

Questions and guide to answers (Q&A) in internal medicine: give an account on compartment syndrome, hyperhomocysteinemia, brain natriuretic peptide, and viral autoimmune manifestations

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Q1: Give an account on compartment syndrome.

A1: Compartment syndrome

Compartment syndrome occurs when excessive pressure builds up inside an enclosed space in the body. Compartment syndrome usually results from bleeding or swelling after an injury. The dangerously high pressure in compartment syndrome impedes the flow of blood to and from the affected tissues. It can be an emergency, requiring surgery to prevent permanent injury.

What happens in compartment syndrome?

Groups of organs or muscles are organized into areas called compartments. Strong webs of connective tissue called fascia form the walls of these compartments.

After an injury, blood or edema (fluid resulting from inflammation or injury) may accumulate in the compartment. The tough walls of the fascia cannot expand easily, and compartment pressure increases, preventing adequate blood flow to the tissues inside the compartment. Severe tissue damage can result in loss of body function or even death.

Legs, arms, and the abdomen are the most prone to developing compartment syndrome.

Compartment syndrome causes

Acute compartment syndrome is the most common type of compartment syndrome. About three-quarter of the time, acute compartment syndrome is caused by a broken leg or arm. Acute compartment syndrome develops rapidly over hours or days.

Yes compartment syndrome can developed from fracture you can see Orthoinfo.aaos.orgtopic cmf last review october 2009. The American Orthopedic Society for Sports Med.

Acute compartment syndrome can also occur after injuries without bone fractures, which include the following:

- (1) Crush injuries.
- (2) Burns.
- (3) Overly tight bandaging.
- (4) Prolonged compression of a limb during a period of unconsciousness.
- (5) Surgery to blood vessels of an arm or a leg.
- (6) A blood clot in a blood vessel in an arm or a leg.
- (7) Extremely vigorous exercise, especially eccentric movements (extension under pressure).

Taking anabolic steroids can also contribute to developing compartment syndrome.

Another form of compartment syndrome, called chronic compartment syndrome, develops over days or weeks. Also called exertional compartment syndrome, it may be caused by regular, vigorous exercise. The lower leg, the buttock, or the thigh is usually involved.

Abdominal compartment syndrome almost always develops after a severe injury, surgery, or during critical illness. Some conditions associated with abdominal compartment syndrome include the following:

- (1) Trauma, especially when it results in shock.
- (2) Abdominal surgery, particularly liver transplant.
- (3) Burns.
- (4) Sepsis (an infection causing inflammation throughout the body).

- (5) Severe ascites or abdominal bleeding.
- (6) Vigorous overtraining utilizing eccentric abdominal exercises (i.e. sit ups on a back extension machine in weight rooms).

As the pressure in the abdominal compartment increases, blood flow to and from the abdominal organs is reduced. The liver, bowels, kidneys, and other organs may be injured or damaged permanently.

Compartment syndrome symptoms

Acute compartment syndrome usually develops over a few hours after a serious injury to an arm or a leg. Some symptoms of acute compartment syndrome include the following:

- (1) A new and persistent deep ache in an arm or a leg.
- (2) Pain that seems greater than expected for the severity of the injury.
- (3) Numbness, pins-and-needles, or electricity-like pain in the limb.
- (4) Swelling, tightness, and bruising.

Symptoms of chronic compartment syndrome (exertional compartment syndrome) include aching or cramping in the affected muscle (buttock, thigh, or lower leg) within a half-hour of starting exercise. Symptoms usually go away with rest, and muscle function remains normal. Exertional compartment syndrome can feel like shin splints and be confused with that condition.

Abdominal compartment syndrome usually develops in people who are hospitalized, critically ill, and on life support. They usually cannot describe their symptoms. Doctors or family may notice the following abdominal compartment syndrome symptoms and signs:

- (1) A tense, distended abdomen.
- (2) Wincing when the abdomen is pressed.
- (3) Urine output that slows down or stops.
- (4) Low blood pressure.

Compartment syndrome diagnosis

A doctor may suspect compartment syndrome on the basis of the type of injury, a person's description of symptoms, and a physical exam. Sometimes, the diagnosis of compartment syndrome is clear from these findings.

