Bone Marrow-Related Syncope

Haim Shmilovich MD\(^1\), Svetlana Trestman MD\(^2\), Stella Bak MD\(^3\), Galit Aviram MD\(^4\), Shmuel Banai MD\(^1\), Arie SteInvil MD\(^1\) and Gad Keren MD\(^1\)

Divisions of \(^1\)Cardiology, \(^2\)Hematology, \(^3\)Pathology and \(^4\)Radiology, Tel Aviv Sourasky Medical Center, affiliated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

**KEY WORDS:** syncope, multiple myeloma, cardiac magnetic resonance imaging (CMR)

---

**PATIENT DESCRIPTION**

A 63 year old healthy man was admitted due to syncope and urine loss for the first time in his life, which occurred while walking and with a prodrome of chest pain for half a minute.

His past medical history was remarkable for effort-related chest pain. Stress echocardiography (sEcho) was performed which demonstrated anterior wall hypokinesis, and he was referred for invasive coronary angiography (ICA). A drug-eluting stent was deployed on a 60% stenosis in the left anterior descending coronary artery (LAD). During the next 3 months he reported the same symptoms. He was referred for stress single-photon emission cardiac tomography, which was normal. The physician’s recommendation was to intensify anti-anginal medications due to the working diagnosis of small vessel coronary artery disease (CAD).

On physical examination, blood pressure was 137/82 mmHg, pulse 72 beats/minute and saturation 98%. Laboratory examination showed normal blood count, and normal renal, liver and thyroid function. Troponin-I levels were mildly elevated at 0.24 pg/dl (normal range < 0.05 pg/dl). Electrocardiogram (ECG) showed normal sinus rhythm and axis without signs of acute ischemia, arrhythmia or conduction defects. There were T-wave inversions in leads II, III, aVF and V4-6. A head computed tomography (CT) scan, which was ordered to rule out an organic pathology that might explain syncope and to rule out head trauma or bleeding, was normal.

At this point, we tried to address the differential diagnosis of syncope. Syncope is defined as a transient loss of consciousness. Cardiac and neurological diseases are the main causes, with vasovagal syncope, arrhythmia, conduction defects and myocardial infarction in the former, and cerebrovascular accident, transient ischemic attack (TIA) or epilepsy in the latter [1]. A history of urine loss points to a neurological entity such as epilepsy. However, the patient denied an aural-like prodrome and post-ictal state. Epilepsy does not usually begin at this age unless there is a structural defect in the brain. A history of effort-related chest pain with non-specific ECG changes does not provoke chest pain or ST changes but can happen when the stent is not deployed properly, or diffuse small vessel disease is present. We had to bear in mind the possibility of another etiology to explain his effort-related chest pain, such as valvular or myocardial disease.

A neurological consultation requested an electroencephalogram to rule out epilepsy, and a carotid artery Doppler to rule out the possibility of TIA. Both studies were normal, whereupon he was referred for echocardiography. Echocardiography showed normal systolic function with a grade II diastolic dysfunction and borderline left ventricular hypertrophy (LVH) with a septum width of 12 mm (probably normal for his body surface area of 2.23 m\(^2\)). A 24 hour ECG Holter recording failed to reveal an arrhythmia. An ECG-gated cardiac CT-angiogram ruled out significant CAD or pulmonary embolism. An exercise tolerance test was performed to a reasonable effort of 9 METs, which did not provoke chest pain or ST changes but demonstrated some multifocal premature ventricular complexes. The possibility of arrhythmia was raised and the patient was discharged with the recommendation for a loop-recorder implantation.

Ten days later, he was readmitted due to syncope with the same prodrome and loss of urine. Physical examination and neurological consultation were again normal, and laboratory tests again showed only a mild elevation of troponin levels, 0.16 pg/dl. ECG showed the same T-wave changes and a repeat 24 hour ECG recording failed to show any rhythm abnormality. At this point we reevaluated his workup. We were bothered by the grade II diastolic dysfunction which was out of proportion to his border-line (if any) left ventricular hypertrophy. The other differential diagnosis of diastolic
dysfunction consists of status-post myocardial infarction, old age, obesity and diabetes mellitus, which did not apply to him.

In view of another etiology – restrictive cardiomyopathy caused by infiltrative disease [2] – he was therefore referred for cardiac magnetic resonance imaging (CMR) which is a robust and well-validated imaging modality for myocardial tissue characterization. CMR showed an ejection fraction of 67%, and diffuse late-gadolinium enhancement, in a non-coronary, mid-wall, patchy distribution. Septal width was 16 mm [Figure 1, top panel]. A septum width of 16 mm was measured, leading to the working diagnosis of hypertrophic cardiomyopathy as a cause of syncope due to malignant ventricular arrhythmia, necessitating a defibrillator implantation [3].

