Info MEDICUS

The essence of medical practice

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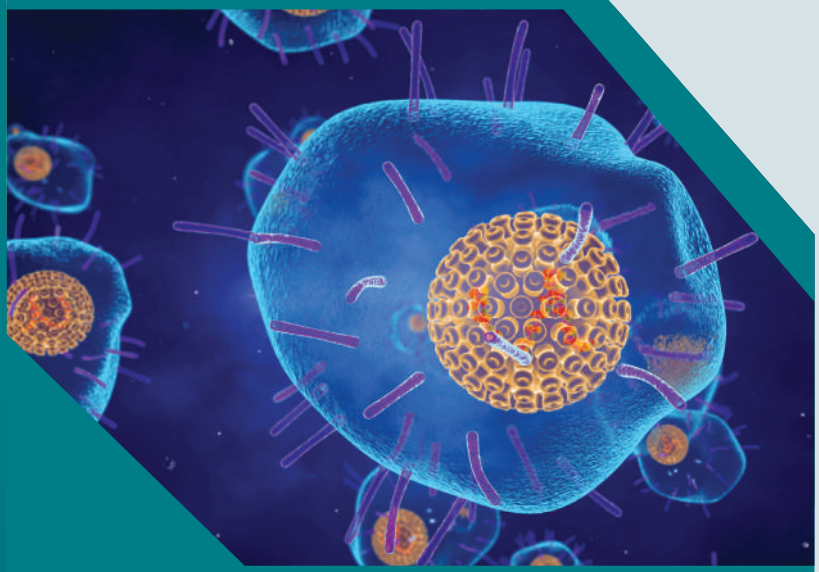
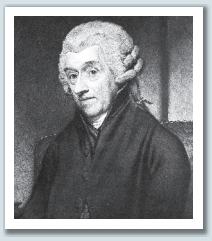


DISEASE HISTORY

Chickenpox

Chickenpox also known as varicella is a highly contagious, vaccine-preventable disease caused by the initial infection with varicella zoster virus (VZV), a member of the herpes virus family. The disease results in a characteristic skin rash that forms small, itchy blisters, which eventually scab over. It usually starts on the chest, back and face. It then spreads to the rest of the body. The disease is usually more severe in adults than in children. Chickenpox is an airborne disease which easily spreads via human-to-human transmission, typically through the coughs and sneezes of an infected person. The incubation period is 10-21 days, after which the characteristic rash appears. It may be spread from one to two days before the rash appears until all lesions have crusted over. It may also spread through contact with the blisters. The first documented use of the term chicken pox was in 1658. Before the 18th century, diseases that appeared to produce "pox," or skin eruptions, were commonly lumped together. This included chickenpox, smallpox and syphilis, which was known as "large pox" or the "great pox". The first scientist to provide a detailed description of chickenpox differentiating it from smallpox was the English physician William Heberden. In 1767, he noted the physical differences between the two diseases and also recorded that people who had chickenpox "were not capable of having it again." In the 1950s, scientists isolated the varicella-zoster virus for the first time, paving the way for efforts to vaccinate against chickenpox and shingles. After that, it took several decades to develop and distribute vaccines for these illnesses. Since its introduction in 1995 the varicella vaccine has resulted in a decrease in the number of cases and complications from the disease.



John Enders
(February 10, 1897- September 8, 1985)

Reference: www.history.com

Artificial Intelligence in Healthcare System

Artificial intelligence (AI) is not one ubiquitous, universal technology, rather, it represents several subfields (such as machine learning and deep learning) that, individually or in combination, add intelligence to applications. Machine learning (ML) refers to the study of algorithms that allows computer programs to automatically improve through experience. ML itself may be categorised as 'supervised', 'unsupervised' and 'reinforcement learning' (RL) and there is ongoing research in various sub-fields including 'semi-supervised', 'self-supervised' and 'multi-instance' ML.

- Supervised learning leverages labelled data (annotated information); for example, using labelled X-ray images of known tumours to detect tumours in new images.
- 'Unsupervised learning' attempts to extract information from data without labels; for example, categorising groups of patients with similar symptoms to identify a common cause.
- In RL, computational agents learn by trial and error or by expert demonstration. The algorithm learns by developing a strategy to maximise rewards.
- Deep learning (DL) is a class of algorithms that learns by using a large, multi-layered collection of connected processes and exposing these processors to a vast set of examples. DL has emerged as the predominant method in AI today driving improvements in areas such as image and speech recognition.

A growing focus in healthcare is on effectively designing the 'choice architecture' to nudge patient behaviour in a more anticipatory way based on real-world evidence. Through information provided by provider EHR systems, biosensors, watches, smartphones, conversational interfaces and other instrumentation, software can tailor recommendations by comparing patient data to other effective treatment pathways for similar cohorts. The recommendations can be provided to providers, patients, nurses, call-centre agents or care delivery coordinators.

Perhaps the most difficult issue to address given today's technologies is transparency. Many AI algorithms - particularly deep learning algorithms used for image analysis - are virtually impossible to interpret or explain. If a patient is informed that an image has led to a diagnosis of cancer, he or she will likely want to know why. Deep learning algorithms may be unable to provide an explanation.

