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Editorial

Malaria

An introduction is mandatory to begin an article. However, the topic is such that it needs no introduction – either for doctors or for laymen.

I shall begin with some well-known facts about a very well-known disease. The word 'MALARIA' means bad (mal) air (aria). The protozoan parasites causing the disease belong to the genus *Plasmodium*. The commonest form of malaria is Benign Tertian Malaria caused by *Plasmodium vivax.* In this form, fever with chill and rigor comes every 48 hours. A close second is Malignant Tertian Malaria caused by *Plasmodium falciparum*. Next comes Ovale Tertian Malaria by *Pl. ovale* and Quartan Malaria by *Pl. malariae.* In Quartan Malaria, fever comes every 72 hours.

Mosquito is the vector of malaria and the commonest vector in our part of the country is the female *Anopheles stephensii.* Other species of Anopheles, Culex and other genera of mosquito may also act as vectors. When a female mosquito with its salivary glands loaded with sporozoites bites a human, the sporozoites enter the blood stream and pass to the liver and enter the hepatocytes. Inside these liver parenchymal cells, the parasite passes a small part of its life and undergoes what is known as exoerythro-cyticschizogony. The end products of this part of the malaria cycle are merozoites. The time spent in the liver is around 6-9 days, depending upon the parasite species. The number of merozoites formed from each sporozoite ranges between 12000-40000. Hence, there is a huge increase in the number of parasites. The merozoites are released into the circulation and enter the erythrocytes to begin the erythro-cyticschizogony. The Pl. vivax attack young RBCs. Since the percentage of young RBCs is not very high (about 2%) in the circulation, Pl. vivax infection usually does not cause overwhelming parasitemia. Pl. falciparum on the other hand is not so choosy and can attack all RBCs. As a result, overwhelming parasitemia is a feature of Pl. falciparum infection. Inside the RBCs, the parasite passes from merozoite to trophozoite form. The early trophozoite is popularly known as the "ring form" as it resembles a signet ring. The size and intricacies of the ring are different in the different parasite species. An expert can identify a species correctly by examining the ring. The trophozoite changes to the schizont which finally forms erythro-cytic merozoites. Now, the number of merozoites produced from each hepatocytic merozoite is between 16-32 depending on the species of the parasite. In case of the falciparum parasite, the stages beyond the ring form occur in the capillaries of the deeper organs hence not usually found in the peripheral blood smear. However, if they are found in the peripheral blood smear, it indicates a bad prognosis. After a few cycles of erythrocyticschizogony, due to some as yet unknown stimulus, some merozoites entering the erythrocytes undergo gametogony rather than schizogony. The gametocytes arising from merozoites from a single RBC are all of the same type – either macro or micro gametocyte. These latter forms are responsible for transmission of the infection to the mosquitoes.

When a female, susceptible mosquito bites an infected human with gametocytes in the peripheral circulation, the macro and micro gametocytes enter the gut of the mosquito and are converted to macro (female) and micro (male) gametes. Fertilization occurs and a zygote is formed. The zygote traverses across the gut lining as an ookinete and then forms an oocyst. Sporozoites develop inside the oocyst which bursts when mature. The sporozoites enter the salivary gland of the mosquito and await their turn to infect a non-infected host.

Such is the life cycle of the malaria parasite. But the parasite readily fools the physician by two important deviations – relapse and recrudescence. Relapse occurs in case of Pl. vivax and Pl. ovale where some sporozoites entering the liver remain dormant, to reawaken after a period of months, giving rise to a fresh attack of malaria. Recrudescence occurs in case of Pl. falciparum infection where the merozoites remain dormant in the erythrocytes, to reawaken after a short length of time. These two phenomena are important from the treatment point of view because the patient may suffer from a fresh bout of malaria (in the absence of mosquito bite) after treatment. Thus in cases of P. vivax and P. ovale, radical cure is necessary.

However, pathophysiology of malaria particularly cerebral malaria is a vast area and covered in a following article of this issue.