In many cases, a definite diagnosis of compartment syndrome requires direct measurement of pressures inside the body compartment. To achieve this, a doctor can insert a needle into the area of the suspected compartment syndrome while an attached pressure

monitor records the pressure. A plastic catheter can also be inserted to monitor the compartment pressure continuously.

In suspected abdominal compartment syndrome, a pressure monitor can be inserted into the bladder through a urinary catheter. High pressures in the bladder, when there are signs of abdominal compartment syndrome, strongly suggest the diagnosis.

Laboratory and imaging tests can support the diagnosis of compartment syndrome. However, no single test other than a direct pressure measurement can make the abdominal compartment syndrome diagnosis.

Compartment syndrome treatments

Treatments for compartment syndrome focus on reducing the dangerous pressure in the body compartment. Dressings, casts, or splints that are constricting the affected body part must be removed.

Most people with acute compartment syndrome require surgery to reduce the compartment pressure. A surgeon makes long incisions through the skin and the fascia layer underneath (fasciotomy), releasing excessive pressure.

Other supportive treatments include the following:

- (1) Keeping the body part below the level of the heart (to improve blood flow into the compartment).
- (2) Giving oxygen through the nose or the mouth.
- (3) Giving fluids intravenously.
- (4) Administering pain medications.

Chronic compartment syndrome can first be treated by avoiding the activity that caused it and with stretching and physical therapy exercises. Surgery is not as urgent in chronic or exertional compartment syndrome, but it may be required to relieve pressure.

Abdominal compartment syndrome treatments include life support measures such as mechanical ventilation, medicines to support blood pressure (vasopressors), and kidney replacement therapies (such as dialysis). Surgery to reduce compartment syndrome pressures may be necessary. The best time to perform surgery in people with abdominal compartment syndrome is often not clear. Surgery for abdominal compartment syndrome may be lifesaving, but can also cause complications.

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Q2: Give an account on hyperhomocysteinemia.

A2: Hyperhomocysteinemia

Most of the relationship between hyperhomocysteinemia and arterial vascular disease and venous thromboembolic disease is epidemiologically based. Suggestive pathophysiologic mechanisms of the effect of homocysteine include increased peroxidation injury, proliferation of smooth vessels, promotion of monocytic chemotaxis, enhanced cytotoxicity and inflammation, promotion of clotting, inhibition of anticoagulation, direct effects on endothelial cells, and activation of platelet aggregation.

Levels of homocysteine are closely related to B vitamins: the conversion of homocysteine to methionine in the remethylation pathway requires folic acid and B₁₂. The conversion of homocysteine to cystathionine and cysteine through trans-sulfation necessitates B₆. Therefore, lowered levels of B₁₂ or B₆ can be associated with elevated homocysteine concentrations. Folic acid deficiency or methylenetetrahydrofolate reductase (MTHFR) deficiency are also causes of hyperhomocysteinemia. The recognition that homocysteine may play a role in hypercoagulability should raise the consideration of nutritional replacement in patients with malignancy or pregnancy. Similarly, patients with known hypercoagulability due to inherited defects of the antigen-presenting cell pathway should maintain adequate stores of folic acid, B₁₂, and B₆ [1].

Causes of hyperhomocysteinemia

Severe hyperhomocysteinemia (>100 μmol/l)

- (1) Hereditary homocystinuria (e.g. homozygosity for defects in cystathionine β-synthase, 5,10-methylenetetrahydrofolate reductase, or other enzymes of methionine metabolism).
- (2) Hereditary disorders of vitamin B₁₂ utilization.
- (3) Severe deficiency of vitamin B₁₂.

Moderate hyperhomocysteinemia (30–100 μmol/l)

- (1) Renal failure.
- (2) Moderate vitamin B₁₂ deficiency.
- (3) Severe folate deficiency.

Mild hyperhomocysteinemia (10–30 μmol/l)

- (1) Heterozygosity for defects in cystathionine β-synthase.

- (2) Homozygosity for the C677T polymorphism of 5,10-methylenetetrahydrofolate reductase.
- (3) Renal insufficiency.
- (4) Renal transplantation.
- (5) Mild folic acid deficiency.
- (6) Mild vitamin B₁₂ deficiency.
- (7) Vitamin B₆ deficiency.
- (8) Hypothyroidism.
- (9) Alcoholism.
- (10) Medications (niacin, fibrates, methotrexate, isoniazid, levodopa, theophylline, phenytoin, nitrous oxide, trimethoprim) [2].