Reference : www.ncbi.nlm.nih.gov

REVIEW ARTICLE

Irritable Bowel Syndrome

Introduction

Irritable bowel syndrome (IBS) is a chronic disorder of the gastrointestinal tract, characterized by abdominal pain and alterations in bowel habits. IBS is the disorder most commonly encountered by gastroenterologists and diagnosis is made according to a symptom-based classification system, the Rome Criteria, with the latest version, Rome IV. Patients with IBS suffer not only from gastrointestinal distress, but approximately 40 - 60% experience comorbid psychological disorders, such as depression or anxiety. In addition, patients with IBS report higher levels of somatization compared to patients without IBS but with gastrointestinal symptoms. Not surprisingly, IBS has shown negative impact on patients' quality of life, as well as it adversely affects society's financial resources.

Pathophysiology

IBS is recognized as a multifactorial disorder, with the following among the proposed mechanisms contributing to symptomatology: gastrointestinal dysmotility, inflammation, visceral hypersensitivity and altered intestinal microbiota. Diet and stress exposure (including early life events) have been proposed as contributing factors to this heterogeneous disorder. Because stress has been identified as a mechanism in the development of IBS, the major components of the stress response system, the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis, have been the subject of numerous investigations of IBS. Lastly, genetic predisposition and environmental interactions, such as familial susceptibility and psychosocial stressors, have been implicated in the multifactorial pathogenesis of IBS.

Physiological and psychological variables have jointly been identified as playing a role in the etiology and perpetuation of IBS symptomatology. In an investigation of risk factors for military personnel developing IBS found the risk of developing IBS to be increased after cases of infectious gastroenteritis and also to be increased in subjects with post-traumatic stress disorder (PTSD), increased number of life stressors and

self-reported anxiety and depression. These findings illustrate the interdependence or cross-talk between the brain and the gut in IBS, a connection commonly known as the brain-gut axis (BGA).

The BGA refers to pathways among physiological systems, including the central nervous system (CNS), the enteric nervous system (ENS) and the autonomic nervous system (ANS). Endocrine, neural and neuroimmune pathways facilitate bi-directional communication between the CNS and the gut. Patients with IBS have been noted to exhibit disturbances in the BGA, including central and autonomic functions, peripheral factors, peptides and hormones. Differences in central processing mechanisms of the BGA have also been demonstrated in IBS patients compared to healthy controls, through the use of neuroimaging techniques. Such investigations illustrate that patients with IBS exhibit differences in brain structure, connectivity and functional responsiveness in comparison to healthy controls. It is proposed that the clinical presentation of IBS patients with pain, psychological comorbidities and altered gut motility may be explained through changes in the BGA, although mechanisms are not fully understood. Despite great progress in understanding the pathophysiology of IBS, such discoveries have not been fully translated to the clinical arena; patient diagnosis remains one primarily of exclusion and treatment interventions remain symptom driven.

Diagnosis

IBS is the gastrointestinal disorder that is most commonly diagnosed; the diagnosis is made from the presence of certain symptoms in the absence of organic disease. IBS has been categorized as a functional bowel disorder, defined by symptom onset greater than six months and recurrence at least three days per month during the last three months. Diagnostic criteria require abdominal discomfort or pain to be associated with two or more of the following: improvement with defecation, onset associated with change in the form of stool or onset associated with a change in the frequency of stool. This diagnostic criteria, known as Rome III classification, also subtypes IBS patients based on their predominant stool pattern: constipation (IBS-C), diarrhea (IBS-D), mixed (IBS-M) or unsubtyped (IBS-U). Rome III has served as the symptom-based, diagnostic criteria for IBS since its release in 2006; in early 2016 the Rome Foundation released Rome IV, an updated classification system for conceptualizing and diagnosing functional gastrointestinal disorders.

Rome Criteria

	Rome III	Rome IV
Diagnostic timeframe	Symptom onset greater than 6 months. Symptom activity during the last 3 months. Symptom frequency at least 3 days per month.	Symptom onset greater than 6 months. Symptom activity during the last 3 months. Symptom frequency at least 1 day per week.
Symptom description	Abdominal discomfort or pain	Abdominal pain
Symptom association (2 or more)	Improvement with defecation. Onset associated with change in the form of stool. Onset associated with a change in the frequency of stool.	Related to defecation. Associated with a change in the form of stool. Associated with a change in the frequency of stool.
Predominant stool pattern of IBS subtype (IBS-C, IBS-D, IBS-M & IBS-U)	Stool type based on bowel movements on all days.	Stool type based on days with abnormal bowel movements.
Tool to categorize bowel habit	Bristol Stool Form Scale	Bristol Stool Form Scale

The Rome IV definition of IBS maintains symptom chronicity (greater than six months) and current activity (present within the prior three months); however, symptom frequency has been changed to at least one day per week (from at least three days per month), specifically requires abdominal pain (discomfort has been eliminated) to be related to (versus improved with) defecation and the "onset" of abdominal pain has been

eliminated from the association of pain with changes in stool. Rome IV also updates the subtyping of IBS patients (IBS-C, IBS-D, IBS-M and IBS-U), in that stool type is based on days with abnormal bowel movements, as opposed to bowel movements on all days. In addition, Rome IV retains the Bristol Stool Form Scale as a useful tool to categorize bowel habit.

In order to make an accurate diagnosis of IBS, it is recommended to incorporate Rome IV Criteria along with the following: patient history (including dietary questions), physical examination (including anorectal examination), limited laboratory tests (such as complete blood count, C - reactive protein or fecal calprotectin, possible celiac disease serology) and when indicated (either due to recommended guidelines for patient age, alarm signs, family history etc), a colonoscopy and/or upper gastrointestinal endoscopy as well as other tests. Alternative diagnoses that should be considered when patients present with IBS symptomatology include celiac disease, microscopic colitis (MC), inflammatory bowel disease (including Crohn's disease and ulcerative colitis), bile acid malabsorption, colorectal cancer and dyssynergic defecation.

