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Carotid disease and stenting (CAS) procedure

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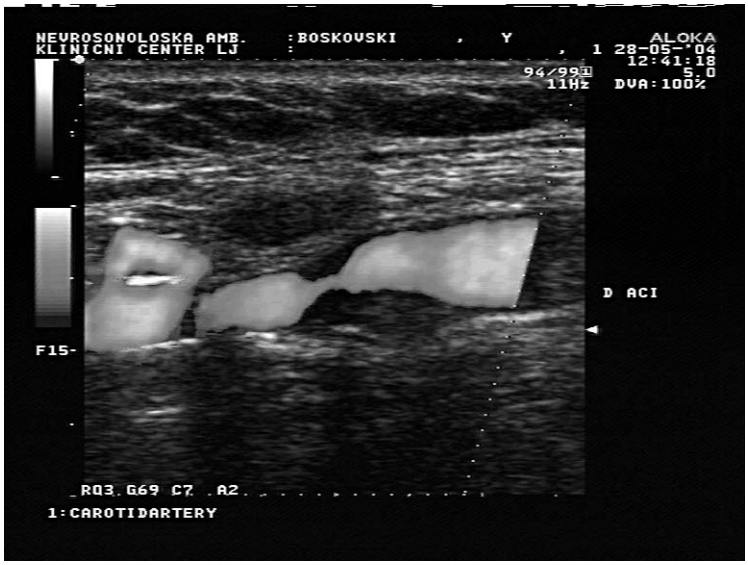
Introduction: Today cerebrovascular diseases are the second cause of death worldwide, while the third in Europe; at the same time they are considered the major cause of disability (Bonita et al, 2004; Kings College London, 2005). The ischemic stroke (IS) represents 75-80% of all strokes - in the USA even more than 90% (Khaw, 1996). The stroke-related costs are among the highest. In Europe and in the USA stroke is considered a medical emergency requiring immediate hospitalization and treatment. At the same time, for stroke prevention similar principles apply as in case of prevention of cardiovascular diseases. It is estimated that 20–50% of transitory ischemic attacks (TIA) are the result of carotid artery stenosis or occlusion (Khaw, 1996; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991).

Epidemiology of stroke: Fifteen million people worldwide suffer from cerebrovascular diseases, 4 million in Europe alone. Five million of those die, 5 millions remain permanently disabled. In Europe around 1.2 million strokes occur each year and around 200.000 patients die. 40% of deaths in Europe are caused by cardiovascular diseases and stroke. The mortality rate due to stroke is 60% higher in Europe than in USA and Canada (Wolf-Maier et al, 2003).

In Slovenia the incidence of stroke is slightly decreasing (Šelb, 2006)). According to the data published by the Institute of public health in Slovenia 4400 stroke patients are treated each year. About 2100 patients die (Šelb, 2006). Mortality rate due to stroke doubles approximately every five years. In Slovenia stroke-related mortality rate is higher in women than in men. In some age groups mortality rate is higher in men than in women, markedly up to the age of 65. Women suffer stroke when older than men. In 2003 the average age of women with stroke was 70, of men 64. Number of deaths caused by stroke is slightly decreasing worldwide. This is probably the result of better treatment and also of better prevention and reduction of risk factors (Šelb, 2006). Mortality due to stroke correlates with the incidence of arterial hypertension which is the major stroke risk factor. It is estimated that the incidence of the arterial hypertension will increase to 60% by 2025 and will affect 1.56 billion people (Kearney et al, 2005).

Carotid artery disease: Carotid artery disease is advanced atherosclerosis in the carotid bifurcation, with stenosis or occlusion of the extracranial portion of the internal carotid artery (ICA). In the pathophysiology of a cerebrovascular ischemic event the most common initial event is the rapture of fibrous cap of an atherosclerotic plaque located in the carotid artery wall. This leads to clot formation at the site of the atherosclerotic plaque rapture; clinical signs are most often the result of arterial embolisms in the intracranial artery. The emboli can originate from the lipid core of the ruptured atherosclerotic plaque or from a clot which breaks off. In some cases the clinical signs result from an instant thrombotic blockage of the ICA (Bonita et al, 2004). Stenosis of the ICA is an important risk factor for the ischemic stroke; in patients with 50% lumen stenosis not causing the symptoms before annual incidence of such stroke is 1–3% (Sacco, 2001). A NASCET study found that in patients with asymptomatic stenosis of 60–99% the annual incidence of the ischemic stroke was 3.2%; of these 45% were lacunar or cardioembolic strokes which were not directly related to the stenosis of the internal carotid artery (Inzitari et al, 2000). The risk of stroke moderately increases with the level of ICA stenosis. The form and the composition of the atherosclerotic plaques are less researched risk factors (Geroulakos et al, 1996; Yuan et al, 2001).