What are the possible symptoms and signs of elevated homocysteine levels?

Elevated homocysteine levels in the body do not cause any symptoms.

- (1) Elevated homocysteine levels affect the interior lining of blood vessels in the body, increasing the risk of atherosclerosis or narrowing of blood vessels. This can result in early heart attack and stroke.
- (2) There is a relationship between the levels of homocysteine in the body and the size of the carotid arteries that supply the brain with blood; the higher the homocysteine level, the narrower or more stenosed the carotid artery.
- (3) The risk of deep vein thrombosis and pulmonary embolism may also be linked to elevated homocysteine levels in the body.
- (4) There may be a relationship between elevated homocysteine levels and broken bones, especially in the elderly.
- (5) Alzheimer's disease and other types of dementia may be more frequently seen in patients with increased homocysteine in the blood.
- (6) In infants who have the genetic condition of homocystinuria, the inherited abnormalities affect the body's metabolism of homocysteine to cysteine. This may result in dislocation of the lens in the eye, a sunken chest, a Marfan-type appearance (long thin body type), mental retardation, and seizures. Neonatal strokes may also be seen with high homocysteine levels.
- (7) During pregnancy, homocysteine levels tend to decrease. Elevated homocysteine levels may be associated with some fetal abnormalities and with potential blood vessel problems in the placenta, causing abruption. There may also be an association with pre-eclampsia.

Diagnosis

The diagnosis of hyperhomocysteinemia is made by measuring the level of total homocysteine in the blood.

Some people inherit defects that cause hyperhomocysteinemia. Most people with inherited defects are only mildly affected. In rare cases, however, inherited defects in genes produce a severe form of hyperhomocysteinemia called homocystinuria. People affected with homocystinuria have a very high risk of blood clots, and may also suffer from mental retardation, bone abnormalities, and visual problems.

Treatment

The primary goal of treatment is to lower blood levels of homocysteine to normal. Treatment may consist of giving supplements of folic acid, vitamin B₁₂, and/or vitamin B₆. It may also include anticoagulant medications (blood thinners), such as aspirin, clopidogrel, heparin, low-molecular-weight heparin, or warfarin, to prevent blood clots.

Patients with the severe form of hyperhomocysteinemia (homocystinuria) are often treated with high doses of vitamin B₆ or betaine, and the amount of methionine consumed in the diet may be restricted [3].

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Q3: Give an account on brain natriuretic peptide.

A3: Brain natriuretic peptide.

Synonym: B-type natriuretic peptide

Brain natriuretic peptide (BNP) levels increase markedly in left ventricular dysfunction, and the level in heart failure correlates with the symptom severity. BNP is therefore an important clinical marker for the diagnosis of heart failure in patients with unexplained dyspnea. Other clinical applications, such as screening for asymptomatic ventricular dysfunction, establishing the prognosis or guiding the titration of drug therapy, and prediction of future cardiovascular events, are under investigation, but have not yet been validated sufficiently for widespread clinical use [1]. BNP is a biologically active peptide of 32 amino acids and has vasodilator and natriuretic properties. BNP is cleaved from the 108-amino acid pro-BNP released from the cardiac ventricles in response to the stretching of the chamber. The second remnant after cleavage, N-terminal probrain natriuretic peptide (NT-proBNP), is a 76-amino acid peptide with no known

biological function, which circulates at concentrations higher than BNP and may represent the cardiac status over longer periods [2].

The release of BNP appears to be in direct proportion to the ventricular volume expansion and the pressure overload. BNP increases with right or left systolic or diastolic heart failure. It is an independent predictor of high left ventricular end-diastolic pressure. BNP levels decrease after effective treatment of heart failure. Although testing for BNP provides a useful adjunct to routine assessment for differentiating acute heart failure from other causes of breathlessness, other factors such as comorbid illnesses, age, renal failure, and body mass may affect BNP levels in ways that can obscure the diagnosis of heart failure, particularly when this marker is used in isolation. Therefore, it is essential that BNP be used to aid diagnosis in addition to the patient's history, clinical signs, and other investigations [3].

Measurement

There is currently no definite evidence of a clinical advantage between using either the BNP assay or the NT-proBNP assay [4].