The symptoms of IBS and other gastrointestinal diagnoses commonly overlap in clinical practice, therefore, investigations have examined the prevalence of such associations. For instance, Halpin & Ford (2012) conducted a systematic review and meta-analysis on IBS symptoms in patients with inflammatory bowel disease (IBD). These authors report that IBS symptoms were significantly higher in IBD patients with active disease and in remission (overall prevalence approximately 40%), than in comparison to non-IBD controls. In order to guide therapy for such patients (IBD with IBS-type symptoms), it has been suggested to measure fecal calprotectin as an initial evaluation and that clinical trials are needed to foster evidence - based approaches. Symptoms also overlap between IBS and another diagnosis, MC, although therapeutic interventions are quite different. This recent systematic review and meta-analysis reported the pooled prevalence of IBS to be approximately 33% in patients with MC, although these odds were not higher than in other patients with diarrhea. Such overlap of symptoms between patients with IBS and other gastrointestinal disorders, has prompted the use of invasive medical procedures in efforts to obtain a diagnosis. This situation has fostered the efforts of biomarker development to aid in the assessment and diagnosis of patients with IBS.

Over the years, various biomarkers have been proposed to differentiate patients with IBS from healthy controls. For instance, proposed a ten biomarker blood-based panel which included a cytokine, nerve growth factor, autoantibody, antibodies etc. A few years later, built on these original ten parameters and compiled an extensive panel (34 markers) that incorporated serological markers, gene expression and psychological measures. Biomarker initiatives have also investigated colonic transit and fecal bile acids, anti-cytolethal distending toxin B and anti-vinculin antibodies for distinguishing patients with IBS-D as well as tests of fecal dysbiosis to characterize patients with IBS. Although these tests are encouraging in their diagnostic ability and highlight the biological underpinnings of IBS, biomarkers have yet to become the gold standard in clinical practice for diagnosing patients with IBS.

Management of IBS

IBS is characterized by a variety of chronic symptoms that include abdominal pain, an alteration in bowel habits and flatulence. The disorder has no definitive treatment but could be controlled by eliminating of some exacerbating factors such as certain drugs, stressor conditions and changes in dietary habits. Hidden drug addiction should be considered as well.

Non-pharmacologic management

Patients should be given sufficient information regarding their disease condition. For instance, patients should be fully informed of the chronic and benign nature of their condition, that their diagnosis is not likely to be altered and he or she should have a normal life span. A detailed medical history and physical examination are frequently useful and the examining physician should pay particular attention to their patient's concerns.

The treatment goal in patients suffering with IBS is to reduce their overall symptoms and a subsequent effort should be made to try and eliminate or decrease the patient's primary symptoms which should be addressed on first encounter with the patient. Some recommendations should be put forward to the patients regarding their dietary habits. It should be noted that the intake of foods does not cause IBS; however the contact of food with the GI tissues can convey various effects in individuals

suffering from IBS through various immunologic, physiologic and biochemical mechanisms. Therefore, recommendations regarding their dietary habits should be based on the following guidelines:

- A reduction in inflammation is desired in all parts of the GI tract and can be achieved by avoiding the consumption of inflammatory stimulants such as allergens or chemicals, namely benzoates, alcohol, methylxanthines and caffeine consumption that cause the release of inflammatory mediators.
- Patients should be educated on how best to consume their three daily meals, by partaking of non-processed and fresh foods that consist of whole grains, fibers and vitamins two or three times a day.
- People who have both IBS and lactase deficiency should avoid dairy products. People with bloating and increased gas (flatulence) should try to avoid foods such as beans, onions, celery, carrots, raisins, bananas, apricots and plums. It is recommended that foods containing vinegar, mustard, ketchup and pickled foodstuffs not be consumed either.
- In essence, IBS patients should avoid foods that trigger an onset of their symptoms, consume a minimum of high fat foods and take part in regular physical activity.

Characteristics of patients affected by IBS according to severity of disease

	Mild IBS	Moderate IBS	Severe IBS
Prevalence	70%	25%	5%
Practice type	Primary	Specialty	Referred
Symptoms constant	-	+	+ + +
Psychosocial difficulties	-	++	+ + +
Health care use	+	++	+ + +

Psychosocial treatments

Since anxiety and depression are the most prevalent psychologic conditions among patients affected by IBS, behavioral treatments may be considered in the IBS patients who have associated stress symptoms. Hypnosis, biofeedback and psychotherapy can help to alleviate anxiety levels in these patients.

It has been shown in studies that physical treatments such as massage therapy and acupuncture may help to reduce symptoms and emotional signs. Although this is not conclusive, as other studies have shown that the efficacy of acupuncture is the same as placebo.

