CONTENTS

CASE REPORTS

CHRONIC HEPATITIS-B WITH HCV AND HEV SUPERINFECTION (TRIPLE VIRUS INTERACTION) -A CASE REPORT

MA RAHIM MIAH, MT RAHMAN, PK ROY

Introduction

Viral hepatitis is a major public health problem worldwide. About 8-10%(450-600 million people) of the world population is infected with either Hepatitis-B (HBV) or Hepatitis-C (HCV) virus both of which can lead to chronic hepatitis, cirrhosis, hepatocellular carcinoma even death.[1,2,3] Hepatitis-A (HAV) and Hepatitis-E (HEV) virus infection are also significant causes of morbidity and mortality in some areas of the world. Only a few limited information is available on the viral interaction or co-infection or super-infection among the HBV, HDV, HCV, HEV and HAV. Hepatitis-B infection is endemic in Africa and Asia; transmitted vertically from mother to newborn or horizontally between close contacts in the early childhood.[4,5,6] Patients with chronic hepatitis-B are at higher risk of progressive liver disease.[7]

Case data

A 26 years young adult unmarried male student who is non-alcoholic, non-smoker and non-diabetic presented on the 12th May/2001 with one and half month complaints of nausea, vomiting, mild pain epigastrium, weakness, fatiguability and jaundice. No history of fever, itching or GI bleeding. He had a history of jaundice followed by development of ascites likely to be sub-acute hepatic failure (SHF) due to HBV in May, 1993 for which he was admitted in P.G. hospital for about a month and received supportive treatment with clinical recovery. No past history of blood transfusion, intravenous drug abuse, sexual exposure or homosexuality or any surgical intervention. Physical examination revealed presence of deep jaundice with palmer erythema but no spider, gynaecomastia or testicular atrophy. Abdomen was not distended, no engorged vein, umbilicus centrally placed and inverted. Liver was 1.5 cm enlarged from RCM along MCL, firm, mild tender, smooth with no bruit. No splenomegaly or clinical ascites. Other system revealed no abnormalities. Laboratory data showed hemoglobin- 15gm/dl; ESR-05mm in 1st hour; TC of WBC-6x 10^9/L with polymorphs-54%, lymphocyte-36%, eosinophil-6%. Serum bilirubin was raised-lowest l0mg/dl and highest 26mg/dl; serum ALT level ranges from 211 - 2000 U/L, and ALP within normal range. Serum total protein was normal (74-87gm/L) but there was hypoalbuminemia (20-31gm/dl) with coagulopathy (prothrombin time ranged from 16.8-23.7 seconds, control-11.9 seconds). Blood electrolytes were within the normal limit. Serological study showed seropositivity for HBsAg, HBeAg, anti-HCV and IgM anti-HEV but negative for anti-HDV. USG of whole abdomen revealed mild hepatomegaly with a coarse hepatic echotexure with mild ascites suggestive of CLD. Endoscopy of upper GI tract was normal; no varix seen.

Discussion

HBV and HCV are the commonest causes of chronic liver disease throughout the world .HBV has a worldwide distribution. About 30% of the world population have serological evidences of HBV infection.[1] The World Health Organization (WHO) reported that about 350 million people in the world are HBV carriers of which about 40 million are in South East Asia countries specially China and Taiwan.[8] Approximately 1.5 million people die per year due to HBV related liver diseases. The WHO estimated that about 170 million people in the world are infected with HCV.[9] HBV, HDV and HCV share common transmission routes and therefore may be diagnosed in the same patient at the same time or at different time and in different combinations. However, till date only a few limited data are available on the super-infection, co-infection or interactions among the different hepatitis viruses including HBV, HDV, HCV, HAV and HEV.

Intravenous drug abuse is a major risk factor for HCV infection with anti-HCV positivity in 50-100% of such peoples. Co-infection of HCV with HBV is common particularly among the drug abusers. HCV can also be detected in>10% of the patients with chronic hepatitis-B or HIV infection[10]; Sub-clinical infection is the rule and only 10% of patients present as acute illness with jaundice. HCV rarely causes fulminant hepatitis[11,12] but about 90% progress to chronic liver disease.[9] In dual infection detection of both HBV and

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HCV in the serum is very unusual possibly because of an inhibitory effect of HCV on HBV replication.

HDV infection can only occur in presence of HBV either as co-infection or super-infection. Peoples who are immunized to HBV are likely to be protected from HDV infection. Co-infection of HDV occurs in 10% of the HBV carriers but recovery is usual and only 2-7% of the infected people develop persistent infection with both the virus. Super-infection may lead to severe hepatitis with acute liver failure (FHF) in 10-20% of cases.[13] Concurrent HCV, HBV and HDV infection may increase the risk of severe hepatitis, fulminant hepatic failure and HCC.[14]

The reported patient presented with a history suggestive of SHF due to HBV infection in 1993 and 1.5 month complaints of nausea, vomiting, mild pain abdomen, weakness, tiredness and clinical evidences of deep jaundice, palmer erythema, firm, tender hepatomegaly but no splenomegaly, palpable GB or ascites. Investigation showed a high level of serum bilirubin (10-26mg/dl), ALT (211-2000U/L) with normal ALP level, marked hypoalbuminaemia (20-31gm/L), gross coagulopathy (16.8-23.7 VS control-11.9 seconds) and Ultrasonographic evidences of coarse hepatic echotexure with ascites. All these are highly suggestive of advanced liver disease with severe liver damage and hepatic decompensation. Sero-positivity for HBsAg since May, 1993 with currently positive HBeAg, anti-HCV and IgM anti-HEV but negative anti-HDV are highly suggestive of CLD due to HBV with activity with HEV super-infection and super (most likely) or co-infection of HCV. As deep jaundice is very unusual in chronic hepatitis-B in the phase of viral replication and sub-clinical infection is usual in case of HCV, such a deep jaundice is very likely to be due to HEV super-infection .Recovery after HDV co-infection is usual so serological diagnosis of HDV co- infection is often very difficult and this may be is the likely explanation of the negative anti-HDV result .Because of lack of laboratory facilities PCR testing for HBV-DNA,HCV-RNA and HDV-RNA could not be done .As the patient recently developed jaundice with positive IgM anti-HEV and acute HAV infection is very unusual in adults test for IgM anti-HAV was not done.

Considering all the clinical, laboratory data and in view of 9 years long history of HBsAg positivity with recent seropositivity for HBeAg, IgM anti-HEV,anti-HCV and negative anti-HDV the case was categorized as chronic active hepatitis-B with super-infection of HEV and HCV.

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CHYLOUS ASCITES: A RARE PRESENTATION OF PERITONEAL TUBERCULOSIS - A CASE REPORT AND REVIEW OF CHYLOUS ASCITES

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Introduction

Chylous ascites is unusual and often a manifestation of an underlying disease process. Here we report a case of peritoneal tuberculosis who presented with chylous ascites. Chylous ascites due to its rarity poses a great difficulty in the diagnosis of peritoneal tuberculosis.

Case Report

A 52 years old lady presented with 3 weeks history of fever, abdominal discomfort and distension as well as anorexia. She had history of contact with tuberculosis, her husband had suffered from pulmonary tuberculosis 1 year back. She had been investigated at local clinic but no diagnosis was determined. On examination, there was only ascites without stigmata of cirrhosis, organomegaly or any abdominal mass. Routine blood investigations revealed the haemoglobin 10 gm/dl, erythrocyte sedimentation rate 60 mm in 1st hour, complete blood count within normal limit, peripheral blood film showed non specific morphology. Her chest X-ray was normal. Liver function tests and serum urea, creatinine were normal. Viral markers HBsAg and Anti HCV were negative. She had normal upper gastrointestinal tract at endoscopy. FCT and ICT for filarial antigen both were negative.

Her tuberculin skin test was 10 mm. Ultrasonogram and CT scan of whole abdomen both showed the presence of ascites, no other abnormality (Fig. 1).

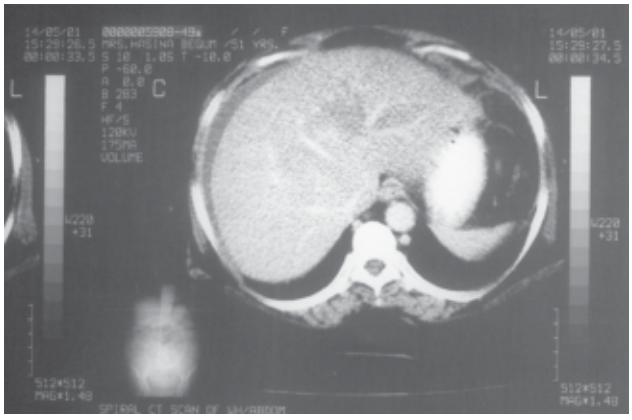

Fig.-1 : CT scan of upper abdomen showing ascites

Diagnostic aspiration of ascitic fluid was done. It was milky white, exudative, total leukocyte count was 1100/cumm, mostly lymphocyte 90%, polymorphs were 7%, no malignant cells were found, AFB was not detected. Triglycerride level of ascitic fluid was 1400 mg/dl, her serum triglyceride level was 79 mg/dl.

At laparoscopy, the peritoneal surface was studded with white nodules and peritoneal cavity was full of the some milky fluid. Histology of the peritoneal nodule revealed chronic granulomatous inflammation consistent with tuberculosis (Fig. 2). Treatment with anti-tuberculous drugs led to an uneventful and complete recovery.

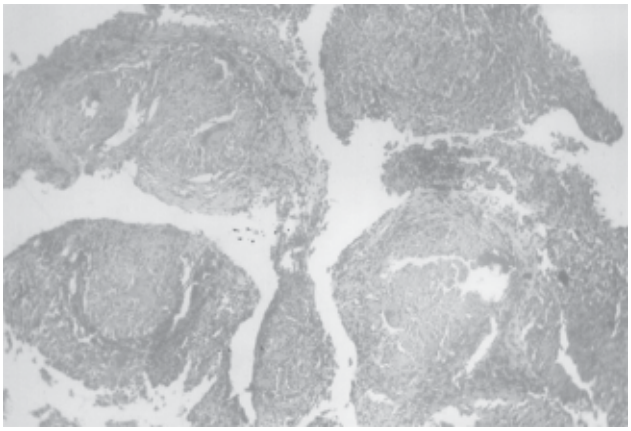

Fig.-2 : *Histopathology of biopsy showing tuberculous granuloma*

Discussion

It is important to emphasize that all cloudy or milky fluids aspirated from the peritoneal cavity are not chyle. True chyle must be differentiated from pus, chyliform ascitic fluid and pseudochyle. The accumulation of lipid-rich lymph in the peritoneal cavity is termed chylous ascites. The diagnosis of chylous ascites is made by analysis of ascitic fluid. The chemical composition of chyle is quite specific. No peritoneal fluid other than chyle has fat content greater than plasma (0.04% - 4%). The triglyceride level in the fluid is often more than 1000 mg/dl always exceeds the plasma level[1]. Albumin and globulin levels are lower than the blood. Chyle seperates into three layers on standing, an upper creamy layer, a dividing watery layer, and a lower colorless opaque layer. Such a fluid has alkaline reaction and stains positive for fat (Sudan III). A turbid fluid due to leukocytes or tumour cells may be confused with chylous fluid (pseudochylous) and it is often helpful to carry out alkalization and ether extraction of the specimen. Alkali will tend to

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dissolve cellular proteins and thereby reduce turbidity, ether extraction will lead to clearing if the turbidity of the fluid is due to lipid. Our patient's fluid was chylous, seperated into three layers on standing and triglyceride content was 1400 mg/dl.

Factors producing chylous effusions can be intrinsic or extrensic mechanical obstruction or injury to cisterna chyli. The possible causes of the ascites vary, depending on the age of the patient and the acuteness of the onset of the illness. In children, upto 60% of cases are associated with a congenital lymphatic anomaly such as lymphocele, lymphangiectasia, or lymphatic atresia. The most common cause in adult is cancer, which is present in 87% of patients[1]. Particularly, intra-abdominal lymphoma that accounts for over half of cases of chylous ascites in adults and disseminated carcinomas from primaries in the pancreas, breast, colon, prostate, ovary, testes and kidney. Inflammatory conditions that involve the lymphatics such as tuberculosis, pancreatitis, portal vein thrombosis and mesenteric adenitis can infrequently be associated with chylous ascites as it was happened to our case. In traumati1c cases, there is peritoneal leak of chyle due to blunt trauma to abdomen, causing laceration or bursting of cisterna chyli. Trauma forms 10-15% of cases, and the most common site is the base of the mesentry. Trauma does not necessarily have to be violent to produce chylous leakage. Even minor trauma, such as severe coughing or attempts at resuscitation may result in injury to delicate lymph channels. Postoperative chylous ascites occurs rarely. The surgical procedures most frequently associated with chylous ascites are repair of abdominal aortic aneurysm, retroperitoneal lymphnode dissection and during creation of a portacaval shunt. The incidence of spontaneous chylous ascites in chronic liver disease is estimated to be 0.5%. The lymphatics rupture, embolic occlusion of subclavian vessels, nephritis, filariasis, bilharziasis and thoracic duct obstruction by aneurysm are other conditions have been reported to be associated with chylous effusion. In some patients no aetiology could be determined.

Once chylous ascites has been documented, should be investigated according to the high index of suspicion of underlying disease. CT scan of abdomen, lymphangiography, lymphnode biopsy, barium studies of gastrointestinal tract, bone marrow examination, exploratory laparotomy all are recommended to find out the underlying cause of chylous ascites. Our patient gave history of anorexia, fever, contact with tuberculosis in addition to ascites. We looked for direct or indirect evidence of tuberculosis. Her erythrocyte sedimentation rate was high from the beginning of her illness, 60 mm in 1st hour. Chest X-ray was normal, tuberculin test was 10 mm, ascitic fluid was exudative but no AFB was found, ultrasonogram and CT scan showed only the presence of ascites. Later on she had laparoscopic peritoneal biopsy which revealed chronic granulomatous inflammation consistent with tuberculosis.

Tuberculous peritonitis is not uncommon. Half of them may have underlying cirrhosis. Despite a high index of suspicion, peritoneal tuberculosis can be difficult to diagnose. Clinical features include fever, anorexia, abdominal tenderness. Eighty percent of patients will present with abdominal swelling and have clinically apparent ascites, while 97% will have ascites documented by ultrasound or laparoscopy. Examination of ascitic fluid from peritoneal tap can be diagnostic if acid fast bacilli are visualized or cultured. AFB smears are positive on ascitic fluid in 5% of patients, and cultures are positive in 20%. Findings of a straw colored exudate with protein concentration of 25 g/L and lymphocyte count of >1000 cells/mm.^{3} are non specific but suggestive of tuberculosis. Chest X-rays are abnormal in about half of patients but active pulmonary tuberculosis is evident in only 14%, skin tests are positive in 70%. Laparoscopy with biopsy remains gold standard in diagnosis of peritoneal tuberculosis, with reported sensitivity of 100% and a low complication rate[2,3]. The peritoneum has typical 'millet seed' and 'violin string' appearance at laparoscopy. Scattered whitish nodules (<5 mm) over the visceral and parietal peritoneum and adhesion between adjacent organs are found. The appearance is characteristics, although carcinomatosis peritonei, milliary crohn's disease are other possible considerations, histological confirmation and response to therapy led to a conclusive diagnosis. Abdominal CT scans are often non specific. Reported abnormalities on CT include ascites, adenopathy and omental and mesenteric thickening[4].