Picture 1. Short, haemodynamically significant stenosis of the internal carotid artery, caused by a lipid plaque of type 1 (Power ultrasound imaging)

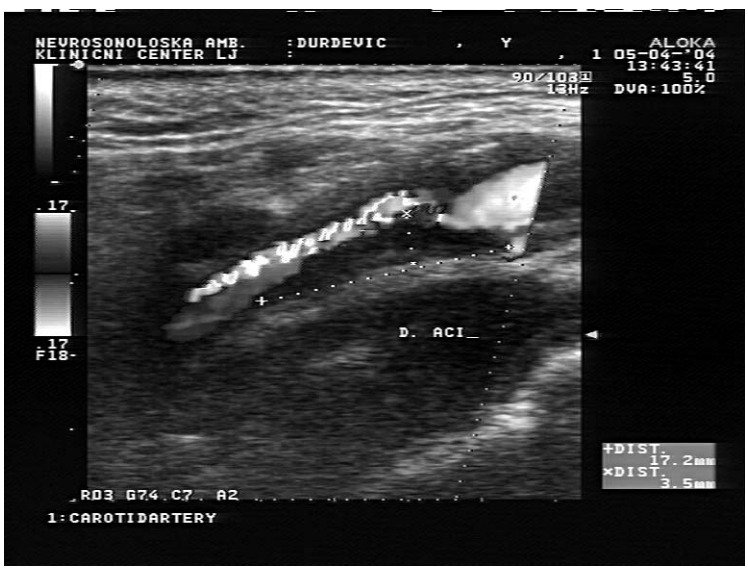
When the stenosis of the ICA causes the symptoms such as TIA or a minor stroke, the risk of ipsilateral stroke is much higher than in case of asymptomatic stenosis. The NASCET study showed that 26% of the patients with symptomatic 70–99% ICA stenosis, who were monitored for two years and treated with medications and no thrombendarterectomy (TEA) suffered a stroke (North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991).

Diagnosis of carotid artery disease

History and clinical picture: We are alerted to the possibility of stenosis of the artery when we detect an arterial murmur above the common carotid artery bifurcation. The arterial murmur has 56% sensitivity and 91% specificity in determination of 70–99% stenosis of the carotid artery (Magyar et al, 2002). In cases where the carotid artery stenosis causes the TIA symptoms and signs, we assess it on the basis of the patient's history and neurological exam. It can show in the form of a transitory visual loss in one eye (amaurosis fugax) or in the form of strongly expressed signs of paralysis on the opposite side and sensory loss. In case of impairment of the dominant hemisphere higher nervous activity disorders can occur – such as aphasia, alexia, acalculia, agraphia; in case of the impairment of the non-dominant hemisphere disorders such as space disorientation and neglect of the impaired side of the body (Timsit et al, 1992). Less specific TIA signs can occur in the form of clonic movements in the extremity mimicking a focal epileptic seizure or partial paralysis where the arm is weaker than the shoulder girdle (Timsit et al, 1992). The patients with suspected recent ischemic stroke – which has occurred less than 2 hours ago – shall receive emergency treatment. These patients can benefit from fibrinolytic treatment, but only after cerebral hemorrhage was ruled out with the help of the computerized tomography (Brainin et al, 2004). In case of the IS – just as in case of a TIA – specific signs occur; but, as distinct from TIA, the signs do not improve within 24 hours. So the doctor or the paramedic shall – with the help of the patient or his/her relatives – fill in a questionnaire on the basis of which it is decided whether or not the patient urgently needs to be transported to the hospital.

Examinations in carotid artery diagnostics: Ultrasound (US) examination of the carotid arteries is a basic exam used for diagnosing stenosis of the carotid arteries. This is a non-invasive, safe method which can be repeated; still, it requires a very skilled examiner. In order to precisely determine the level of stenosis the ICA needs to be shown in longitudinal and transverse direction; then, at an optimum longitudinal cross section with 60-degree illumination angle of the doppler US beam the peak systolic velocity and the end-diastolic velocity in the ICA, as well as the ratio between the peak stolic velocities in the internal and common carotid artery (ICA/CCA) need to be measured. The results are assessed according to standardized tables (Filis et al, 2002). Thoroughly performed US examination makes possible precise localization and measurement of the size of atherosclerotic plaques as well as assessment of their surface and composition. Microemboli in the intracranial part of the ICA can be detected by using a transcranial Doppler (TCD) (Demarin et al, 2003).

Whenever we have to decide – on the basis of the US screening - whether or not to perform a revascularization procedure in patients with heamodynamic stenosis of the ICA, we perform one of the superior screenings: the computerized tomographic angiography (CTA), magnetic resonance angiography (MRA) or digital subtraction angiography (DSA). By means of these examinations we confirm the US findings; we assess the blood flow and the position of the aortic arch, the common carotid arteries and of intracranial branches of the carotid arteries. The results of the CTA correspond to the DSA results; therefore we recommend to most patients with carotid stenosis that they undergo CTA screening of carotid arteries (Cinat et al, 1992) prior to their cases being reviewed by the Carotid Artery Disease Treatment Council. The Council follows the Slovenian recommendations (Žvan, 2004; Žvan 2006).



