Questions and guide to answers

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Received 15 January 2014
Accepted 03 February 2014

The Egyptian Society of Internal Medicine
2014, 26:30–34

Egypt J Intern Med 26:30–34

1110-7782

Q1. Give an account on the assessment and management of atherosclerosis.

Assessments

Ultrasonographic assessment

Brachial artery reactivity

The loss of endothelium-dependent vasodilation is a feature of even the early stages of atherosclerosis. Flow-mediated dilation (assessed by high-resolution ultrasonography) of the brachial artery has been pioneered as a means of evaluating the health and integrity of the endothelium. The healthy endothelium dilates in response to an increase in blood flow, whereas vessels affected by atherosclerosis do not dilate and may paradoxically constrict.

Carotid artery intima–media thickness

B-mode ultrasonography of the common and internal carotid arteries is a noninvasive measure of arterial wall anatomy that may be performed repeatedly and reliably in asymptomatic individuals. The combined thickness of the intima and media of the carotid artery is associated with the prevalence of cardiovascular risk factors and disease and with an increased risk for myocardial infarction and stroke. This association is at least as strong as the associations observed with traditional risk factors.

Intravascular ultrasonography

It is a catheter-based examination that provides images of the thickness and the acoustic density of the vessel wall.

MRI assessment

It may be used to obtain information about blood-vessel wall structure noninvasively and to characterize plaque composition. Abdominal aortic atherosclerosis measurements on MRI were predictive for future adverse cardiovascular events. Investigators assessed aortic atherosclerosis by measuring mean aortic wall thickness and aortic plaque burden and found a significantly increased risk for nonfatal extracardiac events with increasing measurements of both of these variables. However, mean aortic wall thickness, but not aortic plaque burden, was associated with an increased risk for composite events.

Nuclear perfusion imaging assessment

It is performed with the use of single-photon emission computed tomography scanning or PET scanning, which relies on the administration of radionuclide isotope that is accumulated by the targeted tissue [1].

Management

The prevention and treatment of atherosclerosis require risk factor control, including the medical treatment of hypertension, hyperlipidemia, diabetes mellitus, and cigarette habituation [2,3].

Some studies have claimed reversal of atherosclerosis with pharmacologic agents such as statins and cilostazol, but these need to be further tested before it can be determined whether they offer any significant benefit in reducing clinical events.

Advances in the understanding of the vascular biology of atherosclerosis have increased the possibility of using novel therapies to address the various aspects of endothelial dysfunction and the role of endothelial dysfunction in atherogenesis more directly. Potential cellular targets include vascular smooth muscle cells, monocyte/macrophage cell lines, platelets, and endothelial cells. Evidence exists that antiplatelet agents,

antioxidant therapies, amino acid supplementation, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers may prove to prevent or slow the progression of the disease [3].

Screening

New guidelines released in late 2013 by the American Heart Association/American College of Cardiology (AHA/ACC) recommend the use of a revised calculator for estimating the 10-year and lifetime risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event, including stroke (fatal or nonfatal), in a person who was initially free from ASCVD.

For patients of 20–79 years of age who do not have existing clinical ASCVD, the guidelines recommend assessing clinical risk factors every 4–6 years. For patients of 20–59 years of age with low 10-year risk (<7.5%), the guidelines recommend assessing 30-year or lifetime risk [3].

Regardless of the patient's age, clinicians should communicate risk data to the patient and refer to the AHA/ACC lifestyle guidelines, which cover diet and physical activity. For patients with elevated 10-year risk, clinicians should communicate risk data and refer to the AHA/ACC guidelines on blood cholesterol and obesity [2].

Control blood pressure.

Manage dyslipidemia and hyperlipidemia.

Management of diabetes mellitus and familial hypercholesterolemia.

Pharmacotherapy

The following medications may be used in the management of atherosclerosis:

(1) HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme) reductase inhibitors (e.g. pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin).
(2) Fibric acid derivatives (e.g. fenofibrate, gemfibrozil).
(3) Bile acid sequestrants (e.g. cholestyramine, colestipol).
(4) Vitamin E.
(5) Omega-3 polyunsaturated fatty acid [3].

Q2. Discuss the new approaches in the management of severe bronchial asthma.

Definition

Severe bronchial asthma is defined as asthma that requires treatment with high dose-inhaled corticosteroids (CS) and LABA or leukotriene modifier/theophylline for the previous year or systemic CS for 50% or more of the previous year to prevent it from becoming uncontrolled or that remains uncontrolled despite this therapy.