Because chylous ascitcs is a manifestation rather than a disease by itself, the prognosis depend on the treatment of the underlying disease or cause. Supportive measures can relieve the symptoms. These include repeated paracentesis, diuretic therapy, salt and water restriction, and dietary measures. A low fat diet with medium chain triglycerride supplementation can reduce the flow of chyle into the lymphatics. Total parenteral nutrition can be used as a means of achieving complete bowel rest might allow resolution of chylous ascites. This form of therapy is particularly useful in post-traumatic, post-surgical and in some form of congenital ascites. Laparotomy and ligation of the leaking lymphatics, resection of the leaking small bowel segment, and removal of an obstructing tumour have all been attempted with varying degrees of success. Transient success has also been achieved with peritoneovenous shunting.

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ASSOCIATION OF HELICOBACTER PYLORI WITH GASTRIC CANCER, GASTRITIS AND INTESTINAL METAPLASIA

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Abstract

There is strong evidence that H. Pylori causes chronic atrophic gastritis and intestinal metaplasia the precursor lesion for gastric cancer. Gastric cancers are not uncommon in our clinical practice. H. Pylori infection is universal in our population. In this background this study was undertaken to find out the prevalence of H. Pylori infection, gastritis and intestinal metalpfasia in gastric cancer subjects and to compare with a group of control subjects of nonulcer dyspepsia. We also looked for the difference between H. Pylori infection, gastritis, intestinal metaplasia with different histological types of gastric cancer.

A total of ninty seven persons were selected consecutively from the endoscopic clinic B.S.M.M.U. (then IPGMR).Thirty nine gastric cancer patients were diagnosed by endoscopy and histology. Forty controls were selected from subjects of nonulcer dyspepsia. Three to five biopsies were collected from non-necrosed parts of the cancer. Two paired biopsies from a non-cancerous part were also taken. For control subjects two paired biopsies were collected from the antrum and body. One piece of each pair was placed in the urea agar media of CLO test. Other pieces were used for histological examination.

Overall prevalence of H. Pylori was found to be 71.8% (28 among 39) in gastric cancer subjects. It was found to be highly significant (P<0.001). Out of 39 gastric cancer subjects. gastritis, atrophy and intestinal metaplasia were present in 31, 16 and 12 subjects respectively. Association of these pre-neoplastic conditions were statistically significant with gastric cancer subjects.

From this study, it can be concluded that H. Pylori is significantly associated with gastric cancer, its various subtypes and.preneoplastic conditions.

Introduction

Gastric cancer is estimated to be the World's second common cancer and is responsible for approximately 650,000 deaths globally each year[1]. There is a wide variation in the prevalence of gastric cancer throughout the world. It is the commonest cause of cancer related death in Japan and uncommon cause in Srilanka[2]. It is also a major 'problem in India[3]. Although gastric cancer rates are falling in the Western countries, the absolute number of diagnosis and death are likely to increase as a result of changing age structure and improved life expectancy. Because of its dramatic change in incidence from place to place and generation to generation, it has been hypothesized that incidence of gastric cancer is determined by environmental factors. Until recently, research on environmental causes of gastric carcinoma focused primarily on diet[2]. The International Agency for research on cancer (IRAC), sponsored by the World Health Organization in 1994 has categorized Helicobacter pylori (H. pylori) infection as a class l carcinogen and a definite cause of human gastric cancer[4].

In a seroepidemiological survey, the prevalence of H. pylori infection has been reported to be 91% in healthy young adults in Bangladesh[5]. The point prevalence of peptic ulcer disease is about 15% and its association with H.pylori is more than 90% (unpublished data). It is likely that the prevalence of gastric cancer may be high in Bangladesh. In 1996; a total 107 cases of gastric cancer out of 2403 all cancer patients were registered in National Cancer Institute of Bangladesh (personal communication) suggesting that gastric cancer is a common cancer. This study was undertaken to find out the prevalence of H.pylori infection, gastritis and intestinal metaplasia in gastric cancer subjects and to compare them with a group of control subjects of non-ulcer dyspepsia. We also looked for the difference between H. pylori infection, gastritis and intestinal metaplasia with different histological types of gastric cancer.

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Materials and methods

This study was carried out in the department of Gastroenterology, Bangabandhu Sheikh Mujib Medical University (former IPGM&R) Dhaka, Bangladesh from July 1994 to July 1996.

Thirty nine endoscopically and histologically proven cases gastric cancer patients were included in this study. Forty subjects having dyspepsia like symptoms with endoscopically normal gastro duodenal mucosa were included as controls. After selection of patients and controls, informed consent was taken for this study. Three to five biopsies were collected from the non-necrosed region of cancer. Two paired biopsies from noncancerous part preferably antrum, body or body and fundus were taken. For control population having normal gastroduodenal mucosa at endoscopy, two paired biopsies were collected from antrum and body of the stomach. One piece of each paired specimen was placed in the urea-agar media for rapid urease test for detection of H.pylori. Histological slides were made from formalin preserved specimens. Sections were stained with H&E, Alcian-blue, periodic-acid Schiff and modified Giemsa for assessment of tumor type, the presence and degree of gastritis, intestinal metaplasia and H.pylori infection. Data collected were analyzed and significance of difference was determined by using Chi-square test.

Results

Mean ages of cancer and control subjects were 51.05 ± 14.98 and 50.42 ± 15.50 years respectively with male to female ratio of 2.9:1 and 3:1 respectively.

H. pylori were detected in 28 (71.8%) patients among 39 cancer and eight (20%) persons among 40 control subjects. This difference was significant (P<0.001). Out of 23 intestinal type of gastric cancer, H. pylori were found positive in 20 (86.96%) cases. Whereas, six out of 12 diffuse type of gastric cancer had H.pylori infection. Poorly differentiated type of gastric cancer were four in number and H. pylori were positive in two cases (Table-I).

Among the 79 study subjects, a total of 36 subjects were H. pylori positive, of which gastritis, atrophy, intestinal metaplasia were found in 31, 16, 12 subjects respectively. (P<0.01) (Table-II).

Gastritis (chronic active gastritis or chronic superficial gastritis) were present in 33 cancer subjects and 18 control subjects. Atrophic gastritis and intestinal metaplasia were present in 16 and 12 cancer subjects respectively. On the otherhand, in control subjects they were four and three in number. Association of these pre-neoplastic conditions was statistically significant with gastric cancer. When intestinal and diffuse type of cancer were considered separately, it was seen that atrophy was significantly associated with these two types of cancer. Where as only in intestinal type of gastric cancer, intestinal metaplasia showed significant association.

Table-I

Presence of H. pylori in different histologic types of gastric cancer.

Subjects	Total No.	H. pylori Positive No. (%)	Negative No. (%)	P value
Gastric cancer	39	28 (71.80)	11 (28.20)	<0.001
IGCA	23	20 (86.96)	3 (13.04)	0.001
DGCA	12	6	6	0.05
PD	4	2	2	NS
Control	40	8 (20.00)	32 (80.00)	

IGCA = Intestinal gastric carcinoma
DGCA = Diffuse gastric carcinoma
PD = Poorly differentiated
NS = Not significant.

Table-II

Association of gastritis, atrophy and intestinal metaplasia with H. pylori.

H. pylori	Total	Gastritis	Atrophy	Intestinal metaplasia
Positive	36	31	16	12
Negative	43	20	4	3

Table-III

Association of gastritis atrophy and intestinal metaplasia with cancer and control.

Subjects	Total number	Gastritis No. (%)	Atrophy No. (%)	Intestinal metaplasia No. (%)
Cancer	39	33 (84.61)	16 (41.02)	12 (30.77)
IGCA	23	23 (100.0)	10 (43.48)	12 (52.17)
DGCA	12	8 (66.67)	5 (41.66)	0
PD	4	2	1	0
Control	40	18 (44.00)	4 (10.00)	3 (7.50)

Discussion

Gastric cancer is estimated to be the world's second most common cancer. Although there has been a dramatic decline in the incidence of gastric cancer in the United States and Western Europe over the past fifty years, but that on Latin America and Asia still remains very high[1].

Because the incidence of gastric cancer can change dramatically from place to place and from one generation to the next, it was hypothesized that its incidence was determined largely by environmental factors rather than genetic factor. From studies of migrants, it has further been -inferred that the risk is increased by exposure to environmental factors in childhood. Until recently, research on environmental causes of gastric cancer focused primarily on diet. The recent identification of H. pylori in chronic inflammatory condition of the stomach, has, however stimulated interest in its potential role in carcinogenesis[2]. The evidence that H.pylori causes gastritis in human comes from both primary and secondary observations. The most important primary observations are human volunteers and animal model studies and the treatment Studies with antimicrobial agents. Now it can be concluded that H. pylori is definite pathogen for human beings[7].

H. pylori associated gastritis is of the superficial type at the beginning but may progressively change to chronic atrophic. When chronic atrophic gastritis becomes severe and extensive, hypochlorhydria ensues. Hypochlorhydria favours bacterial overgrowth. This causes nitrosation with dietary amines. N-nitroso compounds by their mutagenic properties probably induce preneoplastic conditions like intestinal metaplasia and dysplasia. They ultimately transform into neoplasia[8]. During this process, a series of alteration occurs. They include increase of reactive oxygen species, the reduction of antioxidant substances, the alteration of the balance between antiinflamatory and proinflamatory cytokines and the alteration of the cellular hyperproliferation/ apoptosis[9].

The International Agency for research on cancer (IARC), sponsored by the World Health Organization in 1994 has categorized H. pylori infection as Class I, carcinogen and a definite cause of human gastric cancer[4]. This decision was largely based on epidemiological features of gastric cancer paralleling with H. pylori infection as in Peru. Mexico and Colombia, a sixfold increased risk gastric malignancy of H.pylori infected population and cross-sectional studies showing high seropositivity of H.pylori in gastric cancer patients[10-12].

Gastric cancer precursors, such as gastritis, atrophy and intestinal metaplasia have significant association with H.pylori infection in countries with high prevalence of H.pylori infections and gastric cancer. According to Sipponen's hypothesis : (i) H.pylori is the single agent in more than 86 percent cases with chronic gastritis; (ii) H.pylori positive gastritis will develop into mucosal atrophy and intestinal metaplasia; (iii) risk of gastric cancer is known to be high in people with chronic gastritis[13].

However there are places where the prevalence of H.pylori infection has been shown to be high but there is low incidence of gastric cancer as for example Africa[14]. Such findings do not necessarily negate the role of H. pylori in gastric cancer subject but suggest that, in some countries, necessary additional factors that play a role on gastric carcinogenesis.

In a developing country like Bangladesh, overcrowding, bad sanitation and unhygienic practices favour high prevalence on H. pylori in the population. Children become infected universally during their first few months of life. In a recent sero-epidemiological survey, the prevalence of H. pylori has been reported to be 91.4 percent in health young adults.[5]

The association of H. pylori with gastric cancer study will help us to take a strategy for the management of

H. pylori disease, like gastritis, pre-neoplastic conditions and gastric cancer. It was observed that H. pylori associated gastritis, intestinal metaplasia ware reversed to some extent by anti-helicobacter pylori therapy. [16]

Studies of the prevalence of H. pylori infection in gastric cancer have been conducted in several countries and produced widely varying results ranging from 60-100%. Our study was one of the cross sectional studies carried out in Bangladesh. We have found a prevalence of 72% with no significant difference between the two main histological subtypes of gastric cancer.

In addition we detected a significant association of H. pylori infection with gastritis, atrophy and intestinal metaplasia.

Both H. pylori and gastritis, therefore, occur commonly in association with gastric cancer. However if H. pylori is indeed causally related to atrophic gastritis, intestinal type cancer sequence, we would expect a close association between intestinal type of gastric cancer rather than diffuse type. In our study H. pylori were found in both types. H. pylori is commonly associated with intestinal type. The association with diffuse type is not universal. But the studies done by Wee in 1992 in Singapore, by Clarkson and West in 1993 in U.K. and by Hu et al in 1994 in China showed similar results.[16,17]

Gastritis is a common background for gastric cancer. The pathogenesis of diffuse type of gastric cancer is promoted by a non-atrophic and non metaplastic stomach. Sipponen suggests that if initiation occurs earlier during a non-atrophic stage, diffuse type of gastric cancer Occurs whereas if initiation occurs later, then intestinal type of gastric cancer develops. Substantiation of the link between H. pylori and both Lauren's type of gastric cancer give weight to Sipponen's hypothesis.[13]

Gastric cancer remains a major killer worldwide. This study suggests stronger association of H. pylori with gastric cancer (near about 72 percent). H. pylori infection can readily be diagnosed and eradicated. Eradication of H. pylori infection may decrease the risk of gastric cancer.

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ANALYSIS OF MORPHOLOGY OF LESIONS AMONG STABLE ANGINA PATIENTS

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Abstract

A total of sixty six male patients of stable angina pectoris with positive stress test underwent coronary angiography to analyze their coronary lesion morphology. The mean age of the patients were 51.5±10.48 years. 82% of the patients had one or more major risk factors. Angiographically 6.06% of the patients had normal coronaries, 28.78% cases had single-vessel disease and nearly two-thirds (65.15%) of the cases had multi-vessel disease. Total occlusive disease was observed in one-tenth (9.81 %) of the patients. The number of significant lesions in all the cases was 158. Morphologically 51.26% of the lesions were concentric and 31.02% were eccentric. 7.60% of the lesions were multiple-irregularities in type. No significant difference was observed in prevalence of concentric and eccentric lesions among diabetic ($p>0.05$) and dyslipidaemic ($p>0.05$) patients. Significantly higher percentage of concentric lesions was observed among the smokers ($p<0.001$) and hypertensive ($p<0.01$) patients. To conclude, nearly half of the lesions (44.93%) in stable angina pectoris were difficult (eccentric, multiple irregularities and total occlusion) for mechanical interventions that had no relation with major risk factors.