However, at this stage, we were troubled by another finding. When looking carefully at his ECG, besides the T-wave inversion, there was a pattern of low voltage amplitude of QRS complexes, which is unusual in hypertrophied hearts, unless there is a myocardial infiltrative disease. Here the differential diagnosis comprised amyloidosis, sarcoidosis, Fabry’s disease, hemochromatosis and myocarditis. The patient was referred for endomyocardial biopsy.

Hematoxylin-eosin staining showed amorphous loci between normally apparent myocardial fibers and blood vessel walls. Congo-red staining was positive and electron microscopy showed amyloid lamella. Immunostaining for amyloid A was negative. A diagnosis of cardiac amyloidosis [4] was made with arrhythmia-related syncope as the presenting symptom. Of note, the common presenting symptom of cardiac amyloidosis is heart failure [5]. The patient was referred to the hematology department for bone marrow and urine analysis, which revealed 12% monoclonal plasma cells in the former and a high content of...
kappa-chains in the latter, culminating in the diagnosis of multiple myeloma. He was prescribed a regimen of corticosteroids and proteasome inhibitor with the option for bone marrow transplant if it failed.

**CONCLUSIONS**

The importance of this case report with its unique diagnosis is to emphasize the importance of being alert to subtle findings and working with a multidisciplinary approach. Attention to the differential diagnosis of diastolic dysfunction and subtle “non-specific” changes on ECG is crucial. This patient did not have any of the presenting symptoms of multiple myeloma, general amyloidosis or cardiac amyloidosis, and this early diagnosis may have saved his life or at least prolong it.

**Correspondence**
Dr. H. Shmilovich
Cardiology Division, Tel Aviv Sourasky Medical Center, Tel Aviv 69977, Israel
Fax: (972-3) 697-4976
email: haim.shmilovich@gmail.com

**References**

---

**Critical role of acetylation in tau-mediated neurodegeneration and cognitive deficits**

Tauopathies, including frontotemporal dementia (FTD) and Alzheimer’s disease (AD), are neurodegenerative diseases in which tau fibrils accumulate. Recent evidence supports soluble tau species as the major toxic species. How soluble tau accumulates and causes neurodegeneration remains unclear. Min and co-researchers identify tau acetylation at Lys174 (K174) as an early change in AD brains and a critical determinant in tau homeostasis and toxicity in mice. The acetyl-mimicking mutant K174Q slows tau turnover and induces cognitive deficits in vivo. Acetyltransferase p300-induced tau acetylation is inhibited by salsalate and salicylate, which enhance tau turnover and reduce tau levels. In the PS19 transgenic mouse model of FTD, administration of salsalate after disease onset inhibited p300 activity, lowered levels of total tau and tau acetylated at K174, rescued tau-induced memory deficits and prevented hippocampal atrophy. The tau-lowering and protective effects of salsalate were diminished in neurons expressing K174Q tau. Targeting tau acetylation could be a new therapeutic strategy against human tauopathies.


Eitan Israeli

---

**Virome analysis of transfusion recipients: novel human virus sharing genomic features with hepacviruses and pegviruses**

To investigate the transmission of novel infectious agents by blood transfusion, Kappor et al. studied changes in the virome composition of blood transfusion recipients pre- and post-transfusion. Using this approach, they detected and genetically characterized a novel human virus, human hepegivirus 1 (HHpgV-1), that shares features with hepatitis C virus (HCV) and human pegivirus (HPgV; formerly called GB virus C or hepatitis G virus). HCV and HPgV belong to the genera Hepacivirus and Pegivirus of the family Flaviviridae. HHpgV-1 was found in serum samples from two blood transfusion recipients and two hemophilia patients who had received plasma-derived clotting factor concentrates. In the former, the virus was detected only in the post-transfusion samples, indicating blood-borne transmission. Both hemophiliacs were persistently viremic over periods of at least 201 and 1981 days. Phylogenetic analysis of non-structural genes (NS3 and NS5B) showed that HHpgV-1 forms a branch within the pegivirus clade distinct from HPgV and homologs infecting other mammalian species. In common with some pegivirus variants infecting rodents and bats, the HHpgV-1 genome encodes a short, highly basic protein upstream of E1, potentially possessing a core-like function in packaging RNA during assembly. Identification of this new human virus, HHpgV-1, expands our knowledge of the range of genome configurations of these viruses and may lead to a reevaluation of the original criteria by which the genera Hepacivirus and Pegivirus are defined.


Eitan Israeli