(1) Uncontrolled asthma is defined as at least one of the following:
    (a) Poor symptom control.
    (b) Frequent severe exacerbations: two or more bursts of systemic CSs (>3 days each) in the previous year.
    (c) Serious exacerbations: at least one hospitalization, ICU stay, or mechanical ventilation in the previous year.
    (d) Airflow limitation: after appropriate bronchodilator withhold FEV1 less than 80% predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal) [4].
(2) Controlled asthma is defined as those that worsen on tapering of these high doses of inhaled CS or systemic CS (or additional biologics).

Options in diagnosis and assessment:

Currently available biomarkers to guide therapy

Sputum eosinophil count

Because at the present time, measurement of sputum eosinophils has not yet been sufficiently standardized and is not widely available, we suggest such an approach be used only in specialized centers experienced in this technique. Patients who are likely to benefit from this approach are those who can produce sputum, demonstrate persistent or at least intermittent eosinophilia, and have severe asthma with frequent exacerbations. Clinicians should recognize that different choices will be appropriate for different patients.

Exhaled nitric oxide (FeNO)

It has not shown a cost/benefit effect in the management of severe asthma.

New options in treatment

Bronchial thermoplasty

It was approved by the FDA in 2010, involves the delivery of controlled, therapeutic radiofrequency energy to the airway wall, thus heating the tissue and reducing the amount of smooth muscle present in the airway wall. The ATS 2013 recommend that bronchial thermoplasty is performed in adults with severe asthma only in the context of an Institutional Review Board-approved independent systematic registry or a clinical study.

Monoclonal antibodies

Omalizumab is a recombinant DNA-derived humanized immunoglobulin G monoclonal antibody

that binds selectively to human immunoglobulin E on the surface of mast cells and basophils. The drug reduces mediator release, which promotes an allergic response. It is indicated for moderate-to-severe persistent asthma in patients who react to perennial allergens, in whom symptoms are not controlled by inhaled corticosteroids.

Leukotriene receptor antagonist

Knowledge that leukotrienes cause bronchospasm, increased vascular permeability, mucosal edema, and inflammatory cell infiltration leads to the concept of modifying their action by using pharmacologic agents such as montelukast and Zafirlukast.

5-Lipoxygenase inhibitor

Zileuton inhibits leukotriene formation, which, in turn, decreases neutrophil and eosinophil migration, neutrophil and monocyte aggregation, leukocyte adhesion, capillary permeability, and smooth muscle contractions.

Methotrexate

It is recommended as a steroid-sparing option in treatment and is limited to specialized centers and only in patients who require daily oral corticosteroids [4].

Q3. Give an account on laboratory diagnosis of tuberculosis and its fallacies.

Ziehl–Neelsen staining

Ziehl–Neelsen staining of sputum is a simple five-step process that takes ~10 min to accomplish. It is highly specific for mycobacteria; however, this stain is relatively insensitive, and detection requires at least 10 000 bacilli/ml. Most clinical laboratories currently use a more sensitive auramine–rhodamine fluorescent stain (auramine O). Acid-fast bacteria visualized on a slide may represent *Mycobacterium tuberculosis* or nontuberculous mycobacteria; hence, species identification requires culture and/or nucleic acid amplification (NAA).

NAA tests:

Their results must be interpreted in the context of clinical and epidemiologic factors; contamination and laboratory errors can cause false-positive results. In addition, NAA can detect nucleic acid from dead and live organisms; hence, testing can remain positive even after appropriate therapy. Therefore, this method is only appropriate for initial diagnostic purposes. Moreover, infected pleural fluid may contain inhibitors that diminish the sensitivity of the test. Therefore, a negative NAA result is not sufficient to exclude tuberculosis (TB) [5].

The Xpert MTB/RIF assay

This is an automated NAA test that can identify both presence of *M. tuberculosis* as well as presence of rifampicin resistance. An important limitation of the test is its inability to determine which patients with pulmonary tuberculosis have sputum positive for acid-fast bacilli on microscopy, a tool used to guide infection control practices, contact investigations, and monitor response to treatment [6].

TB blood tests (also called interferon-γ release assays or IGRAs)

These testes measure how the immune system reacts to the bacteria that cause TB. An IGRA measures how strong a person's immune system reacts to TB bacteria by testing the person's blood in a laboratory. Positive IGRA means that the person has been infected with TB bacteria. Additional tests are needed to determine whether the person has latent TB infection or TB disease. A healthcare worker will then provide treatment as needed. Negative IGRA means that the person's blood did not react to the test and that latent TB infection or TB disease is not likely [7].