Introduction

As antheromatous coronary stenosis become more severe it encroaches on the coronary flows reserve in that myocardial segment. Eventually there will be little reserve. The patient may then experience angina through minimal effort[1-5]. The coronary lesions are often complex, with markedly distorted eccentric luminal shapes. An eccentric lesions is a narrowing whose lumen to centerline ratio is >0.7[6]. These complex lesions may exaggerate luminal eccentricity by fracturing or dissecting ateroma[7-9] following mechanical interventions if not stented. Stable angina pectoris has fixed lesions and may have either form of morphology (concentric, eccentric, multiple irregularities or total occlusion) that is prerequisite for planning selection of mechanical interventions. This study was undertaken to analyze the of lesions among sixty six Bangladeshi patients with stable angina pectoris.

Materials & methods

This study was undertaken in the department of cardiology in National Institute of Cardiovascular Diseases, Dhaka during the period of July 2000 to June 2001. Patients having typical effort angina with positive stress test had to undergo coronary angiography. Significant coronary artery disease was defined by presence of 50% or more luminal diameter stenosis of at least one major epicardial coronary artery. Severity of coronary artery disease was classified by number (one to three) of diseased vessels. Significant left main disease was considered equivalent to two-vessel disease. Lesion morphologies were defined as: concentric-symmetric narrowing of coronary artery; eccentric- asymmetric narrowing of coronary artery; multiple irregularities- three or more serial and severe (>50%) closely spaced obstructions in a coronary artery; and total occlusion[10].

Statistical Analysis

Mean±SD values were calculated for continuous variables and relative frequencies were calculated for discrete variables. Student's t test was used to compare continuous variables and Z test was used to compare discrete variables. All variables that achieved a statistical significance of $P<0.05$ were considered significant.

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Results

A total of sixty six patients were included in this study and underwent coronary angiography (CAG). All patients were male. The mean age of the patients were 51.5±10.48 years. 82% of the patients had one or more major risk factors. The prevalence of risk factors is listed in table-1. All the patients were symptomatic with stable angina. All of them were treated with aspirin 75 mg orally along with other anti-anginal therapy. 12 out of 66 patients received lipid lowering drugs prior to their CAG.

6.06% of the patients had normal coronaries and 28.78% had single-vessel disease. Nearly two-thirds (65.15%) of the patients had multi-vessel disease (table 2). One-tenth (9.81 %) of the patients had total occlusive lesions. Lesions morphologies were analyzed. 51.26% of the lesions were concentric and 31.01% were eccentric. 10.10% of the lesions were totally occlusive and 7.60% of lesions were multiple-irregularities in type. The details of lesion morphologies are tabulated in table 3. Smokers ($p<0.001$) and hypertensive ($p<0.01$) patients had significantly higher percentage of concentric lesions. On the other hand diabetic and dyslipidaemic patients had concentric and eccentric lesions almost in equal percentage ($p>0.05$).

Table-I

Prevalence of risk factors (N=66)

Risk factors	No
Smoking	34 (51.51)
Hypertension	29 (43.93)
Diabetes mellitus	23 (34.84)
Dyslip idaemia	22 (33.33)
Family history	15 (22.72)

Table-II

CAG findings (N=66)

Diseased vessel	No.
Zero	4 (6.06)
Single	19 (28.78)
Double	16 (24.24)
Triple	27 (40.91)

Table-III

Type of lesions (n=158)

Lesions type	No. of lesions
Concentric	81 51.28
Eccentric	49 31.02
Multiple irregularities	12 7.60
Total occlusions	16 10.10

Table -IV

Comparison of the lesion morphology (N=129)

Risk factors	Total no. of Lesions No (%)	Eccentric No (%)	Concentric No (%)	P value
Smoking	45	12 (26.67)	33(73.33)	<0.001
Hypertension	30	10 (33.34)	20 (66.66)	<0.01
Diabetes mellitus	31	15 (48.38)	16 (51.61)	>0.05
Dyslipidaemia	16	8 (50.00)	8 (50.00)	>0.05
Family history	7	4 (57.14)	3 (42.86)	>0.05
Total	129	49(100)	80 (100)	

Discussion

Coronary arteriography typically displays eccentric stenosis with scalloped or overhanging edges more frequently in patients with unstable angina than in patients with chronic stable angina[11]. In contrast, lesions with concentric symmetrical narrowing or asymmetrical narrowing with smooth borders and a broad neck are more common in patients with stable angina[11]. Eccentric lesions with a narrow neck due to one or more overhanging edges or irregular scalloped borders or both are the most common morphological features of disease progression. This finding may represent either a disrupted atherosclerotic plaque, a partially lysed thrombus or the combination[12].

The vulnerability and thrombogenicity of atherosclerotic plaques rather than their obstructive capability (stenosis severity), together with the status of collateral circulation, have emerged as the most important determinants for the occurrence, type, and outcome of acute coronary syndromes. The great majority of heart attacks originate from

atherosclerotic lesions that, prior to the acute events, only were mild to moderately stenotic, that is they were haemodynamically insignificant and probably asymptomatic.

Coronary artery disease is a progressive disease. Spontaneous symptomatic improvement due to development of collaterals can occur over periods of time[13-21]. Retardation of disease process has been claimed by some authors by extensive medical therapy including lipid lowering drugs[22-29]. However the disease is multifactorial. Since 1984, the objective of a large number of clinical trials had been to investigate coronary lumen morphology by angiography and the changes induced by long term cholesterol lowering drugs. Over the periods of time, the lesion morphology may undergo changes not only by increasing its stenosis severity but also by changing its shape. Shape of the lesions, concentric or eccentric, has been considered as one of the most important determinant for selection of interventional procedures as well as immediate and long term outcome of the procedures. In consistent with the literature reviewed, morphology of just more than half of the lesions (55.07%) in this series of stable angina pectoris were concentric.

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COMBINATION CHEMOTHERAPY FOR REMISSION INDUCTION OF ACUTE LYMPHOBLASTIC LEUKAEMIA

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Abstract

Combination chemotherapy for remission induction of acute lymphoblastic leukaemia is superior to the sequential administration of single agents for increased rate of remission, prolonging duration of remission and overcoming drug resistance. Vincristine and prednisolone are basic drugs for induction therapy of ALL. But addition of an anthracycline standardizes this induction regimen. L-asparaginase intensifies cyclophosphamide, systemic methotrexate or cytarabine as fourth drug in tensifies the induction therapy and eradicates blasts resistant to standard agents.[19,20] In this study 30 newly diagnosed ALL patients were enrolled and the median age was 14.5 years. 22 patients were male and 8 patients female. For remission induction one patient was treated with vincristine and prednisolone, 3 patients with vincristine, prednisolone and daunorubicin and the remaining 26 patients with vincristine, prednisolone, anthracycline and a fourth drug. An overall remission rate is 90 %. 5 patients (16.6%) needed one cycle (4 weeks), 17 patients (56.6%) 2 cycles and 5 patients (16.6%) 3 cycles of combination chemotherapy to obtain remission. 3 patients (10%) failed to go into remission after 12 weeks of therapy. Among 27 patients those obtained complete remission 7 patients suffered a relapse of their leukaemia during maintenance therapy. 17 patients continue event free survival (EFS) and are on maintenance therapy. 2 patients did not communicate after complete remission and one patient died in first remission due to acute Hepatic failure.

Introduction

The understanding and treatment of acute lymphoblastic leukaemia is one of the undisputed successes of modern clinical haematology. ALL is now recognised as a heterogeneous malignant disorder of lymphoid stem cells with different subtypes those respond differently to treatment.[1] The development of effective combination chemotherapy, the introduction of prophylactic treatment for CNS leukaemia and recently more aggressive strategies involving the earlier use of intensive induction therapy are among the reasons for this success.[2] Improvement in anti-microbial therapy and advances in intensive care are contributed to more favourable outcomes by decreasing the number of mortality due to infections and toxicities of drugs and by shortening interruptions of chemotherapy.[3] Combinations of chemotherapeutic agents are used to reduce the initial blast cell burden to a low level in the induction therapy and to suppress or eradicate residual leukaemic cells during the period of continuation therapy.[4] The intention of induction therapy is to destroy as many leukaemic cells as possible as quickly as possible. Blasts in ALL are selectively responsive to several agents like, prednisolone, vincristine, L-asparaginase and methotrexate. Thus, long term remissions can be achieved in ALL without the necessity of inflicting severe generalized marrow hypoplasia.[5] Evalution of complete haematological remission by physical examination and peripheral blood and bone marrow studies is a euphemism since many leukaemic cells may still haunt the marrow sinuses and are prepared to spring back unless repeated reductions by maintenance therapy are implemented.[5]

Preferred combinations of therapeutic agents include drugs that are selectively cytolytic for leukaemic cells, cell cycle non-specific in mechanism of action and relatively non-toxic for normal marrow elements.[5] The main purpose of this study is to evaluate the rate of complete remission as well as duration of remission with the combination chemotherapy for remission induction of ALL patients. The results of the treatment of thirty ALL Patients are reported here.

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Materials and Methods

Thirty newly diagnosed previously untreated ALL patients aged 3 years and above (upto 26yrs.) were enrolled into this study. These patients were treated at Haematology Department, BSMMU from April 1996 to December 1998. For remission induction 1 or 2 or 3 cycles (1 cycle = 28 days) of therapy were used. Drugs used for remission induction included vincristine 1.4 mg/m^2 (maximum 2 mg) i.v. days 1, 8, 15, 22; prednisolone 40 mg/m^2 daily p.o. days 1 - 28; daunorubicin 45 mg/m^2 i.v. days 1, 2 or doxorubicin 40 mg/m^2 i.v. day1; cyclophosphamide 600 mg/m^2 i.v day 1 or 15 or L-asparaginase 6000 IU/m^2 i.v last 10 days of the 28 days cycle or systemic methotrexate 15 mg/m^2 i.v. days 2 and 10. Bone marrow examination was carried out at diagnosis, at the end of 4 weeks, 8 weeks and 12 weeks. Marrow cellularity and marrow differential were evaluated to announce complete or partial remission. Physical findings and peripheral blood were also evaluated. The patient had M1 marrow (0 - 5 % blast cells; >15 % erythroid; >25 % Myeloid), hyper cellular or normocellular marrow, H1 peripheral blood (Hb $\geq$11 gm/dl; N $\geq$ 2500/cumm; PC $\geq$ 100,000/cumm; blast - 0%) and P1 physical findings (Liver - normal size; spleen and lymph nodes - normal size; leukaemic infiltrates, haemorrhage or infection - absent) to confirm complete remission. After remission intensification was done with new drugs cytarabine 100 mg/m^2 i.v. days 1 - 5 or etoposide 100 mg/m^2 i.v. days 1 - 5 in addition to drugs used during induction. Intrathecal methotrexate 1.0 mg/m^2 once weekly 6 doses were given during induction therapy. Cranial irradiation was completed at Radiotherapy deptt., DMCH after intensification.

Following induction, CNS prophylaxis and intensification all patients were to receive identical maintenance therapy. This consisted of vincristine i.v. 1.4 mg/m^2 every 4 weeks interval, prednisolone 40 mg/m2 p.o. for 5 days at the beginning of each cycle, methotrexate 20 mg/ m^2 orally once weekly and 6-mercaptopurine 75 mg/m^2 daily orally. Doses were adjusted to maintain WBC > 1.0 x 10^9/L and platelets > 100 x 10^9/L. If remission was not obtained by 12 weeks induction therapy those cases were announced as resistant ALL. Their treatment was continued as palliative maintenance therapy.

Results

Between April 1996 and September 1998, thirty Patients were enrolled and follow-up was till the end of December 1998. Distribution of patients by features at diagnosis is shown in the following tables.

The diagnosis was based on morphologic evaluation of leishman's stained blood film and smears of bone marrow and five ALL L2 cases needed cytochemistry i.e. positive staining for periodic acid schiff and negative staining for myeloperoxidase. The immunologic and cytogenetic features of acute lymphoblastic leukaemia did not evaluated since these facilities were not available. Thirty patients were treated initially with remission induction therepy. Among them three patients failed to go into remission after 12 weeks (3 cycles) of therapy. 5 patients achieved remission after 4 weeks of chemotherapy and 17 patients achieved remission after 8 weeks of therapy. 5 patients needed 12 weeks for remission.

Table-I

Distribution of Patients by clinical presentations at diagnosis.

		No. of patients	Percentage
Age	<10	3	10%
Groups	10-19	21	70%
(in years)	20+ (upto 26)	6	20%
Sex	M	22	73.3%
	F	08	26.6%
	Malaise	26	86.6%
	Fever	24	80%
	Bleeding menifestations	17	56.6%
	Bone or joint pain	16	53.3%
	Superficial lymph nodes enlarged		
	Yes	17	56.6%
	No	13	43.3%
Clinical	Mediastinal nodes enlarged		
Presentations	Yes	03	10%
	No	27	90%
	Spleen enlarged		
	Yes	17	56.6%
	No	13	43.3%
	Liver enlarged		
	Yes	11	36.6%
	No	19	63.3%

Table-II

Distribution of Patients by haematological findings at diagnosis.

	No. of Patients	Percentage
Haemoglobin (gm/ dl)		
<10	27	90
>10	03	10
WBC x 10^9/L		
<10	11	36.66
10-49	07	23.33
≥50	12	40
Platelet x 10^9/L		
<30	10	33.33
30-100	8	26.66
>100	12	40
FAB Type		
L1	24	80
L2	05	16.6
	01= Acute Mixed leukaemia	3.3

Table-III

Results of induction therapy

	No. of Patients	Percentage
Remission	27	90
Not in remission	03	10

An overall remission rate is 90%

Time of remission	No. of Patients	Percentage
4 weeks	5	16.6
8 weeks	17	56.6
12 weeks	5	16.6

Among thirty patients one patient obtained remission within 4 weeks by basic regimen (vincristine and prednisolone) only. Three patients were treated with basic regimen and anthracycline in each cycle and obtained remission within 8 weeks. The remaining 26 patients were treated with four drugs in each cycle. In addition to identical three drugs (vincristine, prednisolone and anthracycline) L-asparaginase, cyclophosphamide, systemic methotrexate or cytarabine was used as fourth agent in combination therapy. Among them four patients obtained remission within 4 weeks; 14 patients within 8 weeks and 5 patients within 12 weeks of therapy.

Table-IV

Overall outcome by treatment.

Status	No. of Patients	Percentage
Event free survival and on maintenance therapy	17	56.66
Relapsed in first remission	07	23.33
Died in first remission due to acute hepatic failure	01	3.33
Did not communicate with us after CR	02	6.66
Not in remission	03	10.00

Table –V

Sites of relapse.

Sites of relapse	No. of Patients	Percentage
Bone marrow	05	16.66
CNS	01	3.33
Combined BM + CNS	01	3.33

Table-VI

Present status till the end of December 1998 of 17 patients those continue EFS and on maintenance therapy.

