The Hyperperfusion Syndrome: An Under-Recognized Complication of Carotid Endarterectomy

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Hyperperfusion syndrome is a neurologic syndrome comprising a triad of unilateral headache, seizures, and focal neurologic deficits [1]. It may, however, be complicated by intracerebral hemorrhage that can be severe enough to cause death [2]. HPS was originally described in patients undergoing carotid endarterectomies for high grade carotid stenosis [1], but more recently it was reported also following other means of cerebral revascularization including angioplasty alone or stent-assisted angioplasty [3]. Although HPS is considered a rare complication, it is well known to surgeons or invasive neuroradiologists who are involved in cerebral revascularization procedures. However, the full (and ominous) picture of this syndrome may develop several days after the patient has already left the hospital. Thus, it is the family physician or the emergency room physician who is usually called to treat these patients, and this scenario appears to becoming more common as current trends favor invasive vascular procedures for which the hospitalization time is very short.

Within an 18 month period we treated four patients who developed this syndrome after carotid endarterectomy, all of whom were originally referred and seen by emergency room physicians, internists and neurologists for a presumed diagnosis of stroke, seizure disorder or an unusual vascular headache. We present our HPS patients (one in detail, the others briefly), discuss the pathogenesis of HPS and suggest ways to prevent its occurrence.

**Patient Descriptions**

**Patient 1**
A 53 year old man was admitted to the neurology department after a first episode of generalized tonic clinic seizure and intractable headache. Five days earlier, the patient underwent right CE for an asymptomatic high grade stenosis. He had suffered two episodes of left hemispheric stroke 1 year prior to the surgery and was left with mild right hemiparesis and motor dysphasia. He denied hypertension.

A brain computerized tomography scan prior to surgery revealed an old left frontoparietal infarct, and a carotid duplex showed a complete occlusion of the left internal carotid artery and a 95% stenosis on the right side. These findings were confirmed by angiography that was performed 10 days prior to the CE. The surgery was successful and he was discharged on the third day, at which time he began to complain of severe right-sided headache and was treated symptomatically at home. Upon admission and after, marked fluctuations in his blood pressure were recorded, ranging from 125/85 to 240/130 mmHg, and higher values were associated with severe headache. His neurologic examination displayed expressive dysphasia and mild right spastic hemiparesis and hemihypoesthesia. During his hospital stay he experienced repeated spells of transient global aphasia and bouts of headache. The brain CT scan showed no new lesions and the post-operative carotid duplex revealed a complete patency of the operated right side. Transcranial Doppler sonography showed abnormally high peak systolic velocities along the right and left middle cerebral arteries (178 and 155 cm/sec respectively; upper normal 135 cm/sec). Transesophageal echocardiography was normal and his electroencephalogram showed asymmetric slowing with no epileptiform discharges. Complete workup for the new high blood pressure was negative.

The patient was treated with antihypertensive, antiepileptic and analgesic medications. Within 4 weeks all the new symptoms subsided, and blood pressure as well as a follow-up transcranial Doppler sonography returned to normal.

**Patient 2**
A 70 year old man with hypertension and stable ischemic heart disease underwent a left internal carotid endarterectomy for a 95% asymptomatic stenosis. The immediate postoperative course was uneventful and he was discharged home. Four days after the CE the patient developed head-
ache and became confused. He then had an adverse seizure (forceful movements of his head and neck to the right side) and lost consciousness. He was intubated and admitted to an internal medicine ward with a tentative diagnosis of stroke, possibly hemorrhagic. On neurologic examination he was obtunded and displayed right hemiparesis. Both the immediate and delayed brain CT scans were normal, as was electroencephalogram. Carotid duplex revealed a complete patency of the left side. Phenytoin treatment was begun, which led to a rapid recovery and discharge 4 days later. The follow-up was negative for further epileptic seizures and the EEG remained normal.