Picture 2. Long, haemodinamically significant stenosis of the internal carotid artery caused by a lipid plaque of type 1 (Color-duplex ultrasound image).

Revascularization of patients with stenosis of the internal carotid artery

Revascularization of symptomatic patients with stenosis of the internal carotid artery - recommendations (Žvan, 2004; Žvan, 2006).

1. In accordance with the NASCET criteria the symptomatic patients with □ 70% stenosis of the ICA, who are not severely neurologically impaired, are treated - not later than within 180 days after the ischemic cerebrovascular event has occurred - by TEA or carotid artery angiopalasty with stanting (CAS), if the probability of complication during the revascularization procedure is □ 6% (Level I / III).

2. The patients shall receive antiplatelete drugs before, during and after TEA/CAS (Level I / III).

3. After the procedure they shall continue to treat the risk factors for atherosclerosis and shall modify their lifestyle (Level I).

4. Symptomatic patients with □ 50% carotid stenosis receive antiplatelete drug treatment, with accompanying treatment of risk factors for recurrent stroke; statine is introduced regardless of blood cholesterol level (Level I).

5. The decision whether or not a revascularisation procedure in symptomatic patients with 50 to 69% carotid stenosis will be perform is made in respect to each individual case. From TEA and CAS procedures mostly benefit men between the ages of 75 and 80, with recent ischemic cerebrovascular event and without severe neurological impairment (Level III).

6. If we decide on revascularisation procedure double antiplatelete treatment is administered, risk factors are monitored and treated and statin is administered (Level I).

Revascularization in patients with asymptomatic carotid artery stenosis; recommendations

1. Asymptomatic patients with □ 70% carotid stenosis are treated with antiplatelete therapy and the risk factors for development of atherosclerosis are monitored (Level I).

2. In asymptomatic patients with □ 70% carotid stenosis the decision on revascularisation procedure is taken in respect to individual case. Age and gender are considered, presence and stability of ischemic cardiac disease, prevalence of the peripheral artery disease and the experiences of the surgeon or interventive radiologist. If the risk for complications to occur (death, stroke) during the procedure is ≤ 3% and the patient is expected to live at least another 5 years (younger than 80), we decide on TEA or CAS (Level II/III). If the risk for complications to occur during the procedure is > 3%, asymptomatic patients with carotid disease are treated with antiplatelet drugs and risk factors for development of atherosclerosis are monitored (Level II).

Revascularization treatment of patients with high risk for cerebrovascular ischemic event- recommendations (Žvan, 2004; Žvan, 2006)

1. The CAS is recommended in patients with symptomatic carotid disease, for the risk for complications to occur during TEA is so high that the procedure is contraindicated; in patients with internal carotid restenosis after TEA and in patients with carotid stenosis caused by neck radiotherapy (Level III). Decision on the form of treatment in patients with carotid disease can be made also by the Council for carotid disease treatment (Level IV).

2. Patients shall receive antiplatetet drugs clopidogrel and Aspirin 5 days before CAS, on the day of the procedure and at least one month after it (Level I).

Carotid angioplasty with stenting – the results

Between years 2002 and 2006, 715 CAS procedures were performed in the University Medical Centre Ljubljana (Žvan, 2007). Table 1 shows our CAS results. We analyzed 715 patients with complications that occurred within 30 day after CAS procedure. We divided the patients into the group of symptomatic patients – those who have already suffered a cerebrovascular ischemic event (387 patients – 54%), the group of asymptomatic patients (328 patients – 46%) and the group of patients with severe and minor neurological complications. Here was no incidence of death directly related to the CAS procedure. One patient died one week after the procedure, but her death was due to heart failure. In both groups 8 patients (1.12%) suffered major ischemic stroke: 4 due to ipsilateral embolism, 2 due to stent thrombosis and 2 due to contralateral embolism. One of the patients suffered hyperfusion syndrome with hemorrhage (0.14%). Total of 9 patients (1.26%) suffered severe complications. Of all the patients 7 (0.98%) suffered a minor ischemic stroke, 9 patient (1.26%) suffered TIA and 1 patient (0.14%) suffered hyperperfusion syndrome without hemorrhage – which means 17 (2.38%) patients in total. In both groups – the symptomatic and asymptomatic, 26 patients (3.64%) suffered either minor or major complications. The analysis of separate groups is shown in table 1. It is very important that in the group of symptomatic patients only 19 patients (2.66%; permitted ≤ 6%) suffered complications; in the asymptomatic group only 7 patients (0.98%; permitted < 3%) suffered complications. The results show that, in view of the guidelines for treatment of the carotid artery disease (Žvan, 2004; Žvan, 2006), the CAS method can be used for treatment of both, symptomatic and asymptomatic patients, for the percentage of complications in our group of patients treated with the CAS method was far below the permitted level.