EFS and on maintenance therapy	No. of Patients	Percentage
>2 years	03	10.00
>1.5 years	07	23.33
>1 year	01	3.33
<1 year	06	20.00

Among 27 patients those obtained remission, 17 patients continue event free survival and are on their maintenance therapy. 7 patients suffered a relapse of their leukaemia within the first 2 years of maintenance therapy. One patient died in first remission due to acute hepatic failure; two patients did not comminucate after complete remission.

Discussion

Cure of leukaemia means permanent recovery from the disease. The occasional relapses that occur more than three years after treatment suggest that cure may never be a certainty. Event free survival (EFS) is defined as complete remission in a surviving patient without relapse at any site and without the development of a life-threatening second cancer.[3] Patients who survive without leukaemia for at least three years after the cessation of therapy are classified as long - term survivors. A proper clinical trial of Anti - leukaemic therapy requires an enormous expenditure of time, energy and resources. It is difficult to design and execute a proper clinical trial from which justifiable and long-lasting generalizations can be made.[6] The trend in clinical trial reporting is to express treatment outcome in terms of event-free survival, relapse of any kind and treatment-related death. Combination chemotherapy is superior to the sequential administration of single agents for inducing complete remission, prolonging duration of remission and overcoming drug resistance.[7,8] Full - dosage chemotherapy is superior to half-dosage[9]. Adequate preventive therapy for clinically inapparent leukaemia in the CNS would significantly increase event-free survival.[10] Studies have clearly established the necessity of maintenance therapy during remission.[11] Among the drugs commonly used for remission induction prednisolone and vincristine are highly effective.[12,13] Prednisolone and vincristine act rapidly but do not greatly suppress bone marrow regeneration. Their oncolytic effects but not their toxicities are additive. In combination, these two agents induce complete remission in 85% to 90% children with ALL within 4 to 6 weeks.[14]

In this study one patient age 10 years obtained remission within 4 weeks by this basic regimen only. Other 29 patients were treated with 1 or 2 additional agents plus this basic regimen in each cycle. Anthracycline (daunorubicin or doxorubicin) is effective in treatment of the acute leukaemias.[15,16] 93% complete remission rate had observed for childhood ALL with prednisolone plus vincristine plus daunorubicin[17]. This same regimen yields remission of about 72% in adults with ALL.[5] The induction regimen including an anthracycline is considered now to be standard rather than intensive.[18] In this study 3 patients were treated with prednisolone, vincristine and daunorubicin and obtained remission. The remaining 25 patients were treated with 4 drugs in each cycle. L-asparaginase, cyclophosphamide, systemic methotrexate or cytarabine was used as 4th agent of combination chemotherapy. The induction regimen including these agents as 4th drug in each cycle is evaluated as intensification of early induction therapy, would eradicate blasts resistant to standard agents, reduce leukaemic clone, yield lower frequencies of drugresistant mutants and therefore decrease relapses.[19,20,21] One patient who was diagnosed morphologically acute mixed cell leukaemia was treated with 2 cycles of VAPA (vincristine, adriamycin, prednisolone and are- C) regimen to obtain remission. This combination includes the basic drugs used for both acute leukaemias. The overall remission rate is (27 / 30) 90% in this study. This result is less significaant than those of standard studies like MRC trial because of small number of case, short duration follow up, poor compliance of patients and lack of modern laboratory, nursing and supportive facilities.

Conclusion

The progressive improvement in the outcome of treatment of acute lymphoblastic leukaemia is due to intensified and refined combination chemotherapy for remission induction, successful control of central nervous system leukaemia and repeated reductions of residual leukaemic cells by maintenance therapy. At present in childhood ALL rates of complete remission ranging from 90 to 95 percent and rates of long-term disease free survival about 70 percent are achieved[3]. In contrast, the situation in adult ALL is

quite different from that in childhood ALL. In adult ALL rates of complete remission ranging from 70 to 80 percent are obtained, but diseasefree survival is only 35 percent -half that in childhood ALL.[22] Trials with a poor design or incomplete analysis of data confound and mislead. Well designed and well-analyzed trials, however, continue to pay dividends for many years because the information obtained provides a sound basis for future developments. It is difficult to draw a definite remark from this small scale and short duration study. But it provides future directions for further improvement of chemotherapeutic management and large scale study of ALL.

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ORIGINAL ARTICLES

STUDY OF EFFICACY OF 10 DAYS TRIPLE THERAPY WITH OMEPRAZOLE PLUS TWO ANTIMICROBIALS IN THE ERADICATION OF HELICOBACTER PYLORI IN PATIENTS WITH PEPTIC ULCER DISEASES IN BANGLADESH

MT RAHMAN, MA RAHIM MIAH, PK ROY

Abstract

This prospective study was designed to assess the efficacy of 10 days triple drug therapy with omeprazole plus clarithromycin metronidazole and amoxycillin in the eradication of Helicobacter pylori (H. Pylori) as well as to evaluate the rate of ulcer healing in patients with peptic ulcer diseases (PUDs) in Bangladeshi population with a possible comparison between clarithromycin and metronidazole based regimens (OCA Vs OMA). For this work 50 patients with endoscopically proven PUDs-28 male and 22 female were selected randomly from the endoscopy unit of BSMMU and Popular Diagnostic Centre, Dhaka. Of these 7 patients did not come to the follow up and ultimately remaining 43 with a mean age of 35. 60±11. 20 years were the study sample (19 received OCA and 24 received OMA Regimens). Compliance was excellent and only 5 developed some mild side effects. H. pylori infection was defined as a positive rapid urease test (RUT) and eradication as negative RUT plus histological absence of the bacterium in the gastric biopsy tissue at 4 weeks after completion of therapy. On the other hand, ulcer healing was defined as complete endoscopic re-epithelialization of ulcer crater with or without relief of symptoms at 6 week. H. pylori was eradicated in 36 (83. 72%) - 89. 47% in the OCA group and 79.17% in OMA group respectively without any statistically significant differences between the two regimens. Ulcer healing rate at 4 weeks after completion of therapy were 89. 47% Vs 83. 33% respectively with OCA and OMA respectively (Table-II). Simultaneous ulcer healing and H. pylori eradication were noted in 15 (78. 95%) of OCA group and 17 (70. 83%) in OMA group. All these data are consistent with the data of similar studies completed in other countries in the world. However, as the sample size was very smaller in some group further study with similar triple therapy on large series may provide better and widely acceptable results.

Introduction :

Helicobacter pylori (H. Pylori) is probably the most common bacterial pathogen world-wide with a very high prevalence in the developing countries.[1,2] In Bangladesh 80% of the children below 5 and 92% of the healthy adults are infected with this organism.[3,4] H. pylori is a gram-negative, microaerophilic spiral bacterium which infects the gastric mucosa of up to 50% of the adult western population.[5,6] H . pylori infection is acquired in the childhood and persists indefinitely unless eradicated by therapy and causes chronic antral gastritis in virtually all infected persons.[7,8] It is now considered as the main aetiological agent for chronic active gastritis type-B,[9] peptic ulcer diseases (PUD) specially duodenal ulcer (DU),[10] gastric carcinoma[11] and gastric lymphoma (MALT lymphoma) .[12] Approximately 10% of the world population develop peptic ulceration at some time in their lives.[13] In Bangladesh, the point prevalence of PUD is 15% (DU-11.98% and GU-3.58%),[14] which is much higher than that in the developed countries (15% vs 1.5%). Over 95% (95-100%) of DUs and >80% (56-96%) of GUS are strongly associated with H. pylori infection.[15,16] However, for unknown reason although about 15% of the infected persons develop PUD many infected persons in Africa never develop PUD.[17] A meta analysis of the several controlled clinical trials showed that H. pylori eradication therapy enhances a rapid ulcer healing at a higher rate and marked reduction in the recurrence rate of PUD particularly DU from 80 to 4% yearly.[18,19] On this ground, NIH of America in 1994, European H. pylori study group in the Maastricht consensus conference 1996 and FDA of USA in1998 recommended that all patients with endoscopically documented PUD with H. pylori infection should receive a course of anti-microbial therapy.[20,21,22] Since the discovery of H . pylori in 1983 many different therapeutic regimens have been

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trialed in different countries of the world and till date Bismuth based triple therapy showed a high eradication rate so is the recommended treatment of choice. Recent triple drug therapies with omeprazole+ amoxycillin/clarithromycin+ metronidazole / tinidazole is reported to show a very high cure rate of 90%.[23,24,25] The aims of this study were to assess the efficacy of 10 days triple therapy with clarithromycin metronidazole and amoxycillin based regimens in the eradication of H. pylori as well as to evaluate the rate of ulcer healing in an attempt to find out the most effective, relatively cheaper and well tolerated therapeutic schedule for the Bangladeshi population with PUDs.

Patients and methods

This study was a prospective, randomized, open, clinical trial performed in the department of Gastroenterology of Bangabandhu Sheikh Mujib Medical University (BSMMU) and Popular Diagnostic Centre, Dhaka during the period from January/ 2001 to June/2002.

For this study 50 patients aged 15 to 60 years with history of dyspepsia and endoscopically proven peptic ulcer diseases (PUDs) & Erosive gastritis with evidence of H. pylori infection were selected randomly during the endoscopic procedure both from the out and in-patient departments of gastroenterology to give a 10 days anti-H pylori therapy. A written consent of the study population was obtained. Detailed history and physical findings were recorded properly. Patients aged <15 or>60 years, pregnancy or lactation, co-existing pyloric stenosis or gastric carcinoma; history of active upper GI haemorrhage, chronic alcohol or drug abuse, cirrhosis, continued use of NSAIDs and taking PPI, bismuth compounds or antibiotics in the preceding 4 weeks were the exclusion criteria. Endoscopic examination of all the enrolled patients was performed before the therapy to confirm the diagnosis, location of PUDs &/or erosive gastritis with proper records and to take biopsies from the antral gastric mucosae for the evaluation of H. pylori status of each patient by rapid urease test (RUT). Because about 92%of the adult population in Bangladesh have H. pylori infection and over 90% of PUD are strongly associated with this bacterium, a positive RUT was considered as evidence of H. pylori infection and no other test was done before the treatment.

Study design

All eligible patients were randomly allocated to receive any of the following triple drug regimens for 10 days.

Group-1 (OCA) : Omeprazole (20mg b. d) +Clarithromycin (500mg b. d) +Amoxycillin (lgm b. d) - 25 patients.

Group- 11 (OMA) Omeprazole (20mg b. d) +Metronidazole (400mg t.i.d) + Amoxycillin (1gm b. d) - 25 patients.

In both the group omeprazole was continued for additional 4 weeks to ensure proper ulcer healing.

The patient compliance was assessed by counting the returned study drugs; consumption of fewer than 75% of the prescribed doses was considered as non-compliance. Adverse reactions to drugs were assessed using a questionnaire.

The patients were followed up at 2 and 6 weeks of therapy. At the 2 week visit-compliance, relief of symptoms, any adverse reactions were assessed and at the 6 week visit (4 weeks after completion of therapy) follow up endoscopy was performed to assess ulcer healing and to take gastric biopsy specimens for RUT and histological confirmation of H. pylori eradication. Ulcer healing was defined as complete endoscopic re-epithelialization of ulcer crater with or without relief of symptoms. H. pylori eradication was defined as negative RUT and negative histology at 4 weeks after completion of therapy.

Statistical analysis

Data were analysed by X2 test, Z test and un- paired t-test.

Results

Demographic and clinical characteristics of the studied population were comparable (Table-1) . Majority (58. 14%) were male (Male : Female=1. 38 : 1. 00) with a mean age of 35. 60±11. 20 years. Fourteen (14) patients were smokers-two heavy and twelve mild to moderate smokers. In total 43 patients (19 of OCA Group and 24 of OMA Group) completed the H. pylori eradication therapies and 7 patients did not attend the follow up; compliance of all the patients studied was good and no one did complain of any serious side effects. Only 5 (11. 62%) patients did develop some mild side effects such as anorexia, nausea, loose motion and distaste to food. Follow up endoscopy at the end of 6 weeks showed complete healing of the ulcers in 17 patients (89. 47 %) of OCA Group and 20 (83. 33%) of OMA Group (p>0.05) . H. pylori was eradicated in 36 (83. 72 %) of studied patients—17 (89. 47%) of OCA Group and 19 (79. 17%) from OMA Group without any statistically significant differences in the eradication (p>0.1) as well as ulcer healing rate (Table-II).

Simultaneous healing of PUD and H. pylori eradication were noticed in 15 (78. 95%) of OCA Group and 17 (70. 83%) in the OMA Group with no significant differences (p>0. 05) which is consistent with the data of similar studies conducted in other countries in the world.