Pharmacologic management

Treatment of IBS is based on the main symptoms of the disease such as diarrhea, constipation, abdominal pain or bloating. Determination of disease severity and the patient's major symptoms are deemed as being the main goals of treatment. The characteristics of patients affected by IBS according to disease severity are summarized here:

Management of IBS with predominant pain symptoms

Various medications are used for treatment of this group of patients and the most effective treatments are as follows:

Anti-spasmodic drugs

This group of drugs includes anti-muscarinic agents (e.g., Dicyclomine and Hyoscine), muscle relaxants other than anti-cholinergics (e.g., Mebeverine and Pinaverium) and calcium channel blockers such as Colpermin and peppermint oil. Anti-spasmodic agents are used in the treatment of abdominal pain in IBS patients. In a study comprising 905 subjects it has been shown that these agents were more effective with a response rate of 61% (505 out of 905 patients) in comparison to 34% (458 out of 873 patients) for a placebo subject group.

Anti-depressant drugs

Amitriptyline is one of the tricyclic antidepressant drugs commonly used in the treatment of IBS patients at low doses (10mg per day). Effects of this drug include visceral hyperalgesia, sleep improvement and normalization of intestinal transient time. When used in high doses (e.g., 100 mg or more at bed time) it may help to relieve depression and anxiety. Two meta-analyses have shown that low to moderate doses of TCAs were more effective than placebo in relieving pain and general symptoms of IBS sufferers, however a third meta-analysis rejected the previous findings and reported that TCA anti-depressants were no more effective than placebo. Some studies have shown that SSRIs have beneficial effects on patients affected by IBS and according to other studies these drugs are deemed effective in reducing abdominal pain relief in such patients. SSRIs are effective pain relievers and reduce other symptoms such as fibromyalgia.

Medicinal therapies used in the treatment of bloating and excess gas production		
Medication class	**Examples**	**Comments**
Phenobarbital	β-galactosidase	For treatment of lactose intolerance; variable effectiveness shown in lactose intolerant IBS patients.
	α-galactosidase	Effective when consuming legume - rich meals in healthy subjects.
	Pancreatic enzymes	Exact efficacy in the treatment of gas and bloating unknown.
Absorbents and agents that reduce surface tension	Simethicone	Possible benefits in functional dyspepsia and gas accompanied with diarrhea.
	Activated charcoal	Lack of certainty regarding the benefits in IBS.
	Bismuth subsalicylate	Possible benefits leading to a reduction of malodorous flatus.
Treatments used to modify the gut flora	Antibiotics	Useful for the treatment of bacterial overgrowth secondary to organic disease; possible benefits in IBS.
	Probiotics (Lactobacillus sp.) Prebiotics	Possible benefits in IBS. Lack of certainty regarding the benefits in IBS.
Prokinetic medications	Tegaserod	Leads to a reduction of bloating in IBS. Reduces bloating in IBS; however has been removed from market.
	Neostigmine	Reduces luminal distention in acute colonic pseudo obstructed patients; exact benefits with regards to bloating unknown.

Probiotics

Probiotics have been shown to convey positive effects on intestinal motility, sensitivity and pain relief in IBS patients.

Management of IBS with concomitant bloating

Abdominal bloating, a symptom commonly witnessed in IBS patients, is often observed in constipation predominant IBS patients. Probable mechanisms of bloating may include:

- Psychosocial,
- Weak abdominal muscles,
- Paradoxical relaxation of abdominal muscles and
- Changes in visceral sensitivity.

Antibiotics are effective in the improvement of bloating symptoms. In cases where bacterial overgrowth has arisen, antibiotic treatment may be effective. Short-term antibiotic treatment is recommended to help improve bloating symptoms in IBS patients. The use of non-absorbable antibiotics such as rifaximin leads to relief from symptoms of discomfort and bloating in IBS patients. Short term use of rifaximin has been demonstrated to reduce bloating but relapse is often frequent.

In a placebo controlled study, prescribing SSRIs such as Citalopram and Fluoxetine led to relief from bloating. These drugs may also convey anti-anxiety and anti-depressive effects. A plant extract that contains *Coriandrum sutivum* and *Mentha spicata* has been shown to reduce bloating in IBS patients, as compared to placebo. This is probably achieved via its antispasmodic effects. The table above lists a number of recommended medical therapies for bloating.

Management of IBS-constipation predominant

Constipation is said to be a non-specific symptom witnessed in patients who possess an abnormal colon transient time or defecation disorder with an increase in straining. In such patients treatment modalities are as follows:

The intake of fiber is highly recommended. Often consumption of roughly 12 grams of fiber daily has been shown to be relatively effective in reducing symptoms although this effect is not regarded as being more than the effect that a placebo offers. Osmotic laxatives are predominantly used for the treatment of constipation. Although no specific clinical trials on IBS patients have been conducted, yet fiber supplements are used in the treatment of constipation. This may cause an increase in bloating that often occurs as a side effect.

Long-term use of osmotic laxatives has been proven to be safe and effective. Magnesium, phosphate and emollients containing polyethylene glycols have also been shown to be efficient as well.

Anti-depressants regardless of the type of effects they promote may be beneficial in IBS patients who suffer from abdominal pain and offer a therapeutic effect as well.

In IBS, TCAs and probably SSRIs released endogenous endorphins and the blockage of norepinephrine reuptake leads to an increase in the inhibition of pain pathways. In IBS patients the use of low dose anti-depressants is useful for effective pain relief and is well tolerated by patients in general. A double blind clinical trial has reported that low dose Amitriptyline (10 mg) conveyed effective pain relief in patients who suffer from IBS. In IBS patients suffering predominantly from constipation; SSRIs (e.g., Fluoxetine 20 mg/day) may help to relieve abdominal pain. Sertralin at a dose of 100 mg per day or similar antidepressant drugs could be effective on any underlying depression. In constipation predominant IBS patients, antidepressant drugs such as Amitriptyline, Imipramine and Nortriptyline should be used with caution.