- (1) The most commonly used decision threshold for BNP is 100 pg/ml [5].
- (2) BNP levels of more than 100 pg/ml have greater than 95% specificity and greater than 98% sensitivity when comparing patients without congestive heart failure (CHF) with all patients with CHF [2].
- (3) Even BNP levels of more than 80 pg/ml have greater than 93% specificity and 98% sensitivity in the diagnosis of heart failure.
- (4) BNP levels increase with age. The mean BNP levels are as follows: [5]
 - (a) 26.2 pg/ml in those aged 55-64 years.
 - (b) 31.0 pg/ml in those aged 65-74 years.
 - (c) 63.7 pg/ml in those aged 75 years and older.
 - (d) Women without CHF tend to have higher BNP levels than men of the same age.

Patients should have had an ECG, chest radiography, full blood count, renal function and electrolyte tests, liver function tests, lipid profile, thyroid function tests, and any other investigation relevant to the clinical presentation.

Potential causes of elevated brain natriuretic peptide levels [5]

- (1) Cardiac:
 - (a) Heart failure.
 - (b) Diastolic dysfunction.

- (c) Acute coronary syndromes.
 - (d) Hypertension with left ventricular hypertrophy.
 - (e) Valvular heart disease (aortic stenosis, mitral valve regurgitation).
 - (f) Atrial fibrillation.
- (2) Noncardiac:
- (a) Acute pulmonary embolism.
 - (b) Pulmonary hypertension (primary or secondary).
 - (c) Sepsis (possibly due to tissue hypoxia or secondary myocardial depression).
 - (d) Chronic obstructive pulmonary disease with cor pulmonale or respiratory failure.
 - (e) Hyperthyroidism.
 - (f) Renal failure.

BNP levels may be lower than expected when heart failure is secondary to causes proximal to the left ventricle, for example, acute mitral regurgitation, mitral stenosis, or atrial myxoma.

Potential use of brain natriuretic peptide measurement

Heart failure

Assay of BNP is a potential aid in the diagnosis of heart failure. BNP testing allows a rapid assessment for defining those patients warranting an echocardiogram and also has the potential to enable rapid changes in therapy for those already receiving treatment for heart failure.

- (1) BNP testing is effective in screening for left ventricular systolic dysfunction and reduces the number of patients requiring an echocardiogram [6-8].
- (2) BNP levels correlate closely with the New York Heart Association (NYHA) Classification of Heart Failure and the Goldman Specific Activity Scale of Heart Failure.
- (3) Normal concentrations virtually exclude the diagnosis of heart failure, and very high levels effectively diagnose the condition; intermediate values require further evaluation.
- (4) Assay of BNP has potential as part of a diagnostic triage in patients presenting with symptoms suggestive of heart failure or in screening populations at high risk [2].
- (5) In several pilot studies, BNP levels had a strong correlation with the severity of illness and were very reliable in differentiating heart failure from pulmonary disease [2].

Other potential clinical applications

- (1) Increased plasma natriuretic peptide levels have been shown to predict the risk of death and

cardiovascular events in people without heart failure after adjustment for traditional risk factors. Excess risk was apparent at natriuretic peptide levels well below current thresholds used to diagnose heart failure [9].

- (2) Natriuretic peptides may help in identifying people at risk of stroke and atrial fibrillation [10].
- (3) Admission BNP is an independent and powerful marker of early and late cardiac mortality in patients with acute chest pain without ST-segment elevation [11].

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Q4: Give an account on viral auto immune manifestations

A4: Viral autoimmune manifestations

Viruses and virus-induced lymphokines may play an important role in the pathogenesis of autoimmunity [1]. The occurrence and the significance of autoimmune manifestations after the administration of viral vaccines remain controversial.

Very few patients may develop some autoimmune diseases after viral vaccination (in particular, arthropathy, vasculitis, neurological dysfunction, and thrombocytopenia). For the overwhelming majority of people, vaccines are safe and no evidence linking viral vaccines with type 1 diabetes, multiple sclerosis, or inflammatory bowel disease can be found.

The most frequently reported autoimmune manifestations for the various vaccinations were as follows: hepatitis A virus — none; hepatitis B virus — rheumatoid arthritis, reactive arthritis, vasculitis, encephalitis, neuropathy, thrombocytopenia; measles, mumps, and rubella vaccine — acute arthritis or arthralgia, chronic arthritis, thrombocytopenia; influenza — Guillain–Barre syndrome (GBS), vasculitis; polio — GBS; varicella — mainly neurological syndromes [2].