Table-I

Patients characteristics (n =43)

Variables	OCA-Group (n =19)	OMA-Group (n=24)	Remarks
Mean age (years)	39.29±8.04	34. 21±12.13	Age range 10-60
Sex M : F	14 Vs 5 (2.8 : 1)	12 Vs l2 (1:1)	M : F =1.38 : 1.00
Smokers	8 (42.10)%	6(25)%	Heavy smoker=2
History of dyspepsia	19 (100)%	24(100)%	
DUD	03 (15.79)%	08 (33.33)%	
GU with antral erosions	04 (21.05)%	05 (20.84)%	
Peptic ulcer diseases (DU+GU/Erosions)	12 (63.16%)	11 (45.83%)	

Table-II

Showing the efficacy of different triple drug regimens in the eradication of H. pylori and ulcer healing

Therapeutic regimens	Symptomatic improvement n (%)	H. pylori eradication rate=83.72%	Ulcer healing n (%) DUD	GU+Erosions	PUDs DU+GU/Erosions
OCA (n=19)	17 (89.47)	89.47%	3 (100)	3 (75)	11 (91.66)
OMA (n =24)	20 (83.33)	79.17%	7 (80)	4 (80)	9 (81.81)

Discussion

Eradication of H. pylori is very difficult. Till date many drug regimens have been investigated in different studies in different countries in the world but none of the regimens eradicates H. pylori in 100% of the patients. The optimal therapeutic regimen for H. pylori eradication consists of short term low dose combination therapy using simplified regimens which results in high eradication rates. Thus, triple drug therapy with an anti-secretory agent plus two antibiotics is the current gold standard therapy for H. pylori eradication. Such PPI triple therapy for 10-14 days is reported to have eradication rates of 85-90%.[23,24,25]. In the developing countries, H. pylori eradication rates with different triple drug regimens are reported to be sub optimal[26,27] in some eradication is possible but recurrence rate is very high (almost 100%) at the end of 1 year of therapy. Poor patient compliance, high incidence of anti-microbial resistance specially to metronidazole, high incidence of side effects and high cost of the regimens are the possible limiting factors. High resistance rates to commonly used antimicrobials have been reported from India and Bangladesh-for example 90% of the isolates in migrants from Bangladesh and Calcutta to the UK are resistant to metronidazole[28,29] in comparison to only 15% and 11% in Europe and USA respectively.[30,31] The impact of resistance to antimicrobials on the clinical outcome is different for metronidazole and clarithromycin.[32] In vitro metronidazole resistance impairs the efficacy of metronidazole based triple drug regimens.[33] However, despite a high rate of metronidzole resistance a cure rate of 75% is possible[34] and over all treatment success does not exeed a 10% decrease in the eradication rate for OMA over OCA containing regimens. In contrast impact of clarithromycin resistance is much more important with a cure rate ranges from 0-50% and overall eradication rate may decrease by 7-15%.[35]

The optimal duration of therapy is controversial. In the meta-analysis of Laheij et al[36] treatment duration did not show any influence on the cure rate. However, studies in the United States showed an increment when OCA regimen given for a longer time : 14 days> 10>7days.[37] Lameoulite et al[38] also found a significant difference between 7 and 10 days treatment favouring the 10 days duration therapy. In Southern Europe, USA and many Asian countries the eradication rate associated with 1 week triple therapies consisting a PPI and two antibiotics are <90% sometimes even below 80%.[39]

The present study showed that a 10 days triple therapy with omeprazole plus clarithromycin /metronidazole and amoxycillin resulted in an eradication rate of 83.72%- 89. 47% Vs 79. 17% with the clarithromycin (OCA) and metronidazole based regimen (OMA) respectively without any statistically significant differences (p>0.1). At the end of 6 weeks of the therpy symptomatic improvement was 89. 47% Vs 83. 33%

with OCA and OMA regimens respectively. At the same sitting endoscopic ulcer healing rate was found to be 86. 05% categorically—10 (90. 91%) of DU, 7 (77.78%) of GU and 20 (86.96%) of PUDs. No significant differences between OCA and OMA Group. All these are consistent with the data of the similar studies conducted in other developing countries in the world. Eradication of H. pylori does not vary significantly with age, sex and smoking habit. Healing of PUDs varied in relation to type of ulcers, regimen used and eradication of H. pylori . This study showed a marginally higher eradication rate of H. pylori as well as ulcer healing with OCA therapy in comparison to OMA Regimen (89.47 Vs 79.17 and 89.47 Vs 83.33 respectively) but still it is lower than that of the developed countries most likely due to high incidence of metronidazole resistance in Bangladesh.

In conclusion, the present study of 10 days triple therapy with omeprazole, clarithromycin and amoxycillin resulted in a relatively high healing rate of PUDs and eradication of H. pylori apparently at an acceptable rate without any significant differences between the OCA and OMA therapy. However, sample size of this study particularly patients with DU in the OCA group was very smaller to get a more accurate result which necessitates larger series further investigations. In addition, Bangladesh is a developing country so H. pylori eradication therapy recommended for the developed countries may not be appropriate for the Bangladeshi population and regimens based on culture sensitivity profile may be helpful.

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ACUTE POISONING – SCENARIO AT A DISTRICT HOSPITAL

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Abstract

The prospective study was conducted on 120 adult inpatients with acute poisoning in Noakhali General Hospital Medical wards. It constitutes 7.46% of total admission of 1607 patients during the study period of six months from August/96 to January/ 1997. Cases belong to both sexes with 87 (72.5%) male and 33 (27.5%) females. The diagnosis is mainly clinical on the basis of history and directed physical examination. The objective of the study is to focus the pattern of acute poisoning responsible for hospital admission in the present socio-demographic status. The common causes of poisoning observed in the study are respectively street poisoning with ultrashort acting sedative-hypnotic drugs (33.33%), endrin (organ ophosphorus compound) (22.50%), chlorinated compound (16.66%) and venoms (15%).

Introduction

A poison is a substance capable of producing adverse effects in a living organism. Humans come into contact with a great variety of drugs, chemicals, venomous animals and insects resulting varying degrees of poisoning in varying modes accidental, suicidal and homicidal.[1,2]

Acute poisoning is a common and urgent medical problem all over the world. In Britain, it accounts for 15-20% of all acute medical emergency admission to hospital and in the United States, there are 2.3 millions acute poisonings every year. In developing countries, agrochemicals-organophosphates, carbamates, organochlorines and other pesticides also predominate in fatal poisonings at all level of the health-care delivery systems particularly at the level of the district.

A district general hospital is a key referral center for providing emergency services to these cases. It has a catchment area covering the district and its neighbours, a bed-strength ranging from 50 to 250 with specialised services. Such a hospital is usually overloaded with patients with some limitations. The pattern of poisoning reflects the socioeconomic conditions and varies from country to country and in different regions of the same country. The pattern of poisoning in such an institution deserves attention.

The study was conducted in Noakhali General Hospital having a bedstrength of 150 for providing health - care to more than 2.5 millions people. The aim of the presentation is to find out the mode of admission due to acute poisoning in medical wards and to be aware of the clinical scenario at the district level.

Patients and Methods

This is a prospective observation on hospitalised population. All adult patients admitted into medical wards of Noakhali General Hospital over a period of six months from August/96 to January/97 were included. The patients belong to both sexes, hail from both urban and rural areas and have a variable socioeconomic status. A poisoned patient often fails to give a coherent history. The diagnosis is based on history from the accompanying person or from the circumstantial evidence and by performing a directed physical examination. Some investigations like total blood count, Hb%, ESR, SGPT, SGOT, serum bilirubin, prothrombin time, HBsAg, blood sugar, blood urea, serum creatinine, X-ray of chest P/A view were done when indicated and available to exclude other possibilities. A case note for each patient with treatment sheet and reports of investigations are preserved and used as customary. At the end of each month, all the bed head sheets were evaluated and categorized.

Results

A total of 120 patients were admitted due to acute poisoning. The pattern of poisoning is shown in tabulated forms. Table-1 shows sex incidence, Table-II, III, IV show the pattern of acute poisoning, its incidence in male and female respectively. The leading causes of acute poisoning are street-drug (33.33%), endrin (22.50%), chlorinated compounds (16.66%) and venoms (15%) in descending order.

Table-I

Shows sex incidence (n=120)

Male	Female	Total
87 (72.50%)	33 (27.50%)	120

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Table - II

Shows pattern of acute poisoning (n=120).

Types	Male	Female	Total	Percent
Street poisoning (with hypnotic).	40	00	40	33.33
Organ-ophosphorus compound (endrin)	11	16	27	22.5
Snake-bite	07	02	09	7.50
Rat-killer	07	02	09	7.50
Seduxen	08	00	08	6.67
Hornet-bite	05	01	06	5
Copper - sulphate	02	02	04	3.33
Insect-bite	02	01	03	2.5
Hair-remover	00	02	02	1.67
Dettol	00	02	02	1.67
Cannabis	02	00	02	1.67
Eunoctin	01	01	02	1.67
Dhatura	00	01	01	.83
Kerosine	01	00	01	.83
Tetmosol	00	01	01	.83
Alcohol	01	00	01	.83
Herpic	00	01	01	.83
Chloro-hexidine	00	01	01	.83

Table-III

Shows pattern of poisoning in male (n=87).

Types	Total	Percent
Street poisoning	40	45.98
Endrin	11	12.64
Seduxen	8	9.20
Snake-bite	7	8.04
Rat-killer	7	8.04
Hornet-bite	5	5.74
Insect bite	2	2.30
Copper sulphate	2	2.30
Cannabis	2	2.30
Eunoctin	01	1.14
Alcohol	01	1.14
Kerosine	01	1.14

Table-IV

Shows pattern of poisoning in female (n=33).

Types	Total	Percent
Endrin	16	48.49
Snake-bite	02	6.06
Rat-killer	02	6.06
Dettol	02	6.06
Hair remover	02	6.06
Copper sulphate	02	6.06
Insect bite	01	3.03
Hornet-bite	01	3.03
Tetmosol	O 1	3.03
Herpic	01	3.03
Chlorohexidine	01	3.03
Dhatura	01	3.03
Eunoctin	01	3.03

Discussion

Acute poisoning as a result of accidental or deliberate ingestion of drugs or other chemicals is an important problem globally. In United Kingdom, it accounts for 15-20% of all acute medical emergency admissions to hospital and in the United States, there are 2.3 millions acute poisonings every year. In England, hospital admissions due to acute poisoning are declining -about 100.000 individuals are admitted annually (population base 48 millions). However, the true incidence of acute poisoning may be two or three-fold greater. Of those admitted to hospital, females predominate in nearly all age group. Drugs are the most common poisons taken by adult and rank second only to house-hold products in children. In United Kingdom, alcohol is taken in addition to other poison (s) by 60% of adult males and 40% of adult females—admitted for acute poisoning.

In developing countries, acute pesticide poisoning is a major problem. In Srilanka, agrochemicals account for nearly 60% of all poisoning . Worldwide, pesticides annually account for one million serious unintentional poisoning and two millions hospitalised suicide attempts, predominantly in developing countries. In England and Wales, such agents accounts for less than 1% of hospital admission as a result of poisoning. In Bangladesh, insecticide, house-hold substances, street-drugs and venoms are common causes of poisoning.

In the present observation, acute poisoning accounts for 7.46% of all medical admission with male predominance which is contrary to overseas scenario.[1,2,3] Males are predominating in street -drug poisoning while females are predominating in insecticide poisoning. The leading causes of acute poisoning are sedative-hypnotic drugs, organophosphorus compound (endrin) and venoms. Street-drug poisoning with ultra-short acting sedative hypnotic constitute the highest number of cases -all in males. This finding conforms with other studies[1,2,3] but differs from finding by others.[4,5,6,7,8] The cause of such a big number of cases of acute poisoning with street-drugs may be due to intentional admixture of food with these drugs by some criminals for the purpose of hijacking the belongings of travellers in stations and bazars specially during festivals.

Organophosphorus compound (endrin) poisoning is the leading cause of admission - found by three separate groups of authors in three separate study places.[4,5,6] Organophosphorus compound (endrin) poisoning is found more in females in the present study-similar to that found by others . Males were affected with endrin poisoning more than females in other studies thus differing from the present finding. Socio-economic background is likely to be the underlying provocation. Acute pesticide poisoning is predominant in females in the present observation and endrin poisoning constitutes the second large number of cases which is in conformity with the finding by others[7,8].

Acute poisoning with snake-bite, hornet-bite and other insect-bite are not uncommon and all are found predominantly in males and this is in conformity with finding by others.[9] All cases of snake-bite are nonpoisonous in the present study which is in consistent with others[9]. Alcohol is an uncommon cause of acute poisoning in contrast to western pattern.

In conclusion, it may be noted that the items responsible for acute poisoning are numerous,

variable and curious and are of day-to-day use and will remain as unnoticed causes of morbidities and mortalities throughout the country-rural and urban. The pattern and magnitude of poisoning are thus multidimensional demanding multi-sectorial approach for facing the problem.

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JAPANESE ENCEPHALITIS – A REVIEW ARTICLE

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Abstract

Japanese encephalitis (JE) is the most important mosquito borne arboviral disease in the agricultural region of Asia. More than 30, 000 to 50, 000 cases and 10, 000 deaths are reported each year in this region. JE is a seasonal and a rural disease. Culex mosquitoes are the principal vector. Majority of the cases subclinical. Clinical symptoms varied from flu like illness in the earlier stage to neurological symptoms like convulsions, coma in the later stage. About 25% of the cases are fatal and about one-third of the surviving patients exhibit serious residual neurological disability. Diagnosis is based on high degree of clinical suspicion together with serological tests of spinal fluid and blood. Currently no definitive curative treatment is available. Only supportive and symptomatic treatment can be provided. Vaccination is single most important preventive measure to control JE.

Introduction

Japanese encephalitis (JE), the "plague of the orient" is the most important mosquitoborne arboviral disease in the agricultural region of Asia[1]. More than 35,000 cases and 10,000 deaths are reported annually from the region, affecting mostly the young children and persons above 65 year of age.[2,3] After human immune deficiency virus infection, JE may be the leading cause of viral encephalitis wolrdwide[4]. Most infections are asymptomatic but among people who develop a clinical illness, the case-fatality rate can be as high as 30%. Neuropsychiatric sequelae are reported in 50% of survivors.[5] JE virus is transmitted chiefly by the bites of mosquitoes of the Culex vishnui complex; the individual vector species in specific geographic areas differ[5].

Diagnosis of JE is mainly based on serological tests of blood and spinal fluid. Other diagnostic methods include recently developed dot-blot or immunoprecipitation IgM assays.[6] There is no specific treatment for Japanese encephalitis.

Historical Background

An outbreak of epidemic proportions occurred in the summer of 1924 in Japan and Korea. More than 6.000 cases, 60% fatal were reported from Japan alone. Clinical and epidemiologic features of the illness suggest that this and subsequent outbreaks in 1927, 1934, and 1935 were epidemics of JE.[8,9] In 1924, a filterable agent from human brain tissue was isolated in rabbits and in 1934; Hayaslis transmitted the disease experimentally to monkeys by intra cerebral inoculations.[10] JE viruses isolated from human cases in Japan in 1935.

The virus initially was called Japanese B encephalitis (the modifying B has fallen into disuse) to distinguish the agent from the etiology of Von Economics type A encephalitis, which had different epidemiologic characteristics. The mosquito-borne mode of JE transmission was elucidated with the isolation of JE virus from Culex tritaeniorhynchus mosquitoes in 1938.

The first indication of JE transmission in Southeast Asia was from Sri Lanka where an outbreak that appears to have been JE was reported in 1948. JE was first recognized in India in 1955 and since then many major out-break from different parts of the country have been reported. [11]

Out breaks recurred exclusively in southern India until 1978 when JE epidemics were reported for the first time in the north in Bihar, Uttar Pradesh and West Bengal. [12]

Epidemiology

An estimated 30,000 to 50,000 cases and 10,000 deaths occurred each year, mostly among children. In endemic areas the annual incidence of clinical disease ranges from 10-100 per 100,000 populations. The majority of people living in JE-endemic areas are infected with the virus before the age of 15. JE occurs primarily in three areas (1) China and Korea (2) the Indian subcontinent including India, parts of Bangladesh, Southern Nepal and Srilanka and (3) the

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Southeast Asian countries of Cambodia-China, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand and Viet Nam. The disease occurs in lower frequency in Japan, Taiwan, Singapore, Hong Kong and Russia.

JE is primarily a rural disease. Up to 3% of mosquitoes may be infected in endemic areas.[14] Transmission can also occur near urban areas in some developing Asian Countries.[15] Transmission is seasonal, roughly May to September, in temperate areas of the region: the People's Republic of China, Korea, Japan, subtropical areas of Southeast Asia and certain far-eastern locations in Russia. The transmission season is somewhat longer April through October in more southerly areas of the region. In tropical locations in Southeast Asia and on the Indian subcontinent, viral transmission follows the seasonal occurrence of rains and migratory patterns of avian vertebrate amplifying hosts. Viral transmission may occur year round in some sites.[4]

Table-I

Risk of Japanese encephalitis, by country, region and season.