Tegaserod is a 5-HT4 receptor agonist that in clinical trials has been reported to reduce the general symptoms of IBS patients in comparison to a tested placebo. Lately, with subsequent testing it has been shown that Tegaserod may increase the risk of ischemic heart disease when compared to placebo, therefore the use of this drug was limited in September, 2007. As of July 2007 Tegaserod was only prescribed to women less than 55 years of age who suffer from IBS with predominant constipation symptoms and no apparent signs of cardiovascular disease.

Management of IBS-diarrhea predominant

In this group of patients, anti-diarrheal agents are generally effective but few clinical trials have been conducted for confirmation. There is evidence which suggests that the use of regular low doses of anti-diarrheal agents (e.g., Loperamide every morning or BD) could be effective in such patients. A major double blind clinical trial has been conducted on diarrhea predominant IBS patients using Alosetron (5-HT3 antagonist receptor) in doses of 1 mg, twice daily for a period of 12 weeks. A reduction in the frequency and urgency of defecation, along with reduced abdominal pain and IBS symptoms have been shown, which will in turn help to improve the patient's quality of life. The FDA has restricted the use of this drug to females affected by IBS who display major diarrheal symptoms. Due to some adverse effects such as ileal obstruction, intestinal obstruction, rectal fecal impaction, intestinal perforation and ischemic colitis the use of this drug has subsequently been restricted by the FDA.

Anti-depressants are effective in controlling abdominal pain and leading to diarrheal relief in diarrhea predominant IBS patients. TCAs are able to increase colon transit time through anti-cholinergic effects and may be useful in patients suffering predominantly from diarrhea. Probiotics have also been proven to be useful in diarrhea predominant IBS sufferers. A review of epidemiologic studies suggest the prevalence of IBS in Iran is among the lowest reported in neighboring developing countries and the Asian region and is more common in females than males. For disease diagnosis, a careful history, physical exam and laboratory tests based on symptoms along with simultaneous observation of warning signs is very important. In these patients, the main goal is education and reassurance. Recommendations about dietary habits and drug therapy based on the primary IBS symptoms are recommended. Dietary changes should not disrupt the patient's quality of life.

Prognosis

When diagnosed according to current criteria, IBS is associated with a good prognosis and the diagnosis is unlikely to be changed to that of an organic disease during follow-up. A positive physician-patient interaction may be related to reduced use of ambulatory health services by patients with IBS.

Reference: www.ncbi.nlm.nih.gov

Dengue Hemorrhagic Fever

Dengue hemorrhagic fever is a variant presentation of dengue infection that occurs primarily in children <10 years living in areas where dengue is endemic. Dengue hemorrhagic fever, which has also been called Philippine, Thai or Southeast Asian hemorrhagic fever, frequently requires prior infection with the dengue virus.

Dengue hemorrhagic fever is an immunopathologic disease; dengue virus - antibody immune complexes trigger release of vasoactive mediators by macrophages. The mediators increase vascular permeability, causing vascular leakage, hemorrhagic manifestations, hemoconcentration and serous effusions, which can lead to circulatory collapse (ie, dengue shock syndrome)

Symptoms and Signs of Dengue Hemorrhagic Fever

Dengue hemorrhagic fever often begins with abrupt fever and headache and is initially indistinguishable from classic dengue. Warning signs that predict possible progression to severe dengue include -

- Severe abdominal pain and tenderness
- Persistent vomiting
- Hematemesis
- Epistaxis or bleeding from the gums
- Black, tarry stools (melena)
- Edema
- Lethargy, confusion or restlessness
- Hepatomegaly, pleural effusion or ascites
- Marked change in temperature (from fever to hypothermia)

Circulatory collapse and multi organ failure, called dengue shock syndrome, may develop rapidly 2 to 6 days after onset.

Bleeding tendencies manifest as follows:

- Usually as purpura, petechiae or ecchymoses at injection sites
- Sometimes as hematemesis, melena or epistaxis
- Occasionally as subarachnoid hemorrhage

Bronchopneumonia with or without bilateral pleural effusions is common. Myocarditis can occur.

Mortality is usually < 1% in experienced centers but otherwise can range to up 30%.

IMMUNOLOGICAL BASIS FOR DHF

The key steps by which DENV infection induces DHF have been a subject of controversy. DENV antibodies can influence the course of the disease in various ways. A recent study showed a positive relationship between peak viral load and disease severity in humans. The idea about antibody dependent enhancement (ADE) functions in vivo is supported by the observation that DHF persists after primary DENV infection in infants, born to DENV-immune women who subsequently acquire DENV antibodies through the placenta. Primary DENV and clinically mild secondary DENV infection suggest that other variables are also involved. In patients with severe disease, in vivo immune complex formation has been associated with complement activation. Cross-reactivity of anti-E antibodies with plasminogen has been associated with bleeding in acute DENV infection, but not with DHF. In addition, potential pathologic factors include cytokine production and cytolysis by activated T cells. Elevated levels of activation markers such as soluble TNF receptors, soluble IL-2 receptors and soluble CD8+ have been associated with disease severity.