The most important aspect of any disease is its prevention and control. Malaria prevention is based on mosquito control, early treatment and bite prevention. Malaria vaccines are still in the pipeline and a concept for the future. The parasites have developed clearcut resistance against drugs. We are specially afraid of drug resistance in case of Pl. falciparum as most deaths due to malaria are due to this parasite. Chloroquine, which was the mainstay of malaria treatment in the recent past is now out of use because of widespread drug resistance. The genetic markers of chloroquine resistance have been well established. The present mainstay of treatment is Artemisinin from China and the regime is ACT or Artemisinin Combination Therapy. Great care is being taken to prevent resistance from developing but ACT resistance has already started to show itself in South America and Myanmar. The latter is our next door neighbor and India must maintain strict vigil to prevent ACT resistance from becoming widespread. Africa also is on red alert because it has the maximum number of malaria cases and already holds the dubious crown of having the highest number of malaria deaths every year. Another point of concern is that there are very few new drugs in the pipeline. The antimalarial drugs and their use are being discussed in detail in a seperate article in this issue.

But let us end on an optimistic note – by 2015 new drugs will be available and malaria vaccine development work will also be in a very advanced stage. Let us hope for the best !

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Lipid Profile in Vivax and Falciparum Malaria in Eastern India

Dr. Pradeep Chakrabarty, Dr. Joydeep Mukherjee

Introduction :-

Malaria is a multi-systemic disease. It is caused by Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae & Plasmodium knowlesi. It is a vector-borne disease. It is spread from man to man by female anopheline mosquito. It is highly prevalent in India and many parts of the World. Malaria causes high morbidity and mortality.

In malaria patients, it had been shown that, plasma levels of triglyceride, total cholesterol, HDL-Cholesterol, LDL-Cholesterol, VLDL-Cholesterol & the ratio between total cholesterol and HDL-Cholesterol have marked abnormality[1,2,3,4]. Previous studies had tried to find out the importance of lipid profile changes in malaria patients and correlation between lipid profile abnormality with severity, morbidity and mortality in malaria patients. Our study was an effort to find out the same in patients suffering from malaria in Eastern India.

Materials and methods :-

We had undertaken a hospital-based study in the Medicine ward of Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, Kolkata August, 2009 to July, 2011.

First twenty-one admitted malaria cases, being detected to have malaria with microscopy and/or rapid antigen method, have been selected. OPD cases were excluded. The data was collected from indoor cases of both male and females, from both urban and rural areas of both adult and children who are admitted in medicine ward. No Sampling technique was used. We had recorded retrospectively their age, gender, hospital serial number and type of malaria from hospital record sheet.

Each patient has undergone following investigations, namely plasma triglyceride, plasma total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol and plasma albumin.

Persistence of symptoms during treatment, duration of hospitalisation and cost of treatment were also recorded as a marker of morbidity.

The data were entered on to an Excel spreadsheet, which was cross-validated monthly. The mean value and standard deviation were measured with MS-Excel software. Data was analysed using Graph Pad Instat software. Unpaired t test was used for parametric comparisons. Proportions were examined using Fisher's exact test. A multiple logistic regression model was used to determine risk factors for different outcomes. $p < 0.05$ was taken as the cut-off for significancce. Data were presented below as mean [Standard deviation].

Results :-

In our study, we found age of the patients to be 33 [14] years. Sixteen (76%) patients were male. Fourteen (67%) patients were suffering from malaria caused by Plasmodium vivax, six

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(28.5%) patients were suffering from Plasmodium falciparum malaria and one (4.5%) patient was suffering from mixed malaria (both Plasmodium vivax and Plasmodium falciparum).

Patients had presented within 5[3] days of symptom onset and during treatment, they had became afebrile within 2[2] days. They are admitted for 6[3] days and the expense of treatment was rupees 5305[3967] only.

We had found marked changes in lipid profile parameters in our study population [table 1]. There was marked elevation in plasma triglyceride level and marked fall in plasma cholesterol level, especially HDL cholesterol level than normal population. It had been also found that the ratio between total cholesterol and HDL cholesterol is markedly elevated than reference range.