Country	Affected areas/Jurisdiction	Transmission season	Comments
Bangladesh	Few data,but probably widespread	Possibly July to December	Outbreak reported from Tangail district, Dhaka Division; sporadic cases in Rajshahi division
Bhutan	No data	No data	No comments
Myanmar	Presumed to be endemic-hyperendemic as in Malaysia	Presumed to be May to October	Repeated outbreaks in Shan State in Chiang Mai valley
India	Reported cases from all states except Arunachal, Dadra,Daman,Diu, Gujrat,Himachal, Jammu,Kasmir, Lakshadweep, Meghalaya, Nagar Haveli,Orissa, Punjab, Rajasthan, and Sikkim.	South India :May to October in Goa; October to January In Tamil Nadu;and August to December in Karnataka. Second peak, April to June in Mandya district. Andra Prodesh: September to December. North India: July to December	Out breaks in West Bengal, Bihar, Karnataka, Tamil Nadu, Andra Prodesh, Assam, UttarProdesh,Manipur, and Goa. Urban cases reported(for example, Luchnow)
Nepal	Hyper endemic in southern lowlands (Terai)	July to December	Vaccine not recommended for travelers visiting only high altitude areas.
Pakistan	May be transmitted in central deltas	Presumed to be June to January	Cases reported near Karachi; endemic areas overlap those for West Nile Virus. Lower Indus valley might be an endemic area.
Sri Lanka	Endemic in but mountainous areas. Periodically epidemic in northern and central provinces.	October to January; secondary peak of enzootic transmission May to June.	Recent outbreaks in central (Anuradhapura) and northwestern provices.

Transmission

Japanese encephalitis is not spread from person to person. The disease is caused by an arbovirus. Like most arboviruses, the JE virus is spread by infected mosquitoes.[6] The mosquitoes bite in the late afternoon and early evening. JE virus is transmitted chiefly by the bites of mosquitoes in Culex vishnui complex. In China and many endemic areas in Asia, Culex tritaeniorhyncus is the principal vectors.[5]

The mosquito's breeds in flooded rice fields, marshes and standing water pools in planted fields. Pattern of JE transmission vary regionally, within individual countries and from year to year. In most regions the period of transmission starts in April or May and lasts until September or October.

In tropical and Subtropical areas, disease incidence is highest during and shortly after the rainy season. People living in rural areas where the disease is common are at increased risk of disease transmission. For travelers to endemic areas, the risk of infection is very low, as low as 1 per million, for short-term travel (less than 4 weeks) depending on factors such as season, location and duration of travel.[6] Expatriates and travelers living for prolonged periods in rural areas where JE is endemic or epidemic are at greatest risk.[5] Travelers with extensive unprotected outdoor, evening and night-time exposure in rural areas, such as bicycling, camping or engaging in certain occupational activities, may be at high risk even if their trip is brief.[5]

Life cycle of JE virus

The JE virus is transmitted by zoophilic mosquitoes, which are the only known vector. The most important reservoir is pigs and wading birds e.g. herons and egrets. In high endemic areas vector mosquitoes and their reservoir pigs, wading birds and ducks are found in abundance in agricultural areas.

The life cycle of the virus is maintained by biological transmission between susceptible vertebrates and the blood-sucking mosquitoes. It multiplies in the vertebrate, is transmitted to the arthropods at times of peak viraemia, multiplies in the tissue of the mosquitoes and is passed on to new vertebrates. In Japan epizootic cycles have been shown to start with appearance of virus activity in pigs, then in mosquitoes associated with pigs and later in cattle, egrets and herons, In India, similar cycles have been suggested.

Man is dead end host, as viraemia in man is short lived.

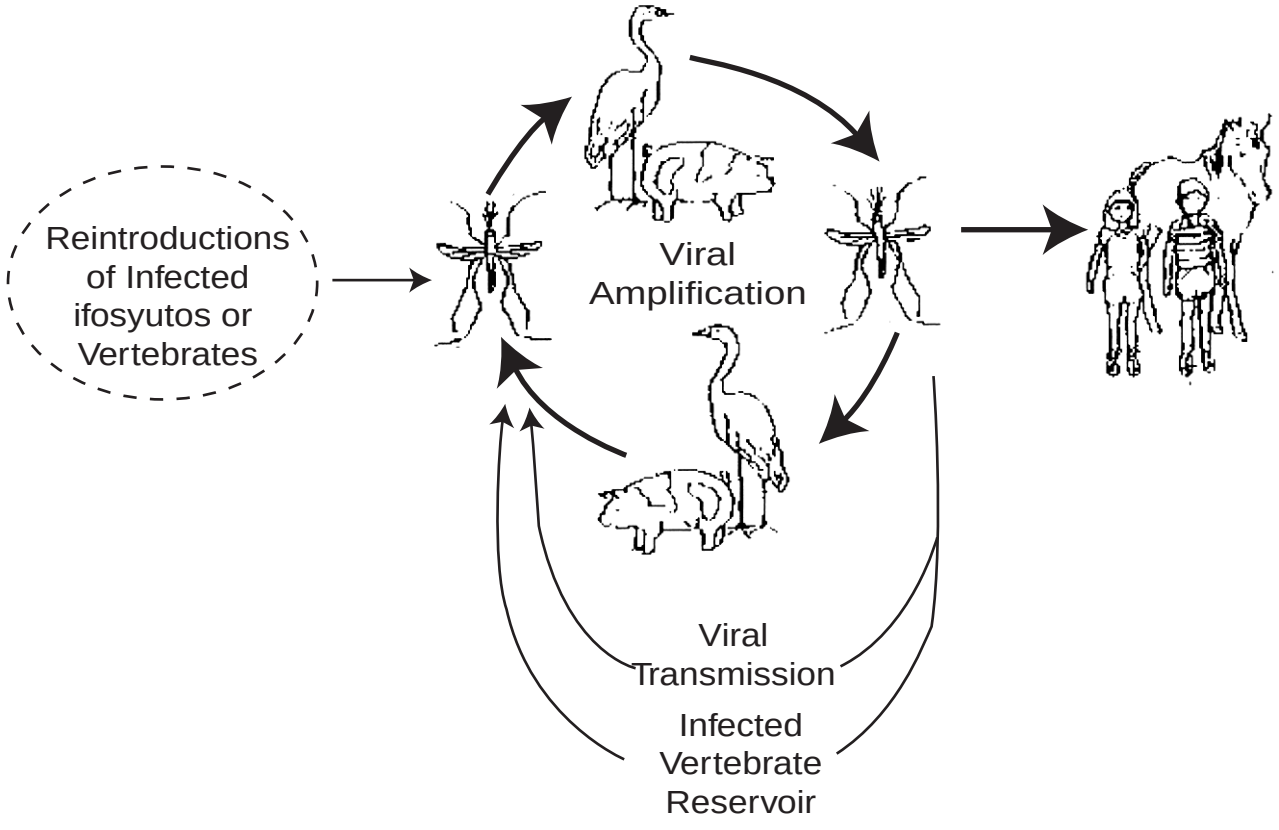

Fig. -1 : *Transmission Cycle of Japanese Encephalitis Virus*

Virologic characteristics

JE virus is one of 66 flavi viridae, enveloped, positive sense, single stranded RNA viruses than largely are vector borne,[16,17] Morphologically, flavi viruses are spherical, approximately 40 mm in diameter, and composed of a lipid bilayer surrounding a nucleocapsid containing the 11 kb genome complexed with a capsid (C) protein surface projections on the membrane are composed of a glycosylated envelope (E) and membrane (M) proteins.

A pre M glycoprotein, present in intracellular nascent virions, is cleaved to the M protein found in mature extracellular virions. Important biological activities are associated with the 53 KD E protein including haemagglutination, viral neutralization, virion assembly, membrane fusion and viral binding to cellular receptors.

Binding of JE virions to certain cells of CNS lineage may be associated with the presence of specific neurotransmitter receptors.[18]

JE virus is antigenically related to St Louis encephalitis (S L E) virus, west Nile virus and several flaviviruses found in Australia, e.g. Murray valley encephalitis, Kinjin, Alfuy and Kokobera viruses.[19,20]

Pathogenesis of JE

After an infectious mosquito bite, viral replication occurs locally and in regional lymph nodes. Virions disseminate to secondary sites where further replication contributes to an augmented viraemia. CNS invasion probably occurs from the blood, by antipodal transport of virions through vascular endothelial cells.[23,24,25] Sensitized T helper cells stimulate an inflammatory response by recruiting macrophages and lymphocytes to the perivascular space and into the parenchyma.[23,25]

The reasons that only one in several hundred infections develops into symptomatic neuro invasive disease are enigmatic factors that contribute to risk for neuroinvasion are only partially known but probably include genetic and acquired host factors[26,27]. Circulating antibody plays a critical role in modulating infection by limiting viraemia in the preneuroinvasive phase and both JE viral specific and heterologus (e.g. Dengue) antibodies contribute to protection. Concomitant CNS infection act as a cofactor in JE pathogenesis. [4]

Pathology

Pathologic abnormalities are found chiefly in the CNS; however, inflammatory changes in the myocardium and lung and hyperplasia of reticuloendothelial cells in the spleen, liver and lymph nodes have been descibed.[21] Cerebral edema and congested leptomeninges are visible on gross examination of the brain and punched-out necrolytic lesions in the grey matter may be conspicuous. Histopathologic examination discloses a characteristic pattern of microglial proliferation with the formation of microglial nodules surrounding dead or degenerating neurons in which viral antigen can be demonstrated by immunohistochemical staining. Gliomesenchymal nodules are distributed in the superficial and deep grey matter, including the brain stem, thalamus, basal ganglia, hippocampus and anterior horn cells of the spinal cord. Similar destruction of and microglial reaction around Purkinjee cells also are evident in the cerebellum. Necrolytic lesions appearing, as cysts are found in a similar distribution in the grey matter. In patients with residual neurologic impairment dying several years after resolution of the acute illness, scarred rarified foci are found in a characteristic distribution in the thalamus, substantia nigra and hippocampus.[22]

Clinical features

The majority of infections are sub clinical, resulting in mild symptoms or no symptoms at all. It is estimated that, on average, 1 in 300 infections results in symptomatic illness. Symptoms usually appear within 4-14 day after infection and are characterized by a flu-like illness, with sudden onset of fever, chills, headache, tiredness, nausea and vomiting. In children, gastrointestinal pain and dysfunction may dominate the early stage of the illness or an acute convulsion may be the earliest objective signs of illness in an infant or child. After 3-4 days signs of neurological involvement occur with a change in the level of consciousness ranging from confusion to coma. Children often present with seizures.[6] Conversely, headache and meningismus are more common in adults.

A majority of patients become totally unresponsive or responsive only to pain generalized weakness and changes in tone, especially hypertonia and hyper reflexia, are the most common motor abnormalities, but focal motor deficits, including paresis and hemi and tetraplegia, cranial nerve deficits (especially central facial palsy), and abnormal reflexes also may be present. Sensory disturbances are seen less frequently. Central hyperpnea, hypertension, pulmonary oedema and urinary retention also may complicate the illness. Although symptoms suggest elevated intracranial pressure in many cases, papilloedema and other signs of raised intracranial pressure are rarely seen and dexamethasone therapy does not improve out come.[23,28] Signs of extra pyramidal involvement, including tremor, mask-like facies, rigidity, and choreoathetoid movements are characteristic of JE, but these signs may be obscured initially by generalized weakness.

Diagnosis of JE

During epidemics the index of suspicion is high and considered together with the fever and signs of meningeal involvement, the diagnosis is readily suspected.

(1) Hematological examination discloses moderate peripheral leucocytosis with neutrophilia and mild anaemia.

(2) The CSF usually is under normal pressure. pleocytosis typically is in the range of ten to several hundred and rarely more than a thousand cells per cubic mm; however a significant proportion of patients have fewer than 10 cells on an initial examination. Neutrophils may predominate in early samples but a lymphocytic pleocytosis is typical. CSF protein is moderately elevated in about 50% of cases.

(3) EEG: The EEG changes are often non-specific. Three patterns of EEG were noted which included diffuse continuous delta, diffuse delta with spikes, non-modulating nonresponsive alpha activity.[30]

(4) Imaging: Computed tomographic (CT) and magnetic resonance imaging (MRI) scans reveal low density areas and abnormal signal intensities in the thalamus, basal ganglia and putamen.[29]

(5) Virology and serology: Definitive diagnosis requires virological or serological confirmation. JE virus may be recovered from the CSF in about one third case.

Among the serological test IgM capture ELISA (88% sensitivity, 97% specificity), 29 haemagglutination inhibition, complement fixations or neutralization are being used.

PCR for detection of JE viral genome is now being increasingly practised. Other diagnostic methods include recently developed dot blot or immunoprecipitation IgM assays.[6]

Treatment

Currently there is no specific treatment for Japanese encephalitis. Antibiotics are not effective against the JE virus and no effective antiviral drugs have been developed to treat the disease. Care of patients centers on treatment of symptoms and complications.

Out come of JE

Approximately 25% of cases are fatal, some occurring after a brief prodrome and fulminant course lasting a few days and others after a more protracted course in coma. Young children (under 10 years) are more likely to die, and if they survive, they are more likely to have residual neurological deficits. Overall, approximately one third of surviving patients exhibit serious residual neurological disability. Principal sequelae include memory loss, impaired cognition, behavioral disturbances, convulsions, motor weakness or paralysis, and abnormalities of tone and coordination. Persistent EEG abnormalities are common in children.[4]

Poor prognosis has been associated with a short prodromal interval, clinical presentation in deep obtundation, respiratory dysfunction, prolonged fever, status epilepticus and the presence of Babinski's sign.[4] The presence of virus in cerebrospinal fluid (CSF), high CSF alpha interferon levels, and low CSF levels of viral specific IgM antibodies are highly associated with a fatal outcome. These clinical laboratory findings are intercorrelated and together they probably reflect uninhibited CNS viral proliferation as the underlying cause of poor outcome.

Infection during the first and second trimesters of pregnancy may result intrauterine infection and abortion. Infections that occur during the third trimester of pregnancy have not been associated with adverse out comes in newborn.

Differential Diagnosis: The differential diagnosis includes the viral encephalitis as well as cerebral malaria and treatable bacterial, mycobacterial and fungal infections of the central nervous system. Epidemiological features provide important clues to the diagnosis.