Similar associations with disease severity were found for the expression of activation markers on circulating CD8+ T cells and for an increased population of DENV epitope-specific T cells. Acute DEN infection leads to increased production of several cytokines, including IFN, TNF, IL-10 and chemokines. Although both type 1 and 2 cytokine levels are elevated in DHF, the timing of their synthesis appears to be critical as induction of type 1 cytokines occurs earlier and is associated with more severe disease. Analysis of T cell responses to DENV revealed an association between in vitro TNF responses to DENV antigens.

Diagnosis of Dengue Hemorrhagic Fever

Dengue hemorrhagic fever is suspected in children with World Health Organization defined clinical criteria for the diagnosis:

- Sudden fever that stays high for 2 to 7 days
- Hemorrhagic manifestations
- Hepatomegaly

Hemorrhagic manifestations include at least a positive tourniquet test and petechiae, purpura, ecchymoses, bleeding gums, hematemesis or melena. The tourniquet test is done by inflating a blood pressure cuff to midway between the systolic and diastolic blood pressure for 15 minutes. The number of petechiae that form within a 2.5 cm diameter circle are counted; > 20 petechiae suggests capillary fragility.

Complete blood count, coagulation tests, urinalysis, liver tests and dengue serologic tests should be done. Coagulation abnormalities include

- Thrombocytopenia (≤ 100,000 platelets/mL [≤ 100 x 10^9/L])
- A prolonged prothrombin time (PT)
- Prolonged activated partial thromboplastin time (APTT)
- Decreased fibrinogen
- Increased amount of fibrin split products

There may be hypoproteinemia, mild proteinuria and increases in aspartate aminotransferase (AST) levels.

Serological diagnosis can be made using the IgM capture enzyme-linked immunosorbent assay (MAC-ELISA). Combined with the dengue virus RNA amplification test, it can provide a diagnosis within the first 1 to 7 days of illness. The plaque reduction neutralization test (PRNT) is specific and sensitive. Titers in acute and convalescent phase serum samples can reliably establish dengue virus infection and may indicate the specific dengue virus type involved. The PRNT requires live dengue viruses for the test and is labor-intensive and expensive. Many laboratories are not able to do the PRNT.

Patients with World Health Organization-defined clinical criteria plus thrombocytopenia (≤ 100,000/mL [≤ 100 x 10^9/L]) or hemoconcentration (Hct increased by ≥ 20%) are presumed to have the disease.

Treatment of Dengue Hemorrhagic Fever

Patients with dengue hemorrhagic fever require intensive treatment to maintain euvolemia. Both hypovolemia (which can cause shock) and overhydration (which can cause acute respiratory distress syndrome) should be avoided. Urine output and the degree of hemoconcentration can be used to monitor intravascular volume.

No antivirals have been shown to improve outcome. Supportive care is needed.

References: 1. www.msdmanuals.com
2. www.iwaponline.com

CASE REVIEW

B-cell Acute Lymphoblastic Leukemia Associated with Hypereosinophilia: A case report

INTRODUCTION

Eosinophilia is a condition determined by an elevated absolute eosinophil count (AEC). In case of severity, it is divided into three grades: Mild (AEC = 500 - 1500/mm); Moderate (AEC = 1500 - 5000/mm) and Severe (AEC > 5000/mm). It can also be classified into primary (PE) and secondary (SE) forms. PE is mainly related to clonal abnormalities of myeloid cells, while SE is often reactive to the T cells' cytokine production. Various conditions can cause SE, such as infections (especially parasites), allergic reactions, pulmonary, dermal, renal or autoimmune diseases, immunodeficiencies and malignancies. Nevertheless, in very few cases (less than 1%), hypereosinophilia (HE) is associated with acute lymphoblastic leukemia (ALL). This condition is mainly caused by the translocation t(5;14)(q31;q32), which leads to over expression of interleukin (IL)-3 through a fusion gene called immunoglobulin heavy locus (IGH) - IL3. Urticarial rash, fever, arthralgia, myalgia, sweating and dyspnea are the common symptoms in these cases. Notably, the lack or absence of blasts in the peripheral blood smear (PBS) is the characteristic feature in ALL with eosinophilia (ALL - eo).

Hypereosinophilic syndrome (HES), a rare hematological disorder, occurs when eosinophils invade the vascular system, resulting in multi-organ failure. It is defined as the existence of persistent eosinophilia (AEC >1500 per mm) along with evidence of organ damage. It can affect almost all the organs including the skin, pulmonary and cardiovascular systems, central nervous system, peripheral nervous system, eyes, gastrointestinal tract and coagulation system.

CASE PRESENTATION

A 16-year-old male patient presented with urticaria and generalized itching to the emergency department. He was referred with leukocytosis (WBC = 160,000/µL (normal range: 4500 - 11,000/µL)), with 90% eosinophils), anemia (Hb = 9.11 g/dL (normal range: 13.5 - 17.5 g/dL)), and thrombocytopenia (platelets = 69,000/µL (normal range: 150,000 - 450,000/µL)). In the initial skin examination, erythematous and urticaria lesions were observed scattered in all parts of his body. Only a splenomegaly was detected about 6 - 7 cm below the rib edge during the physical examination.

PBS showed eosinophilia with different shapes and hypogranular appearances. However, no blast was observed (Figure 1). He had no notable past medical, family or psycho-social history.