**Patient 3**

A 68 year old woman with ischemic heart disease and non-insulin-dependent diabetes mellitus underwent a right CE for a severe asymptomatic stenosis. Ten days later she developed headache (right hemi- crania), vomiting, and focal seizures of her left hand and face and was admitted to the neurology department. Physical and neurologic examinations were normal, as were a brain CT scan and the cerebrospinal fluid content. Her EEG disclosed right-sided epileptic discharges and she was treated with phenytoin. A rapid improvement of symptoms was noted and she remained asymptomatic thereafter. Carotid duplex scan confirmed excellent surgical results.

**Patient 4**

An 80 year old man with hypertension and remote stroke underwent left internal carotid endarterectomy for bilateral 95% stenosis. After an uneventful course he was discharged home 3 days later. He then started to complain of headache, drowsiness and episodic slurred speech, and his blood pressure was high reaching 210/110 mmHg. Since these complaints persisted for 10 days he was examined by a vascular surgeon who, after confirming good surgical results by carotid duplex, sent the patient to the emergency room. In the emergency room the patient developed a seizure that started in his right extremities and became generalized. When he recovered he was found to be aphasic and had right hemiparesis. Following further seizures he was started on phenytoin infusion. A brain CT scan was negative for hemorrhage and there were no clear signs of an infarct. The patient recovered quickly and was left with minimal right-sided hemiparesis.

**Comment**

The relief of high grade carotid stenosis by carotid endarterectomy or stent insertion causes an increased blood flow through the new widely patent artery. This can result in a hyperperfused state in the relevant part of the brain and may be manifested, in vulnerable brain tissue, by various symptoms and signs. Although HPS is associated with tighter stenoses and longer clamp time intraoperatively, it is not merely a local phenomenon. It may be induced by disturbances in the blood-brain barrier and cerebral autoregulation, leading to an increase in intracranial pressure and to global brain edema. The oscillation in blood pressure can also result from injured carotid body and nerve at the time of the CE.

The term HPS is used for all the delayed postoperative neurologic complications that have been reported since the introduction of CE, including postoperative strokes, which usually present as intracerebral hemorrhage [2]. Most HPS, however, are associated with only transient neurologic dysfunction – focal and generalized – the usual manifestations being severe ipsilateral headache, focal (secondary generalized) seizure and transient neurologic dysfunction (e.g., hemiparesis, aphasia or confusion). HPS usually occurs 3–5 days following the procedure, yet the time range is wide (1–18 days).

HPS was always considered a rare complication of CE (about 1%), but this was based on its clinical definition. With the use of intra- and postoperative monitoring (such as TCD) and by using hemodynamic parameters for HPS [1,4,5], it is diagnosed nowadays much more frequently at rates as high as 9% [5]. Many of these cases may not manifest significant clinical features. The current approach is to diagnose the very early signs of HPS in order to prevent its progression to the full-blown picture. The first cases of HPS were associated with a twofold increase in their postoperative cerebral blood flow (measured by Xe 133 inhalation) [1]. In recent years TCD has become the method of choice to help in diagnosing HPS, in addition to continuous blood pressure monitoring. HPS can be diagnosed by different methods: a) persistence of middle cerebral artery velocities >1.5 times the pre-cross-clamp values [4] and b) >100% increase in peak flow velocity or >100% increase in the pulsatility index of the ipsilateral middle cerebral artery after declamping [5]. In order to detect and follow all patients at risk of developing HPS, TCD should be repeated daily following CE. Other – less specific – means to suspect HPS include EEG and perfusion single photon emission computed tomography.

Since HPS is a hyperperfused state in under-protected brain tissue with loss of cerebrovascular reactivity and inability to control blood pressure elevations, it is of the utmost importance to prevent the abrupt increase in blood pressure and cerebral blood flow in order to prevent its development. Once increased velocities (by means of TCD) or increased cerebral blood flow (by SPECT) are observed, these patients should be kept in hospital and monitored for any changes in blood pressure. Preventing rapid oscillations in blood pressure will reduce the incidence of HPS.