Preventive measures

Vaccine: Vaccination is the single most important measure to control Japanese encephalitis. Currently, there are three types of JE vaccines in large-scale use:

- Mouse brain-derived inactivated vaccine
- Cell culture-derived inactivated vaccine
- Cell culture-derived live attenuated vaccine.

The mouse brain-derived inactivated JE vaccine is produced in several Asian countries.[6] It is the only vaccine that is commercially available in the international market.

Vaccination should be considered for adults and children over one year of age who plans to live in areas where JE is endemic or epidemic and travelers whose activities include trips into rural, farming areas.[5] Due to likely interference with remaining maternal antibodies, children are usually not vaccinated before the age of one year.[6]

Japanese encephalitis vaccine[6]

Doses	Subcutaneous route		Comments
	1 through 2 years of age	3 years of age or older	
Primary Series 1, 2 and 3	0.5 milliliter	1.0 milliliter	Days 0, 7, and 30
Booster	0.5 milliliter	1.0 milliliter	I does at 24 months or later

An abbreviated schedule of days 0,7 and 14 can be used when the longer schedule is impractical because of time constrain.[5] The last dose should be administered at least 10 days before commencement of travel.[5]

Controlled studies showed that the JE vaccine is efficacious and without serious side effects.

The three dose series of vaccine gives 90% protection.[6]

JE vaccine is associated with local reactions and mild systemic side effects, fever, headache, myalgias, and malaise in about 20% of vaccines. More serious allergic reactions, including generalized urticaria, angioedema, respiratory distress and anaphylaxis, have occurred within minutes to as long as one weak after immunization in about 0.6% of patients.[5]

Vaccination during pregnancy should be avoided.[5]

Other preventive measures: Travelers should be advised to stay in screened or air-conditioned rooms, to use bed nets when such quarters are unavailable, to use aerosol insecticides and mosquito coils as necessary, and to use insect repellents and protective clothing to avoid mosquito bites.

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REVIEW ARTICLES

AN OVERVIEW OF THE PROTECTIVE ROLE OF THE METABOLIC MODULATOR TRIMETAZIDINE IN CORONARY ARTERY DISEASE

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Introduction

Trimetazidine 1(2, 3, 4-trimethoxybenzyl-piperazine dihhydrochloride; TMZ), has been reported to exert antiischemic properties without affecting myocardial oxygen consumption and blood supply[1]. The beneficial effect of this has been attributed to preservation of phosphocreatine and ATP intracellular levels[2] and a reduction of cell acidosis[3, 4], calcium overload[4] and free radical induced injury caused by ischemia[5]. More importanfy, TMZ affects myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from FFA to glucose oxidation[6, 7]. Recent evidence indicates that this effect is predominantly caused by selective blockade of long-chain 3-ketoacyl coenzyme A thiolase activity, the last enzyme involved in beta-oxidation[7]. Seven clinical studies have shown that TMZ alone or in combination with other anti-anginal drugs can substantially improve exercise tolerance and increase the ischemic threshold in patients with effort angina[8-13].

Manipulation of cardiac metabolism

A number of different approaches have been used to manipulate energy metabolism in the heart[14]. These involve both indirect measures and the use of agents that act directly on the heart to shift energy substrate utilization away from fatty acid metabolism. One way to increase glucose oxidation and to decrease fatty acid metabolism in the heart is to decrease circulating fatty acid levels. This can be achieved by the administration of glucose/insulin solutions[15], nicotinic acid[16] and beta-adrenargic blocking agents[17-18]. Another approach consists of directly modifying substrate utilization by the heart. Experimental studies with metabolic modulators suggest that inhibition of oxidative phosphorylation and fatty acid substrates can shift substrate utilization from fatty acid oxidation to glucose[19-20]. In the study by Fragasso et al, the beneficial effects of TMZ were operative, regardless of the level of FFA which were not affected by TMZ. Rather than reducing FFA blood levels, TMZ probably inhibits the utilization of fatty acid substrates.

Effects of TMZ on Cardiac Metabolism

In isolated rat hearts undergoing ischemia/ reperfusion, TMZ delays the occurrence of ischemic contracture and improves recovery of post-ischemic left ventricular dysfunction[19], as well as accelerates the recovery of mitochondrial oxidative phosphorylation and phosphocreatine resynthesis[20]. Fantini et al. [6] observed that the utilization of palmitoyl-carnitine by isolated cardiac mitochondria is inhibited by high doses of TMZ, in the absence of significant changes in pyruvate and citrate oxidation. Additional studies also suggest that TMZ acts by affecting myocardial substrate utilization, because the drug inhibits oxidative phosphorylation and utilization of fatty acid subtrates and shift metabolism from fatty acid to glucose oxidation[20]. Specifically, the agent inhibits beta-oxidation by selectively blocking the activity of 3-ketoacyl coenzyme A thiolase, the last enzyme of the oxidative chain[7]. The preferential oxidation of glucose observed during TMZ infusion affords often greater protection during reperfusion than during acute ischemia[21]. The reported reduction, by TMZ, of cellular acidosis induced by ischemia[2] is probably secondary to the mitochondrial function. All of these effects may contribute to reduce the deleterious effects of the ischemic insult, and, because they occur in the absence of detectable changes in systemic and coronary haemodynamic variables, the in vivo effects of TMZ on the ischemic myocardium are likely to depend on direct cytoprotection.

Effects of heparin and TMZ on ET-1 release

In patients with stable CAD, heparin may significantly decrease the ischemic threshold, probably by increasing plasma concentrations of FFAs, which can adversely affect the metabolism of the ischemic

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myocardium[34]. The administration of TMZ appears to completely abolish the deleterious effects of the heparin-induced increase of FFAs, probably by promoting the mitochondria's utilization of glucose and nonfatty substrates, allowing improvement of it's ability to sustain ischemia. Besides altering the metabolic balance of ischemic myocardium, increased FFA release may adversely influence endothelial function [25]. Different studies show, all patients exhibit a marked increase in ET-1 during exercise. However, ET-1 release significantly decreased with exercise when patients were taking TMZ. The decrement was greater during saline than during heparin It has been shown[26] that, in physiologic conditions, coronary endothelial cells predominantly utilize exogenous glucose for energy production. In these cells, glucose effectively suppresses the oxidation of lactate and palmitate, which are the preferred substrates for the whole heart. Similar to the cardiac muscle, both ischemia and an increase availability of FFA may negatively affect the endothelial cell's metabolism and cause the release of endothelial factors. One hypothesis is that improved myocardial and endothelial metabolism, together with the recent confirmation that TMZ reduces intracellular acidosis during ischemia[27], which could not only influence myocardial but also endothelial membranes, may help to explain the reduction in exercise-induced ET-1 release(and ischemia) observed with TMZ. A second hypothesis is that, by just decreasing the severity of myocardial ischemia, TMZ can inhibit ET-1release. Experimental data support the hypothesis that myocardial ischemia, by itself, contributes to the release of ET-1 in plasma[28, 29]. Infact, apart from endothelial cells[30] and vascular smooth muscle cells[29], cardiomyocytes[31] have also been found to produce ET-1 in response to myocardial ischemia. Furthermore, it has been shown very recently that endothelin release is a marker of ischemic severity rather than ischemia itself[32], and that TMZ, in the presence of high triglycerides levels, may improve both myocardial contractile recovery and ET- 1 release after low-flow ischemia[33]. Therefore, the decrease in ET-1 release with TMZ could likely be linked to a TMZ-indced reduction of myocardial ischemia, although, conversely the increase in ET-l release after heparin could be related to a greater magnitude of ischemia during this arm of the study by Fragasso et al. The hypotensive effects of endothelin-converting enzyme inhibitors and endothelin receptor antagonist could be useful in the treatment of different cardiovascular diseases. Development of such agents will increase our knowledge of the physiologic and pathologic roles of the endothelins and should generate drugs with novel benefits. Whether TMZ could play a role in this setting has yet to be determined.

Effects of TMZ in ischemic heart diseases

TMZ is an antianginal agent that increases cell tolerance to ischemia. The beneficial effects of oral TMZ on the frequency and severity of anginal attacks, as well as exercise capacity have been shown in several clinical studies[8-13]. The results of the study by Fragasso et al confirm previous finding by showing that, compared with placebo, TMZ increased the ischemic threshold when patients are receving saline. Furthermore, Fraggso study shows that in the experimental setting of increased FFA availability, as generated by unfractioned heparin, the addition of TMZ partly reverses the negative metabolic effect of these metabolites. These findings are consistent with the notion that TMZ, in addition to providing symptom relief and functional improvement in patients with angina pectoris, also has a cytoprotective action during ischemia.

Conclusion

In patients with stable CAD, heparin reduces the ischemic threshold. TMZ appears to reduce the effects of heparin, probably by inhibiting oxidative phosphorylation and FFA oxidation and by enhancing glucose metabolism. The concomitant novel observation of reduced ET-1 release is likely to be also dependent on TMZ-induced improvement of endothelial metabolism. Both mechanisms are likely to contribute significantly to the beneficial effects of TMZ. We believe that our observations are important and potentially relevant to the management of patients with a variety of cardiovascular conditions.

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SCLERODERMA - A CASE REPORT

AFTAB YUSUF RAJ, M N ISLAM

Introduction

Scleroderma is a generalized disorder of collagen, characterized by excessive fibrosis and degenerative changes in the skin and internal organs.[1] The concept of diffuse collagen disease was introduced by klemperer and his colleagues in 1942. Scleroderma classically involves skin, but cutaneous involvement may occur in focal patches (Morphea), in a linear distribution (Linear scleroderma), or in generalized, symmetric distribution.[2] The last is usually associated with systemic involvement (progressive systemic sclerosis) and is the usual adult from. Scleroderma in children usually has a focal distribution (morphea), systemic involvement is uncommon. The article presents a case report, presented to us with blackish discolouration of the skin over the upper limb, neck and back, contracture and wastening of the left upper limb, there was no systemic involvement.

Case Report

Asma, a I l years old girl, was admitted in BSMMU in the dept of Paediatrics in August 2001 with the complaints of blackish discolouration and hardening of skin over lift upper limb for the last 9 months. On admission, the patient was thoroughly examined. The skin over the affected part was fixed to the underlying tissue, it could not wrinkled, the elasticity was lost. There was no tenderness, pain or raised temperature over the involved skin, but there was wastening of the underlying muscles.

Fixation of the skin and assoicated muscular wasting leads to contracture of the left uppper limb, due to contrature, there was limited movement in the left elbow and wrist joints both during extension and flexion. The small joints of the left hand showed stiffness leading to clawhand deformity. The skin involvement(e.g. discolouration and hardening) which begin in the left upper extrimity and tip of the left hand, initially had a patchy, focal distribution, gradually the lesion extended peripherally and coalesced to involve the entire left upper extremity and neck. The skin over the back had similar course. There was muscular wasting with reduced tone and power in the left upper limb. Systemic examination showed nothing abnormality.

Investigations

Hb%-63%, TLC-11.600 cu.mm., poly-60%, lympho-15%, mono-03%, X-ray chest (P-A view), Echocardiography, Barium meal of the esophagus revealed normal pattern. Renal function test was also normal. But antinuclear factor and Rhuematic factor was positive. The skin biopsy result was suggestive of scleroderma.

Management

No specific therapy is known. But establishing a correct diagnosis is the first step in the management of scleroderma. Patient education is important to enable them to understand and participate in the management of their disease. Over the years, many encouraging uncontrolled studies extolling treatments of sclearoderma have appeared. Some of these studies hint at a possible beneficial effect of immunomodulating therapy e.g. azathioprine , 5-fluoro-uracil, cyclosporin, interferon-gamma, etc.

Factor XIII has only limited data using controlled trials, but what does exists seems positive. Apheresis is encouraging. Ongoing with photopheresis and the mast cell stabilizer ketotifen appear exciting. On another level, new insights into genomic alteration in skin fibroblasts and Tcell proto-oncogene expression have contributed to the understanding of the pathogenesis of this disease at the cellular level and new methods to measure changes in disease will help to find out response to therapy. Besides these, those who develop Reynaud's phenomenon may be helped by topical nitrates, ketanserin, nifedipm and vasodilator prostagi.andin. D-penicillarnine may be tried for patients with generalized scleroderma of less than 3 years duration. Angiotensin enzyme inhibators, while probably life saving in renal crises, do not affect the underlying systemic sclerosis per-se. Our patient was treated with topical steroids. Skin care and protection from trauma and cold and physiotherapy to retard contracture were taught.

Discussion

Seleroderma is an acquired disorder of connective tissue characterized epidemiologically by several distinctive features. The skin is most commonly affected, but the kindeys, heart, muscles and lungs are also frequently involved.[3] In some patients the disease appears to remain confined to the skin for many years, but in the majority, it progresses to

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visceral involvement. There is increased accumulation and turnover of collagen and other component of extra cellular matrix.4 From a demographic view point, the disease spares children and its incidence increases steadily with age, is much more frequent in women, especially during the childbearing years, occurs most frequently and severely in young black women; but overall has no prominent racial predilection . It is predominantly a female disease, with most patients having the limited form of disease characterized by the presence of the Anti-nuclear antibody and a mean survival of 27 years.[5] Family and genetic studies suggest a weak genetic predisposition. Persons with HLA-Al, B8, DR-3 appear to be genetically predisposed. Raised HLA-AIB-8 frequencies, correlate with a high, pathological immune response (Auto-immune disorders), as in progressive systemic sclerosis. In contrast, A3B7/DR2 prevalence, correlate with a low immune response, as in morphea. HLA typing may contribute to clinical differential diagnosis. The cause of systemic sclerosis remains unknown. The role of trans forming growth factor beta (TGF beta) in initiating fibrosis is well established.[6] Three main lines of investigation have been purposed to explain the excessive deposition of collagen. One is concerned with the factors leading to increased collagen synthesis. Early skin lesions show infiltration of the dermis with TLymphocytes before fibrosis occurs and there is T-Cell sensitization to collagen. A delayed hypersensitivity to collagen might cause the release of cytokines such as TNF-L and IL-I, which can attract fibroblasts and promote collagen synthesis. The newly deposited collagen may well perpetuate a vicious circle of cytokine such as hypergammaglobunemia(50% of cases), antinuclear antibodies(70-90% of cases), and rheumatic factor (25% of cases), points to a possible role for disordered humoral immunity as well. Autoantigens such as DNA topoisomerase I, centromere proteins , RNA polymerase I were shown to be specific targets of scleroderma patients. Autoantibodies in scleroderma are not only valuable diagnostic tools but also prognosticators of the disease. At last, it has been suggested that scleroderma is a disease of the microvasculature. With regard to vascular leisions (e.g. reynaud's phenomenon, telangectasia, renal artenopathy); TGF-BETA (transforming growth factor BETH) has been shown to promote angiogenesis in VIVO. An injurious activity of TGF-BETA can microvascular eudothelial cells could explain the intimal proliferation and microvascular obliteration seen in scleroderma . An important effect of TGF-BETA is its stimulation of fibroblast collagen and fibronection synthesis and their deposition into the extracellular matrix. Platelet activation is well documented in scleroderma. Endothelial injury followed by platelet aggregation leads to release of platelet factors that incrase vascular permeability and stimulate fibroblasts. Thus initially there is perivascular edema that is followed by pert adeventitial fibrosis and ischemic injury.