We had found plasma triglyceride to be positively correlated with duration of symptoms before hospitalisation and the length of hospital stay; both the correlations were statistically significant [table 2].

Plasma cholesterol was positively correlated with plasma albumin and it was statistically significant [table 2].

Plasma HDL cholesterol is positively correlated plasma albumin and it was statistically significant [table 2].

We also tried to find out significant difference in lipid profile between patients suffering from malaria caused by Plasmodium vivax and Plasmodium falciparum; but no statistically significant differences had been found [table 3].

Table 1. Alteration in Lipid profile in study population.

Lipid profile parameter	Plasma level in study population Mean [SD] mg/dl	Normal value mg/dl
Triglyceride	254 [128]	<150
Cholesterol	94 [26]	<200
HDL-C	18 [10]	40-59
LDL-C	47 [17]	70-130
VLDL-C	29 [11]	20-40
Total cholesterol/HDL-C	6.6 [3.6]	<4.5

Table 2. Correlation between Lipid parameters with other parameters.

Lipid parameter correlated with other parameters	Other parameter correlated with lipid parameter	r value	p value
Triglyceride	Duration of symptoms (days)	0.58	0.009
	Length of hospital stay (days)	0.53	0.03
Cholesterol	Plasma albumin (gm/dl)	0.41	0.03
HDL-C	Plasma albumin (gm/dl)	0.54	0.0002

Table 3. Comparison of vivax and falciparum malaria patients regarding lipid profile changes.

Lipid Profile	Plasmodium vivax (n=14)	Plasmodium falciparum (n=6)	p value
Triglyceride	209 [90]	333 [161]	0.12
Cholesterol	88 [20]	106 [37]	0.30
HDL-C	18 [10]	18 [11]	>0.99
LDL-C	43 [12]	55 [25]	0.30
VLDL-C	27 [11]	33 [9]	0.22
Total cholesterol/ HDL-C	6.4 [3.6]	7.7 [4]	0.51

Discussion :-

Only few studies were done on plasma lipid profile changes in malaria patients. Kittl EM et al[1] from Zentrallabor, Germany had tried to find out HDL cholesterol to be a sensitive diagnostic parameter in malaria. They had found that at the time of admission, there was hyper-triglyceridemia, hypo-cholesterolemia, and an extreme decrease in HDL-cholesterol level, both in falciparum and vivax malaria cases. They had found low HDL cholesterol to have high diagnostic sensitivity but no specificity for malaria.

Kang YH et al[2] from Kwandong University College of Medicine, Goyang, Korea evaluated the usefulness of a panel of tests composed of malaria non-specific tests as a surrogate marker for diagnosis of malaria. They had found malaria antibody test showing sensitivity of 97.1% and specificity of 99.1%. Each parameter of platelet count, NRBC (%), D parameter and HDL-cholesterol showed sensitivity of 86.8%, 41.2%, 81.8%, and 70.6%, and specificity of 85.9%, 96.3%, 72.3%, and 81.7%, respectively. Panel test without including HDL-cholesterol showed sensitivity of 91.2% and specificity of 81.6%, and that including HDL-cholesterol showed sensitivity of 91.2% and specificity of 86.2%. So inclusion of HDL cholesterol had increased specificity of malaria tests.

Krishna A. P. et al[3] from K. S. Hegde Medical Academy, Mangalore, India had studied lipid profile changes in malaria patients and found that plasma HDL cholesterol to be lower and plasma triglyceride, total cholesterol, LDL cholesterol and VLDL cholesterol to be higher in malaria cases than control group.

Mohanty S et al[4] from Ispat General Hospital, Orissa, India, had studied plasma lipid profile changes in 60 falciparum malaria patients (37 severe and 23 mild) and compared with 83 healthy controls. They had found that plasma triglyceride level was lower in patients than controls but the difference was significant only those with severe malaria ($p < 0.001$). Patients with severe malaria had significantly higher plasma lipid abnormality than patients with mild malaria ($p < 0.001$). They had also found LDL cholesterol to be significantly less in malaria cases than healthy controls ($p < 0.001$) and plasma albumin was reduced significantly and it was positively correlated to HDL cholesterol levels ($r = 0.715$ and $r = 0.895$) in both mild and severe malaria cases respectively.