Physicians not directly involved in cerebral revascularization procedures should be familiar with this not so uncommon syndrome, and those involved in CRP should realize the magnitude of this problem. Besides frequent blood pressure measurements following CRP, transcranial Doppler or perfusion SPECT could be of help in detecting those patients at risk for HPS. These patients should then be treated until stabilized.

**References**


TCD = transcranial Doppler

SPECT = single photon emission computed tomography

CRP = cerebral revascularization procedures
Idiopathic Liver Involvement in Turner Syndrome

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Key words: Turner syndrome, chronic liver disease

Turner syndrome is a relatively common chromosomal abnormality with a frequency of 1:2,500 liveborn female infants. The most common chromosomal aberration is the complete loss of one X chromosome (45X0), but many other chromosomal abnormalities result in the same phenotype – 45X0/46XX, 45X0/46 Xi (Xp), 45X0/46 Xi(Xq), 45X0/46XX/47XXX and 45X0/46XY. Only 0.3% of the embryos with the 45X0 genotype survive to term [1].

Typical findings include low hair line, small suture, epicanthal fold, webbed neck, shield chest, cubitus valgus, multiple pigmented nevi, peripheral edema, streak ovaries, left-sided heart defect (coarctation of the aorta), and renal abnormality (horse-shoe kidney). There is also a relatively high prevalence of Hashimoto thyroiditis, inflammatory bowel disease, insulin resistance and ovarian malignancy [1]. The association of liver involvement in Turner syndrome is not well understood. We present a patient with Turner syndrome and idiopathic liver involvement, and a review of 55 medical charts.

Patient Description

A 49 year old patient with Turner syndrome, known to have elevated liver enzymes for 5 years, was admitted for evaluation of jaundice. Her past medical history was remarkable for Turner syndrome and an aortic coarctation repair 22 years earlier. She also presented with hypertension and hypothyroidism. Physical examination revealed jaundice, small suture, webbed neck, shield chest and peripheral edema. Laboratory tests showed aspartate aminotransferase of 1,098 u/L, alanine aminotransferase 1,349 u/L, alkaline phosphatase 413 u/L and bilirubin 4.8 mg/dl. Viral serology for hepatitis A, B and C, as well as cytomegalovirus/Epstein-Barr virus and Toxoplasma was negative. The immunologic workup revealed anti-smooth muscle antibodies; antinuclear factor, antimitochondrial and antiparietal cell antibodies were negative, and immunoglobulin levels were normal.

Abdominal computerized tomography and ultrasound showed no evidence of biliary tract obstruction. Endoscopic retrograde cholangiopancreatography was normal. Liver biopsy demonstrated a few neutrophils and eosinophils in the portal space and intrahepatic cholestasis, in addition to feathery degeneration and fibrosis around the central veins. The final diagnosis was idiopathic cholestasis.

A review of 55 medical charts

To determine the frequency of liver involvement in patients with Turner syndrome, we retrospectively reviewed 55 medical charts of patients with Turner syndrome admitted to Hadassah University Hospital between 1980 and 2000. Results of AST, ALT, gamma-glutamyltransferase, and ALP were available for 25 of them. The charts were reviewed for all causes of liver function disturbances. Abnormality in one of the enzymes was observed in 24 of the 25 patients. Nine of them had isolated elevation of alkaline phosphatase at a young age. Four patients received hormonal therapy and three others had unrelated disorders associated with liver function disturbances. Eight patients (32%) – 6 adults and 2 children with a mean age of 28.5 years (range 1-49) – had idiopathic liver involvement. Their liver enzymes were elevated as follows: GGT with a mean of 197 IU (range 41-479) in seven of the eight patients, ALP with a mean of 158 IU (range 153-161) in four, AST with a mean of 153 IU (range 56-206) in five, and ALT patients with a mean of 189 IU (range 142-265) in four.

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