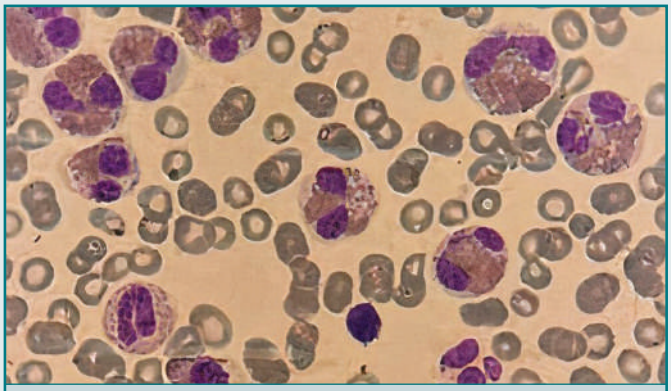


Figure 1. Peripheral blood smear demonstrated eosinophilia with different shapes and hypogranular appearance but with no blasts.

Due to hypereosinophilia, cardiac examination and high-sensitivity cardiac troponin check were performed, which were reported positive (15 ng/L (normal range: >14 ng/L)). Due to leukocytosis and bicytopenia, bone marrow biopsy was performed and fluorescence in situ hybridization (FISH) was performed for fibroblast growth factor receptor 1 (FGFR1), platelet-derived growth factor receptor alpha (PDGFRα) and platelet-derived growth factor receptor beta (PDGFRβ). Moreover, breakpoint cluster region (BCR):Abelson murine leukemia 1 (ABL1) and Janus kinase 2 (JAK2) V617F mutation were also requested. A normal result or a negative result was obtained from these tests (Table 1). Cytogenetic examination of bone marrow showed the patient's karyotype was 47, XY, +mar in half of the analyzed cells and 46, XY in the other half (Figure 2). An examination of the bone marrow at another center revealed a negative translocation of t(5;14). A bone marrow examination showed more than 20% lymphoid blasts, along with eosinophilia and terminal deoxynucleotidyl transferasepositiveand CD20-positive lymphoid blasts. Sections of the trephine bone biopsy showed 100% cellularity in which a mixed population of eosinophils precursors and some small blastoidcells were seen. Morphological study and FISH staining were in accordance with acuteprecursor B lymphoblastic leukemia/lymphoma with eosinophilia (Table 2).

Table 1. Evaluation of common cellular abnormalities in the bone marrow biopsy.

Abnormality	Specific assay techniques	Finding
8p11.2 (FGFR1 sep)	FISH	Normal
4q12 (PDGFRα translocation/ deletion)	FISH	Normal
5q32 (PDGFRβ sep)	FISH	Normal
JAK2 V617F mutation	PCR	Negative
BCR::ABL1*	RT-PCR**	Negative

BCR: breakpoint cluster region; FISH: fluorescence in situ hybridization; RT-PCR: real-time polymerase chain reaction

*The types of BCR::ABL1 analyzed were p190, p210, and p230.

**It contains translocation t(9;22)(q24;q11).

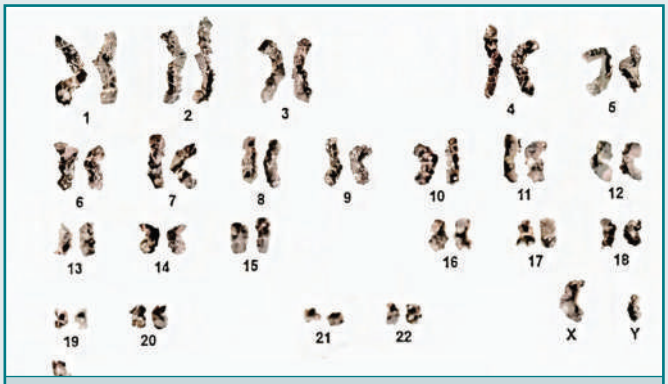


Figure 2. Cytogenetic examination of bone marrow specimens demonstrates the patient's 47, XY,+mar karyotype.

Table 2. Results of immunohistochemical staining of the bone marrow biopsy.

Marker	Finding
CD3	Positive in a few scattered small lymphocytes
CD7	Positive in a few scattered small lymphocytes
CD19	Highlights interstitial infi ltration of cells
CD20	Positive
CD34	Positive in blastoid cells in the interstitial pattern
TdT	Positive in blastoid cells
Ckit	Positive in maturing myeloid cells

According to cardiac conditions, glucocorticoid pulse therapy (methylprednisolone 1000 mg IV daily for three consecutive days) was started. Before starting the glucocorticoid pulse, ivermectin (200 µg/kg per day) was also initiated due to the high prevalence of *Strongyloides stercoralis* in the local area.

The patient has been diagnosed with B-ALL and was treated with Berlin-Frankfurt-Munster (BFM) protocol. He was then transferred to another institute to continue his therapy. A 6-month follow-up shows that the patient has been in complete remission without recurrence.

DISCUSSION

HES is divided into three classifications: (1) Idiopathic HES (no evidence for any underlying condition); (2) Primary, neoplastic or clonal HES (including myeloproliferative disorders, chronic myeloid disorders and acute leukemias) ; (3) Secondary or reactive HES (caused by conditions like infectious diseases, medications, allergic reactions, autoimmune diseases, metastases and endocrinopathies). The first step in the classification of HE patients is the assessment of secondary causes. In this regard, providing an excellent medical history, evaluation of clinical manifestations and para-clinical investigations can make identifying the underlying cause more available. After excluding secondary causes of HE, primary bone marrow disorders must be assessed. It requires analyses over PBS and morphologic, immunophenotypic and cytogenetic features of bone marrow.