Table 1. Results of CAS

Complications within 30 days after the procedure	Total		Symptomatic patients		Asymptomatic atients	
	N	%	N	%	N	%
Severe complications						
Death	0	0.00	0	0.00	0	0.00
Major IS – ipsilateral embolism	4	0.56	3	0.42	1	0.14
Major IS – stent thrombosis	2	0.28	1	0.14	1	0.14
Major IS – contralateral embolism	2	0.28	2	0.28	0	0.00
Hyperperfusion – hemorrhage	1	0.14	1	0.14	0	0.00
Total	**9**	**1.26**	**7**	**0.98**	**2**	**0.28**
Minor complications						
Minor IS	7	0.98	5	0.70	2	0.28
TIA	9	1.26	6	0.84	3	0.42
Hyperperfusion – no hemorrhage	1	0,14	1	0,14	0	0,00
Total	**17**	**2,38**	**12**	**1,68**	**5**	**0,70**

IS – ischemic stroke; TIA – transitory cerebrovascular ischemic attack; Symptomatic patients – patients who suffered a cerebrovascular ischemic event; Asymptomatic patients – the patients who did not suffer a cerebrovascular ischemic event

Treatment of patients with carotid artery disease the Stroke Unit

Immediate treatment of stroke patients and their rehabilitation, including revascularization treatment, proved very effective. The WHO in its Helsinki Declaration recommends that all stroke patients be treated in a Stroke Unit (Aboderin et al, 2006). The results of the treatment in the Stroke Unit, with early hospitalization and individually planned treatment strategy, also speak in favour of this. A multidisciplinary medical team with extensive knowledge of cerebrovascular diseases participates in the treatment (Lausanne et al, 2003). In the Strake Unit the goals of the stroke patient care are control and prevention of neurological and other complications, improvement of neurological impairment caused by strike and preventing reoccurrence of stroke. The major progress in treatment of stroke patients is realization that organization of care in a Stroke unit decreases mortality, invalidity and institutionalization.

Monitoring of patients during and after a revascularization procedure

All the patients who were determined suitable for CAS procedure by the Council for Treatment of Carotid Artery Disease are admitted, on the day of the procedure, to the Neurology Clinic at the University Medical Center in Ljubljana. During the CAS procedure the patient's vital functions are monitored by an anesthesiologist; 5-6 hours after the procedure the vital functions, the sticking point in the groin and the overall state of the patient are constantly monitored by a nurse in the Stroke Unit. If there are no complication the patient is discharged the next day and given instruction for further treatment and monitoring. Before the discharged the stent and haemodynamics in the carotid artery are checked by means of the ultrasound screening.

The patients with asymptomatic stenosis of the internal carotid artery are usually submitted to the ultrasound screening of the carotid arteries once a year. After TEA procedure the successfulness of the revascularization must be checked by means of ultrasound exam after few days, then once per year. After the CAS procedure the checking has to take place more often – first after one day after the procedure, then within next 6 months (Žvan, 2004) or in accordance with the examination protocol. The purpose of monitoring is both, detection of nonrevascular stenosis of the internal carotid artery or recurrence of stenosis after revascularization and planning of further treatment.

Conclusion

The guidelines of the European Stroke Initiative (EUSI) recommend the CAS procedure in patients with symptomatic carotid artery disease for the risk for complications to occur during TEA is so high that the procedure is contraindicated; in patients with internal carotid restenosis after TEA and in patients with carotid stenosis caused by neck radiotherapy (Level III) (www.eusi-stroke.com/2004) Decision on the form of treatment in patients with carotid disease can be made also by the Council for carotid disease treatment (Level IV) (Žvan, 2004).

Due to the fact that in the University Medical Center in Ljubljana the CAS procedure generates very few complications (the risk of death and stroke during the procedure – in asymptomatic patients 0.70%, in symptomatic patients 1.68%), the CAS can be applied in treatment of all patients pronounced suitable by the Council for Carotid Disease Treatment (Level I/III).

After the revascularization procedure on the carotid artery all patients must follow the principles of secondary prevention of ischemic cerebrovascular events of atherotrombotic origin.

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AGNIESZKA SŁOWIK

Genetics of stroke

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Stroke is a major cause of death and the major cause of neurological disability worldwide. Epidemiological data suggest that genetic factors affect significantly stroke risk.

Several genes in single gene disorders associate with stroke have been discovered, including NOTCH3 gene in patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL). Little is known, however, about the genes associated with complex multifactorial stroke. Genetic-association studies on candidate