In our study, we had found that plasma triglyceride level was elevated and plasma

cholesterol (total, HDL, LDL) was reduced than normal level in malaria patients (table 1). Patients with falciparum malaria had more elevated plasma triglyceride level and patients with vivax malaria had more reduced plasma cholesterol level than their counterparts, but statistically not significant (table 3). Ratio between total cholesterol and HDL cholesterol was high in malaria patients than in normal population (table 1) and this elevation was more marked in patients with falciparum malaria, but statistically not significant (table 3). So our study results were corroborating with previous studies.

We had found statistically significant relationship between lipid profiles with other parameters in malaria patients (table 2). Patients with higher plasma triglyceride level had presented with longer duration of symptoms ($r = 0.58$; $p = 0.009$) and their hospital stay was also longer ($r = 0.53$; $p = 0.03$). Patients with lower plasma total cholesterol level had lower serum albumin ($r = 0.41$; $p = 0.03$). Lower serum albumin had positive correlation with lower plasma HDL cholesterol ($r = 0.54$; $p = 0.0002$) in patients with malaria.

So patients with higher plasma triglyceride level were most likely to have higher duration of hospital stay. Those malaria patients, who were suffering from longer period of time, were found to have higher plasma triglyceride level. Serum albumin, being considered to be a negative acute phase reactant and become low in acute stress; was found to be positively correlated with plasma HDL cholesterol level. So it was time to think whether HDL cholesterol was also a negative acute phase reactant or not.

Though the ratio between total and HDL cholesterol was very high, which was supposed to be an atherogenic cardiovascular risk factor, whether it had caused increased cardiovascular morbidity and mortality in malaria patients was not known.

Why the patients suffering from malaria were having plasma lipid profile abnormalities, was not known. But probably, either malaria parasite factors or host factors were the culprit in causing disturbance in lipid metabolism in the patients suffering from malaria. Whether those changes were transient or long lasting, would be the topic of future research.

Conclusion :-

- Malaria patients were suffering from plasma hyper-triglyceridemia which was positively correlating with their morbidity.
- Malaria patients were suffering from lower plasma total and HDL cholesterol; both had positive correlation with lower plasma albumin level; a negative acute phase reactant.
- There was no statistically significant difference between patients suffering from vivax and falciparum malaria in regard to lipid profile changes.

Limitation :-

Study population were just twenty-one and the study was a cross-sectional retrospective one; without having provision for follow-up for studying lipid profile changes in those patients.

Recommendation :-

More study is needed with larger study population with a study design comprising of follow-up to show series of changes of lipid profile in malaria patients during disease and recovery.

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Evaluation of Multimodality Treatment of Vocal Fold Nodules

Dr. Soumitra Ghosh[1], Dr. Amitabha Roychoudhury[2], Dr. Prasenjit Dey[3], Dr. B. K. Roychaudhuri[4]

Abstract

Objective :-

The aim of this study was to assess the efficacy of the different modalities of treatment for vocal fold nodules, namely voice therapy and microlaryngoscopic surgery.

Study design :- Prospective study.

Participants :-

Ninety patients with vocal fold nodules attending the Voice Clinic of the Department of ENT and Head and Neck surgery, Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, Kolkata, were selected for the study from July 2010 to June 2012.

Methodology :-

Ninety patients who were diagnosed to be suffering from vocal fold nodules were included in the study. All of these patients were examined by 70 degree rigid fibreoptic laryngoscope before their inclusion.

Inclusion criteria : Patients presenting with hoarseness persisting for more than 6 weeks in spite of adequate conservative therapy were included.

Exclusion criteria : Patients with vocal cord polyp, Reinke's oedema, infective aetiology, sulcus vocalis and clinical suspicion of malignancy were excluded.

There were 20 patients with hard nodules (Group A) and 70 patients with soft nodules (Group B). The patients with hard nodules were subjected to microlaryngeal surgery followed by voice therapy. Patients with soft nodules were subjected to voice therapy alone. All the patients were reassessed at 3 months and 6 months interval by rigid fibreoptic laryngoscopy and perceptual change of voice based on GRBAS scale.