ALL - eo shares some similar features with HES. First, they are both more common in males (76%). Second, they are both presented with non - specific constitutional symptoms. Last, their morbidity rate is mainly related to the site of eosinophilic infiltration and the extent of it. Nonetheless, ALL - eo has been reported to occur at younger ages (mean age of 14 years, with an age range of 2 - 58 years). HE-related manifestations commonly precede classic ALL signs and symptoms. ALL - eo - related indications are similar to HES and can exacerbate multi - organ damage and thrombocytopenia. As mentioned before, due to severe eosinophilia, HES was suspected. Thus, we performed heart monitoring and required paraclinical tests to evaluate cardiac disorders. High-sensitivity cardiac troponin was reported to be positive with a titer of 15 ng/L, suggesting eosinophils infiltrating the heart, causing progressive restrictive cardiomyopathy that may result in Loeffler endocarditis or even death as a possible consequence of HES. Anemia, thrombocytopenia and hepatomegaly are some of the characteristics associated with ALL - eo. A clonal eosinophilic proliferation, blast crisis or a soft tissue tumor of myeloblasts (granulocytic sarcoma) can all indicate ALL - eo. The patient also presented skin lesions, including urticaria and generalized itching, as reported in the previous studies. Histopathological investigations of the lesions revealed eosinophils, polymorphonuclear leukocytes and monocytes infiltrating the perivascular area with different numbers. Urticarial lesions are usually present as a skin manifestation of HES. However, unlike classic urticarial lesions, HES - related lesions are persistent for more than 24 h. In contrast to urticarial vasculitis, they also demonstrate no vasculitis features in histopathological studies.

The exact mechanism of the association between HE and ALL has not been completely understood. It could be due to neoplastic antigens or exogenous agents (like viral infections), which may stimulate T cells and result in the overproduction of eosinophil - stimulating growth factors. Nevertheless, given the development of HE in ALL patients, it appears to be the result of a mixture of reactive and clonal pathways. A group of abnormalities such as absent CD3 marker, the presence of abnormal and immature T cells, increased expression of CD5 on CD3 - CD4+ cells, and the absence of surface CD7 and CD27 marker expression has been frequently reported in these patients. Lymphocytes carrying the mentioned abnormalities can lead to the overproduction of Th2 - related cytokines, including IL - 3, IL - 4, IL - 5 and IL - 13, leading to the increased production and prolonged survival of eosinophils.

Most ALL patients with hypereosinophilia are treated with corticosteroids first. There has been no study to determine the best initial dose and duration of prednisone therapy in these patients; however, a dose of 40 mg of prednisone is recommended for hypereosinophilia. Generally, this dose is effective for most patients. To achieve the lowest dose possible, the dose should be gradually tapered down while closely monitoring the eosinophil count. Patients undergoing long-term steroid treatment need to be evaluated for bone density and receive adjunctive treatment to prevent bone loss. Based on cardiac conditions, we started glucocorticoid pulse therapy (methylprednisolone 1000 mg IV daily for three consecutive days). After completing the BFM protocol, the patient is currently in remission after 6 months. It is suggested that complete treatment according to the BFM protocol should be done concerning corticosteroid administration.

Reference: journals.sagepub.com

World Lung Day

25 September, 2024

World Lung Day (WLD) is a dedicated global awareness and action towards better lung health observed on September 25th, every year, globally to celebrate the most recent achievements in lung health.

Lungs, the essential organs responsible for exchanging gases in the human body, are increasingly under threat from multiple factors such as smoking, pollution, respiratory infections, etc. Respiratory conditions can affect people in all countries; however, it disproportionally affects low and middle-income countries (LMICs) where there is a scarcity of resources for management, prevention and research. The lung is highly vulnerable to damage and infection from external environmental factors due to constant exposure to chemicals, particles and infectious organisms in the air.

World Lung Day acts as an essential medium to emphasise healthy lungs, the pressing need to identify, prevent and treat several lung conditions and increase awareness regarding lung illnesses, promote lung health and support improved healthcare access.

Reference: www.firsnet.org

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Info MEDICUS
The essence of medical practice

INFO QUIZ CARD

(BMDC registered doctors only)

AMM/FM Territory Code……...

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Qualification _____

Address _____

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Mobile No. _____

Read the questions, tick (√) the correct answers and hand over the Info Quiz Card attached to the Info Medicus to your nearest ACI representative by 30 September 2024.

1. **What is the primary diagnostic criteria used to identify Irritable Bowel Syndrome (IBS)?**
   (a) Elevated C-reactive protein (CRP) levels (b) Positive findings on colonoscopy
   (c) Rome criteria (d) Elevated fecal calprotectin levels

2. **What is the most severe form of Dengue Hemorrhagic Fever?**
   (a) Grade I (b) Grade II (c) Grade III (d) Grade IV

3. **What is the primary complication associated with chickenpox in adults?**
   (a) Encephalitis (b) Pneumonia (c) Hepatitis (d) Myocarditis

4. **What genetic abnormality is commonly associated with B cell acute lymphoblastic leukemia (B-ALL)?**
   (a) Philadelphia chromosome (BCR-ABL1 fusion) (b) (8;21) translocation
   (c) (15;17) translocation (d) NPM1 mutation

5. **What is the term for heightened sensitivity to pain often experienced in neuropathic pain conditions?**
   (a) Analgesia (b) Hyperalgesia (c) Allodynia (d) Dysesthesia