Adenosine deaminase

It is a purine-degrading enzyme that is necessary for the maturation and differentiation of lymphoid cells. Adenosine deaminase activity (ADA) of body fluid has been proposed as a useful nonculture method of detecting TB infection. A meta-analysis of 12 prospective studies encompassing 264 patients found that ADA levels had high sensitivity (100%) and specificity (97%). However, the sensitivity is substantially lower in patients with cirrhosis (~30%) because of the characteristically poor humoral and T-cell-mediated response of cirrhotic patients. As a result, ADA measurement has its greatest utility in settings where TB peritonitis is suspected in noncirrhotic patients.

T-cell-based testing for M. tuberculosis (ELISPOT)

It is an FDA-approved enzyme-linked immunospot assay (ELISPOT) measuring γ-producing T-cell responses to early secreted antigenic targets of *M. tuberculosis*, which has shown promising results. The ELISPOT assay on peripheral blood or ascitic fluid may prove to be a useful adjunct in the diagnosis of active TB, but is not available in many institutions, and additional data are needed [7].

Q4. How to deal with a case presenting with convulsions for the first time?

Strategic points

(1) Epileptic seizures result from electrical hypersynchronization of neuronal networks in the cerebral cortex. Epilepsy is characterized by recurrent epileptic seizures due to a genetically determined or acquired brain disorder.
(2) Some seizures are provoked – that is, they occur in the setting of metabolic derangement, drug, and acute neurologic disorders such as stroke or encephalitis. Such patients are not considered to have epilepsy, because the presumption is that these seizures would not recur in the absence of provocation.

Thus, the primary goal in evaluating a patient's first seizure is to differentiate whether the seizure resulted from a treatable systemic process or intrinsic dysfunction of the central nervous system and, if the latter, the nature of the underlying brain pathology. This evaluation will determine the likelihood that a patient will have additional seizures, assist in the decision whether to begin anticonvulsant therapy, and direct appropriate treatment to the underlying cause, if known [8].

Etiology of seizure

Less than half of epilepsy patients have an identifiable cause. It is presumed that epilepsy in most of these other patients is genetically determined. In the remainder of the patients in whom an etiology can be determined, the causes of epileptic seizures include the following:
(1) head trauma,
(2) brain tumors,
(3) stroke,
(4) intracranial infection, and
(5) congenital brain malformations [8].

Imitators of epilepsy

Several conditions must be differentiated from epileptic seizures. The most prevalent of the nonepileptic paroxysmal events that can be mistaken for epilepsy differ significantly by age group. In adolescents and young adults, these diagnoses can be classified into five broad categories:
(1) syncope,
(2) psychological disorders,
(3) sleep disorders,
(4) paroxysmal movement disorders, and
(5) migraine.

More common in the elderly are

(1) transient ischemic attack,
(2) transient global amnesia, and
(3) drop attacks.

A careful history taking, physical and neurologic examinations, and laboratory evaluation are usually helpful in making an accurate diagnosis.
(1) A detailed description of the seizure should be obtained from the patient and witnesses and should include the circumstances leading up to the seizure, the ictal behaviors, and the postictal state.
(2) Other items in the past medical history (medications and family history) and physical and neurological examinations are also important in the evaluation of a first seizure. The neurologic examination should evaluate for lateralizing abnormalities, such as weakness, hyperreflexia, or a positive Babinski sign, which may point to a contralateral structural brain lesion.
(3) Diagnostic studies should include laboratory studies (electrolytes, glucose, calcium, magnesium, hematology studies, renal function tests, liver function tests, and toxicology screens), an electroencephalogram, and a neuroimaging study. Depending on the clinical situation, a lumbar puncture may also be indicated [8,9].

Hospitalization and treatment

Hospitalization may be required for patients who have a first seizure associated with a prolonged postictal state or incomplete recovery. Other indications for hospitalization include status epilepticus, the presence of a systemic illness that may require treatment, a history of head trauma, or questions regarding compliance.

Antiepileptic drugs (AEDs) are not always indicated after a first seizure [10].

When to start AED therapy

AED therapy is generally reserved for patients who are at increased risk for recurrent seizures. Depending on a number of considerations, AED therapy may not be indicated after a first epileptic seizure, particularly if that seizure was provoked (i.e. an acute symptomatic seizure). AED treatment is generally started after the second seizure because seizure recurrence indicates that the patient has a substantially increased risk for additional seizures.

Studies have identified three high-risk features for seizure recurrence after a first unprovoked seizure:
(1) Epileptiform abnormalities on EEG.
(2) Remote symptomatic cause as identified by clinical history or neuroimaging (e.g. brain tumor, brain malformation). Acute symptomatic seizures have a lower risk for subsequent epilepsy.
(3) Abnormal neurologic examination, including focal findings and intellectual disability [10].

Acknowledgements

Conflicts of interest

There are no conflicts.

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