Result :-

Sixteen out of 20 patients of hard nodules recovered following microlaryngeal surgery and the rest of the 4 patients continued to have voice therapy. Fifty-five patients out of 70 patients with soft nodules recovered with voice therapy alone.

Conclusion :-

Thus in a well organised voice clinic, voice therapy alone or along with microlaryngeal surgery, when required, is effective in improving voice quality as assessed by self rated and observer rated methods.

Key words :-

Hard and soft nodules, GRBAS, voice therapy, microlaryngeal surgery.

Introduction :-

Vocal fold nodules are small bilateral swellings less than 3 mm in diameter situated at the junction of anterior one-third and posterior two thirds of vocal cords (Andrews M, 1999). They may be classified as hard or soft nodules depending upon the degree of keratinisation. Vocal abuse or misuse or overuses have been

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suggested as the probable etiopathogenesis of vocal fold nodules (Yamaguchi et al, 1986).

Voice therapy encompasses a myriad of techniques which seek to eliminate potentially harmful vocal behaviors, alter the manner of voice production, and/or enhance vocal fold tissue healing following injury. It is an effective and appropriate method of therapy either in itself or as a complement to other treatment modalities (e.g. surgery, medications). Surgery for vocal fold nodules is in the form of phonomicrosurgery with the help of operating microscope.

Objective :-

The purpose of this study is to assess the role of multimodality therapy namely voice therapy and microlaryngoscopic surgery in managing vocal fold nodules.

Materials & Methods :-

Study design :- A prospective study.

Set up : Voice clinic at the Department of ENT and Head-Neck Surgery, Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, Kolkata.

Study Period :- July 2010 to June 2012.

Patient Criteria :-

Inclusion criteria : Patients presenting with hoarseness persisting for more than 6 weeks in spite of adequate conservative therapy were included.

Exclusion criteria : Patients with vocal cord polyp, Reinke's oedema, infective aetiology sulcus vocalis and clinical suspicion of malignancy, were excluded.

The hard nodules were found to be larger, more prominent, pointed and whitish on rigid fibreoptic laryngoscopy as compared to the soft nodules. Of the 90 patients 64 were females and 26 were males. The number of patients with hard nodules was 20 (Group A) and those with soft nodules were 70 (Group B).

All the patients were assessed in our voice clinic by laryngologists and speech and language pathologist of our department. The advice offered to the patients comprised of (a) vocal hygiene, lifestyle and dietary advice, (b) voice therapy, (c) medical treatment & (d) microlaryngoscopic surgery, depending on the type of nodule. Co-existent acid reflux, upper respiratory tract infections and allergies were treated medically.

Group A patients were subjected to initial one month of voice therapy followed by microlaryngoscopic surgery (Kleinsasser O, 1991) & followed by voice therapy again. Voice therapy before and after surgery, was executed in order to undo the faulty phonatory habits, which may have led to nodule formation.

The microlaryngeal surgery was performed under general anaesthesia, where the vocal folds were inspected and the nodules excised using an operating microscope with lens of f = 400 mm. The centre of the nodule was grasped with grasping forceps and gently retracted medially towards the opposite cord. Micro-scissors were used to cut the mucosa close to its base, thus preserving normal vocal fold mucosa, maintaining a straight vibratory edge and preventing a secondary notching. Both nodules were removed at the same sitting without damaging the anterior commissure. The patients were subjected to complete voice rest for the first 48 hours followed by 10 days of restricted voice use when the voice is used sparingly. Postoperatively voice therapy was started 2 weeks after surgery and continued for about 2 months.

Group B patients were offered voice therapy alone for 3 months. Voice therapy was applied to each patient for 45 minutes a week on an average. The patients were asked to perform some home exercises for 10 minutes 4 times a day.