Multiple arms of the immune system may be involved in the autoimmune pathology. Antigens are taken up by antigen-presenting cells (APCs) such as dendritic cells and processed into peptides, which are loaded onto major histocompatibility complex (MHC) molecules for presentation to T cells through clonotypic T-cell receptors. Cytolytic T cells (T_c, activated by MHC class I on APC) can directly lyse a target, whereas T-helper cells (T_h, activated by MHC class II) release cytokines that can have direct effects or can activate macrophages, monocytes, and B cells. B cells themselves have surface receptors that can bind surface antigens. On receiving signals from T_h cells, the B cell secretes antibodies specific for the antigens. The antibody may bind its specific target alone or may bind to and activate macrophages simultaneously through the Fc receptor.

There are multiple mechanisms by which host infection by a pathogen can lead to autoimmunity. The pathogen may carry elements that are similar enough in amino acid sequence or structure to the self-antigen that the pathogen acts as a self-‘mimic’. Termed ‘molecular mimicry’, T or B cells that are activated in response to the pathogen are also cross-reactive to the self and lead to direct damage and further activation of other arms of the immune system. The pathogen may also lead to disease through epitope spreading. In this model, the immune response to a persisting pathogen, or direct lysis by the persisting pathogen, causes damage to self-tissue. Antigens released from damaged tissue are taken up by APCs, and this initiates a self-specific immune response. ‘Bystander activation’ describes an indirect or nonspecific activation of autoimmune cells caused by the inflammatory environment present during infection. A domino effect can occur, where the nonspecific activation of one arm of the immune system leads to the activation of other arms. Lastly, infection may lead to autoimmunity through the processing and presentation of ‘cryptic antigens’. In contrast to dominant antigenic determinants, subdominant cryptic antigens are normally invisible to the immune system. The inflammatory environment that arises after infection can induce increased protease production and differential processing of the self-epitopes released by APCs [3].

Infections by the viruses responsible for hepatitis B, C, and D are accompanied by a number of immunopathological manifestations. A link between infection and autoimmunity is particularly well documented for the hepatitis C virus. Immunopathological manifestations range from the production of autoantibodies to overt autoimmune disease, including thyroiditis and autoimmune hepatitis, and to immune-complex-mediated disorders, including cryoglobulinemia, glomerulonephritis, and vasculitis. Several of these manifestations improve with successful antiviral treatment, directly incriminating the virus in their pathogenesis [4].

Chronic infections with hepatitis C virus are associated with various autoimmune manifestations, that is, mixed cryoglobulinemia, membranoproliferative glomerulonephritis, autoimmune thyroid diseases, sporadic porphyria cutanea tarda, and B-cell lymphoma. As exacerbation of hepatitis occurs in 5–10% of hepatitis C virus patients receiving interferon- α treatment and may be successfully treated by immunosuppression afterwards, hepatitis C was also suspected to be associated with autoimmune hepatitis. LKM3 autoantibodies in chronic hepatitis D virus infection and epitope recognition are discussed. Lately, endogenous and exogenous retroviruses have been investigated for the induction of autoimmune diseases. Human A-type retroviral particles (HIAP), reverse transcriptase activity, and anti-HIAP autoantibodies were detected in patients with Sjögren’s syndrome. Anti-HIAP and anti-HIV p24 autoantibodies are seen in systemic lupus erythematosus, primary biliary cirrhosis, and multiple sclerosis. Multiple sclerosis was even associated with a new human retrovirus called multiple sclerosis-associated retrovirus. In diabetes, long terminal repeats were detected in the HLA DQB1 locus, which was shown to be associated with an increased risk of diabetes. A second retrovirus called IDDMK_{1,2}22 was reported to code for a superantigen, which was implicated as a potential cause of diabetes. This hypothesis, however, was challenged repeatedly. Until now, it is unknown whether endogenous retroviruses are etiological agents of autoimmune diseases or an epiphenomenon, induced by coinfecting viruses (e.g. herpes viruses) and inflammatory processes [5].

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Conflicts of interest

There are no conflicts of interest.