In most cases; the disease presents with symmetric edema and thickening of the hands and fingers or with reynaud's phenomenon. Systemic involvement may be manifestated as dysphagia, intestinal obstruction, malabsorption syndrome with weight loss, respiratory difficulties due to pulmonary fibrosis, malignant hypertension etc. The outlook appears to be worse in those with malignant hypertension leading to fatal renal failure , systemic involvement, late onset etc. The lungs are frequently affected and pulmonary disease may influence morbidity and mortality. The overall five years survival is 70%. The causes of death include pulmonary insufficiency,ventricular dysfunction, renal failure, malabsorption.

Conclusion

The course of the disease is variable , frequent relapses and remissions are common. Some may become quiescent and even regress, while some become progressive and rapidly fatal. There are no specific laboratory tests diagnostic of scleroderma, as well as no specific treatment. The group of "Chromosomal Breakage Syndrom" should now be expanded to include "Scleroderma". In these conditions,there is a tendency towards malignancy, particularly of myeloprociferative type, later in life.

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PSYCHIATRIC DISORDERS AMONG NEWLY DIAGNOSED THYROTOXIC PATIENTS

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Summary

The psychiatric manifestations of thyroid diseases have long been recognized. This study was carried out in the 'Thyroid and Endocrine Clinic' of Bangabandhu Sheikh Mujib Medical University to find out the psychiatric disorders among thyrotoxic patients. One hundred newly diagnosed untreated thyrotoxic patients were taken consecutively as a study subjects and same number of age and sex matched healthy subjects were taken as control. Among the cases 37% were male and 63% were female. In the control 35% were male and 65% were female. Mean (±SD) age of the patients and controls were 34.57±9.95 and 33.43±9.87 years respectively. Four types of thyrotoxicosis were diagnosed e.g Graves' disease (67%), Subacute thyroiditis (15%), Toxic multinodular goiter (14%) and Toxic adenoma (4%). The prevalence of psychiatric disorder was found 76% and 8% among the study and control groups respectively. In the study subjects, generalised anxiety disorder was 51%, panic disorder was 8%, somatization disorder was 2% and major depressive disorder was15%. In the control group, generalised anxiety disorder was 3%, panic disorder was 1%, somatization disorder was 1% and major depressive disorder was 3%. These results were statistically highly significant (P<001). Anxiety disorder was more prevalent in Graves' disease (67.15%) and subacute thyroiditis (66.66%). Major depressive disorder was more prevalent in toxic adenoma (50%) and toxic multinodular goitre (42.81%). The results were statistically significant (P<.05). This study shows that the psychiatric disorders among newly diagnosed thyrotoxic patients are very common and it varies with the types of thyrotoxicosis.

Introduction

Thyrotoxicosis occurs when the body's tissues are exposed to excessive amounts of circulating thyroid hormones. The disorders may arise as a result of hyperactivity of thyroid gland, ingestion of high level of thyroid hormone or secretion of thyroid hormone from an ecotopic site.[1] The prevalence of thyrotoxicosis in western country is about 20/1000 in female whereas 4/1000 in male.[2] According to 'Thyroid and Endocrine Clinic' report 23% of total attending thyroid patients were suffering from thyrotoxicosis among which Graves' disease was the commonest.[3]

Psychiatric disorders frequently found in thyrotoxic patients.[4] Prevalence of psychiatric disorders among thyrotoxic patients is 70%.[5] Thyrotoxicosis usually associated with psychiatric symptoms resemble of anxiety disorders and depressive disorders. However other psychiatric disorders like obsession, phobia, psychosis etc. may occur.[6]

As early as the 18th century, psychiatric symptoms have been observed among hyperthyroid patients. Complaints of these patients were appetite disturbances, weight loss, insomnia, weakness, tremor, palpitation and hyperkinisis. Hyperthyroidism may be associated with cognitive and intellectual changes, particularly poor concentration, attentional difficulties and poor mental control.[7,8,9]

The precise nature of the relationship between thyrotoxicosis and the various mental pehnomena is unkonwn. The disease has been characterized as a metabolic disease manifested by impaired psychobiological integration particularly involving the autonomic nervous system.[10] The sympathetic nervous system plays role in the direct cause of palpitations, tachycardia, sweating, tremor and hyperreflexia.[11] The clinical sign and symptoms of hyperthyroidism are mediated by increased serum level of the thyroid hormones - thyroxine (T_4) & triiodothyronine (T_3) which cause direct stimulation of sympathetic nervous system to release excess catecholamine.[12] Beta-blocker can ameliorate many hyperthyroid symptoms without affecting levels of thyroid hormones.

Whybrow et al. 1969[5], Mac Crimmon et al. 1979[13], Trzepaz et al. 1988[12], stated that psychiatric

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disorders, such as anxiety and depression are very common in hyperthyroid patients. Conway et al. 1978[14], Whybrow and Prange 1981[15] described that it is possible that beta-adrenergic receptors in central nervous system may be altered and this alterations was due to excess levels of thyroid hormones and such alterations may be related to psychiatric manifestations.

Thyroid hormones can modify brain sodium concentration. Shaw demonstrated that affective disorders may be manifestation of altered brain excitability produced by an abnormal distribution of sodium and potassium across neuronal membrane.[16] Thus, thyroid hormone induced electrolytes shifts may have a role in producing mental disturbances in thyrotoxicosis.[17]

Thyrotoxicosis is a common thyroid disease worldwide including Bangladesh. The psychiatric manifestations of thyrotoxicosis are well established for a long period. But unfortunately there is no such study in Bangladesh. So, this study was done to find out the psychiatric disorders among thyrotoxic patients.

Materials & Methods

This is a cross sectional, analytical and comparative study done on one hundred newly diagnosed untreated thyrotoxic patients attending in 'Thyroid and Endocrine Clinic" of Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh from January 2001 to December 2001.

Patients were collected by consecutive random sampling method. Thyrotoxicosis were diagnosed on the basis of clinical features and relevant investigations. Prior to interview the consent of patients were taken and assured that full confidentiality would be maintained. Separate data sheets were used for diagnosis of thyrotoxicosis, collection of socio-demographic informations and mental state examination. Psychiatric assessment were done with SCID (Structured Clinical Interview for DSM-111R). Seriously cognitive impaired, pregnants or lactating patients were excluded from the study.

SCID was produced by Spitzer et al in 1986.[18,19] This is used to diagnose the case in research setting according to DSM-111R (Diagnostic and Statistical Manual 3rd edition for Research) diagnostic criteria. These are the revised criteria of the 3rd edition of American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorder. Analysis was done by computer software statistical program for social service (SPSS).

Results

One hundred thyrotoxic patients were interviewed for psychiatric assessment. One hundred age and sex matched healthy controls were included in this study. Mean (±SD) age of the study and control subjects were 34.57 ± 9.95 and 33.34±9.87 years respectively. Among the study group, male and female were 37% and 63% respectively. Male female ratio was 1:1.7. In the control group, male and female were 35% and 65% respectively (table-I).

Table-I

Age and sex distribution of thyrotoxic patients (N=100)

	Number of patients in percentage								
	GD (n=67)		SAT (n=15)		TMNG (n=14)		TA (n=4)		Total
Age in years	M	F	M	F	M	F	M	F	M+F = t
15-25	6	10	0	5	0	0	0	0	6+15=21
26-35	14	15	2	3	1	3	0	1	17+22=39
36-45	9	8	2	3	1	3	0	0	12+14=26
>45	2	3	0	0	0	6	0	3	2+12=14
Total	31	36	4	11	2	12	0	4	37+63=100

GD=Graves Disease, SAT-Subacute thyroiditis, TMNG=Toxic Multinodular Goiter, TA=Toxic Adenoma, M=Male, F=Female

Among 100 thyrotoxic patients, 67 were Graves' disease (GD), 15 were subacute thyroiditis (SAT), 14 were toxic multinodular goiter (TMNG), and 4 were toxic adenoma (TA) (Table-I).

Most of the Graves' (66.16%) and subacute thyroiditis (66.67%) patients were in younger age group (<36 years) (Table-I). Most of the toxic multinodular goiter (71.43%) and toxic adenoma (75%) patients were in age group of >35 years (Table-I).

Common presentations of the thyrotoxic patients were– palpitation (95%), excessive sweating (95%), weight loss (95%), heat intolerance (94%), weakness (93%), cold preference (92%), fatigueness (87%), irritability (80%), nervousness (80%), sleep disturbance (71%), warm hand (94%), moist hand (74%), tremor (87%), tachycardia (84%) and goiter (88%) (Table-II).

Seventy Six percent of thyrotoxic patients fulfilled the criteria for diagnosis of psychiatric disorders. Only 8% of controls fulfilled the criteria for diagnosis for psychiatric disorder. The results were statistically highly significant (P<0.001).

In the study group generalized anxiety disorder (GAD) was 51%, panic disorder (PD) was 8%, somatization disorder (SD) was 2% and major depressive disorder (MDD) was 15%. In the control group generalized anxiety disorder (GAD) was 3%, panic disorder (PD) was 1%, somatization disorder (SD) was 1% and major depressive disorder (MDD) was 3% (Table-III).

Psychiatric disorder was more common (80.6%) in Graves' disease than other varieties of thyrotoxicosis. Anxiety disorder (Generalized anxiety disorder +Panic disorder) was more common in Graves' disease (67.15%) and subacute thyroiditis (66.66%) whereas, depressive disorder was more common in toxic adenoma (50%) and in toxic multinodular goiter (42.8%) (Table-III). These results were statistically significant (P=<.05).

Table–II

Common presentations of the thyrotoxic patients (N=100).

Palpitation	95%
excessive sweating	95%
weight loss	95%
heat intolerance	94%
weakness	93%
cold preference	92%
fatigueness	87%
irritability	80%
nervousness	80%
sleep disturbance	71%
warm hand	94%
moist hand	74%
tremor	87%
tachycardia	84%
goiter	88%

Table-III

Distribution of psychiatric disorders in thyrotoxic patients (N=100) and control group (n=100)

		With psychiatric disorder					Without psychiatric disorder
	TYPE	GAD	PD	SD	MDD	TOTAL	Total
Study group	GD (n=67)	39 (58.20%)	6 (8.95%)	2 (2.98%)	7 (10.44%)	54 (80.60%)	13
	SAT (n=15)	9 (60%)	1 (6.66%)	0	0	10 (66.66%)	5
	TMNG (n=14)	3 (21.42%)	1 (7.14%)	0	6 (42.8%)	10 (71.42%)	4
	TA (n-4)	0	0	0	2 (50%)	2 (50%)	2
	N=100	51	8	2	15	76	24
Control group	n=100	3	1	1	3	8	92

GAD=Generalised Anxiety Disorder, PD=Panic disorders, SD= Somatization Disorder, MDD=Major depressive disorder, GD= Graves' disease, SAT=Subacute Thyroiditis, TMNG=Toxic Multinodular Goiter, TA=Toxic Adenoma.

Discussion

Thyrotoxicosis is a common thyroid disorder worldwide including Bangladesh. It can occur in any age.[6] In this study, 21% patients were under the age of 25 years, 39% patients were in age of 26-35 years, 26% patients were in age group of 36-45 years and 14% were above 45 years. It was also found that 65% patients were in age group of 25-45 years which is consistent with Hossain's study.[20] 37% were male and 63% were female. Male -female ratio was 1:1.7. This relatively lower ratio in comparison to western country was also revealed in Hossain's study.[20] In western country, the study of Wartofsky[21] and Edwards et al[3] we found that this ratio is much higher (1:7). This variation might be due to less female attendance in our hospital from sociocultural and economical problem.

The most common presentations of thyrotoxic patients were excessive sweating (95%), weight loss (95%), palpitation (95%), heat intolerance (94%), warm hand (94%), cold preference (92%), tremor (87%), tachycardia (84%), irritability (80%), nervousness (75%), sleeplessness (71%) and goiter (88%) which were consistent with the study of Hossain and Stern et al.[20,6]

Among the thyrotoxicosis, Graves' disease was the commonest (67%) which is consistent with the study of Alam et al.[1] and Stern et al.[6] but percentage is less than those above studies. It might be due to a significant number of subacute thyroiditis patients (15%) were found in our study. This increase incidence of subactue thyroditis might be explained by increase viral infection and availability of modern diagnostic facilities. 14% toxic multinodular goiter and 4% toxic adenoma were found in our study which is consistent with the study of Stern et al.[6]

Seventy six percent of the patients met the DSM-IIIR criteria for diagnosis of psychiatric disorder at the time of interview. This result was consistent with the study of Kathol et al[5], Whybrow et al[22] and Chowdhury.[23] But in the control group, 8% met the same criteria for diagnosis of psychiatric disorder. Psychiatric disorder in general population was 6.5%in the study of Chowdhury et al. and 13.5% in an ECA study.[26]

Generalized anxiety disorder was more common in subacute thyroiditis (60%) and Graves' disease (58.20%) but less common in toxic multinodular goiter and absent in toxic adenoma. This variation might be due to variation of hormonal level as well as short duration of the disease. Hormonal level more higher in Graves' disease and in subacute thyroiditis. Anxiety symptoms are related to the level of thyroid hormones.[22] Major depressive disorder was more common in toxic adenoma (50%) and toxic multinodular goiter (42.8%) and less common in Graves' disease (10.44%) and absent in subacute thyroiditis. This discrepancy might be explained as prolong duration of suffering with prominent cosmetic disfigurement in female patients. Generally females are more predisposed to depression than male (2:1) and any chronic disease and disfiguration are the risk factors for depression.[27]

In the study group, anxiety disorder was the commonest (59%) followed by depressive disorder (15%). Similar findings also found in the study of Kathol et al.[5] Whybrow et al.[22] and Trzepaces et al.[12] In the control group, anxiety disorder was 4% and depressive was 3%. These results are consistent with the study of Chowdhury et al.[24] and Jenkins et al.[25]

Conclusion

The psychiatric disorders among newly diagnosed thyrotoxic patients are very common and it varies with the types of thyrotoxicosis . Generalized anxiety disorder is the commonest type of psychiatric disorder followed by depressive disorder. Early diagnosis and treatment of psychiatric disorders of thyrotoxic patients improve the patents quickly and effectively. So, co-operation of Endocrinologist and Psychiatrist are needed for better management of the thyrotoxic patients.

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