22-24]. However, even in cases with familial dissections such alterations were localized to various gene loci, underlining heterogeneity in aetiology [25-27]. Clinical signs such as skin hyperelasticity or joint hyperextension have not been described so far [9,28]. In addition, contribution of autoimmune processes is discussed in the genesis of arterial dissections. In one study [29], an increased frequency of autoimmune thyreoiditis was found in patients with dissections (31%), as compared with patients with ischemic cerebral infarction of other etiologies (6.9%). Increased induction of proteolytic enzymes as a result of an increased immune response results in an increased degradation of extracellular matrix proteins, and

Table 3. Epidemiological Factors

Epidemiology Risk Factors				Diagnostic Examination	
Sex:	M(65%)/ W(35%)	arterial hypertension	35,2%	MRI	70,4%
Age:	24-78 J, MW: 47J	hypercholesterolemia	46,5%	Ultrasound	
Vessel:	ICA (40,8%)/	increased CRP *	51,6%	DSA	7,1%
	VA (59,2%)	hyperthyreosis	26,9%		
		trauma	33,8%		

*At admission.

vessel wall proteins may not be exempted from this process. Another hint towards contribution of immune processes are increased CRP values [30]. In spontaneous coronary artery dissections, histopathological examination revealed inflammatory infiltrations [31] that were absent in dissections caused by catheterisation during coronary angiography. Considering the relevance of such systemic factors, it is unclear at present, why our patients usually experienced one cervical artery dissection event, but never presented with repeated dissection events. The present work was not designed to analyse genetic aspects (a recent summary can be found in [25]). Regarding the hypothesis of autoimmune pathology, alteration in thyreoid hormones (14 patients; 26.9%) as well as increased CRP-plasma levels at admission (33 patients; 51.6%) were found. Other authors reported an association with preceding infection [25,32]. Obviously, it was not possible to prove causal pathological relevance of such factors.

Clinical Presentation and Course

In 49.3% patients, headache was the first symptom. In these patients, on avarage 10.9 days passed before hospital admission. In other series, a median latency of 7 days before admission has been described [14]. Decreasing this latency should be a promising way towards further improvement of therapy and prognosis. Information campaigns should specifically address younger people. Newly arising headaches in combination with other, even transient, fluctuating or altering CNS symptoms should particularly arouse attention, in the population as well as in doctors. In this context, we asked if patients with early initiation of treatment would have a better neurological outcome as compared to patients in which therapeutic anticoagulation was initiated only with delay or even omitted.

Therapy and Outcome

There are no prospective, randomised, multicentre, clinical studies available on acute therapy and secondary prophylaxis of cervical artery dissections [33,34]. Therapeutic guidelines, and eventually standard operating procedures have emanated from clinical experience. They suggest treatment of cerebral ischemia caused by arterial wall dissections as ischemic strokes, e.g. in specialized units, such as certified stroke units that have been widely established in large hospitals in Germany. Recommendations for secondary prophylaxis include early anticoagulation with i.v. Heparin and regular controls of coagulation parameters (PTT). After the acute phase, oral anticoagulation with vitamin K antagonists is recommended for 3–6 months (guidelines of the German Society of Neurology [35]). However, oral anticoagulation is no more unequivocally recommended [4,15,25,36-38].

In all patients of the present series, treatment was initiated within the first 4 days (in 50 patients, treatment was started on day 1). There was no significant difference between these patient groups with respect to clinical outcome. Initial i.v. Heparin bolus injection did nod affect clinical outcome, although therapeutic PTT-levels were reached sooner. The effect of initial i.v. ASA bolus has not yet been investigated prospectively [37]. In our series, 7 patients were initially treated with 500 mg ASA i.v. before detection of the arterial dissection as putative cause of ischemic cerebral infarction. These patients showed even better clinical improvement (significantly increased difference BI – ER-BI, 55.7 *vs* 18.1 points; $r = 0.3$; $p<0.05$). This may hint towards a contribution of thrombocytes in thrombus formation in the early phase of symptomatic vascular pathology, and a therapeutic role of ASA in preventing thrombus formation, similarly to its action in myocardial infarction [21]. Owing to the retrospective nature of the present study, location, numbers and heterogeneous aetiology of dissections, these results are not statistically significant and must be subject to further and larger trials [33,37]. Recently, several groups reported on similar outcomes in patients treated with ASA as compared to heparin followed by oral anticoagulation [36,37,39]. While there are no data from prospective, randomized studies available on this issue, ASA may be an adequate alternative to anticoagulation. Moreover, an initial i.v. ASA bolus provides immediate anti-aggregation action, while administration of i.v. heparin often results in several days delay before therapeutic PTT levels are achieved. From a pathophysiological point of view, anticoagulation may still be preferred in high grade stenosis, vessel occlusion with risk of embolisation before recanalisation, presence of multiple embolic lesions, and with formation of pseudo-aneurysms (provided no major bleeding risk is present). Thrombolytic treatment may be warranted in individual patients and appears to be safe. Angioplasty with stenting may be accomplished, e.g. in high degree stenosis, or when a large intimal flap is present. This is technically feasible, yet there are no systematic data on effectiveness, and no prospective data available [25,37].

Neurological outcome after cervical artery dissection was generally good, consistent with reports from the literature [25,32,36-38]. However, effects on social behaviour and professional performance, and self-assessed quality of life may be more relevant than recognized to date [25,40].

While we cannot exclude that single patients may have presented to a different center at later time points, all of the patients analysed here had their first dissection event, and none of our patients reported for another event during the study period. Therefore, we have no indication for recurrences in our patients, consistent with previous reports [25, and references therein].

CONCLUSIONS

Cervical artery dissections may be the sequelae of trauma, or may be caused by alterations in vessel wall architecture or immune processes (Table **4**). Better understanding of different aetiologies may increase the future options for more specific therapeutic approaches. Naturally, retrospective analyses do not allow to draw unequivocal conclusions. Prospective, multicentre studies are warranted in order to determine optimal, and possibly differential therapy of cervical artery dissections. With regard to acute treatment, at present initial high dose i.v. ASA appears to be at least equal to i.v. anticoagulation with Heparin [36,37]. However, this has not been addressed in prospective, randomized trials. In order to further improve prognosis, it is crucial to establish the diagnosis of cervical artery dissection as early as possible. This includes alertness of both patients and doctors on the one hand, and early MRI

Table 4. Prognostic Factors and Perspectives

Prognosis	Relevant	Not Relevant
	NIHSS/FRBI	age/sex
	ASA bolus injection i.v.	heparin bolus injection i.v.
	variation in vessel anatomy	initiation/duration of heparin treatment
Perspectives	**Putative Etiologies**	**Possible Perspectives for Future Therapies**
	genetic causes	immune suppression (e.g., prednisolone)
	autoimmune disorder±	statins
	thyroid disease	initial i.v. ASA bolus injection

imaging including contrast enhanced MRA of cervical arteries.

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