The study population was reassessed at 3 months and 6 months interval based on fibreoptic laryngoscopic findings, perceptual evaluation of voice based on GRBAS (Grade, Roughness, Breathiness, Asthenia, Strain) scale (Takahasi et al, 1976) and subjective improvement based on Verbal Rating Scale (VRS). In GRBAS scale each dimension is rated on a four point scale, where:

0 = no perceived abnormality,

1 = mild,

2 = moderate and

3 = severe abnormality.

The dimensions of GRBAS scale are as follows:

Grade : overall degree of voice deviance from normal;

Roughness : irregular fluctuation of fundamental frequency;

Breathiness : turbulent noise produced by air leakage;

Asthenia : overall weakness of voice;

Strain : impression of excess effort during voice production.

Statistical Analysis :-

The results were obtained after analyzing the GRBAS data given as arithmetic mean +/- standard deviation. Determination of statistically significant differences in subjective parameters before and after voice therapy was achieved by Wilcoxon signed-ranks test. The differences were considered statistically significant for $P < 0.05$.

Result :-

Sixteen (80%) out of 20 patients with hard nodules (Group A) who underwent micro-laryngoscopic surgery followed by voice therapy had near normal voice quality and the rest 4 patients with hard nodules continued to have voice therapy Fig.1(a). Fifty-five (78%) out of 70 patients having soft nodules (Group B) who underwent voice therapy had normal voice quality as assessed by patients ratings (VRS) and by observer (GRBAS) Fig.1(b).

Graphical representation of the results obtained after treatment of hard and soft vocal cord nodules. The y-axis shows the number of cases.

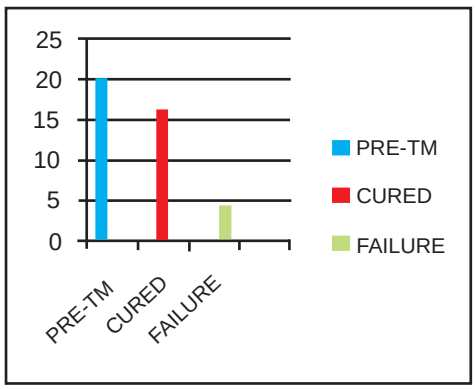

Fig.1 (a): HARD NODULES treatment outcome

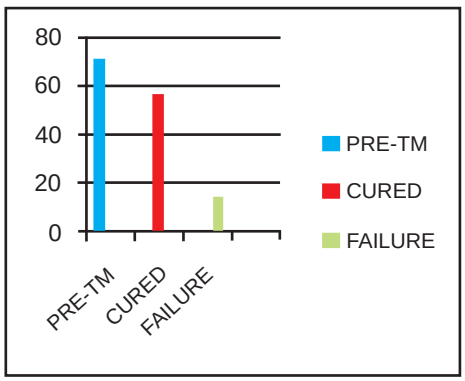

Fig.1 (b): SOFT NODULES treatment outcome

The GRBAS values before and after treatment are shown in Table-1. P values on Wilcoxon signed-ranks test, mean +/- standard deviation of pre-treatment and post-treatment measures are reported *Asthenia is not included in statistical analysis. P values < 0.05 were considered statistically significant. A general reduction of severity was found for all parameters both after surgery and voice therapy. The difference on Wilcoxon signed-ranks test was statistically significant, the only exception being the A parameter. The A parameter was not included in the statistical analysis, because it was considered 0 both before and after treatment for all patients.

Table 1: Shows perceptual voice analysis (GRBAS scale) before and after treatment.

N=90	Before treatment	After treatment	P value
GRADE	1.8+/- 0.5	0.7+/- 0.6	<0.0001
ROUGHNESS	0.8 +/- 0.7	0.2 +/- 0.4	<0.0001
BREATHINESS	1.2 +/- 0.3	0.6 +/- 0.4	<0.0001
*ASTHENIA	0	0	
STRAIN	0.2 +/- 0.4	0	0.003

Discusstion :-

Voice therapy is an established and effective modality in treating vocal cord nodules (Blood GW, 1994/Verdolini-Marston K et al, 1995). The present study corroborates with the findings of the previous authors. Seventy-eight per cent of our patients with soft nodules had resolution of their nodules with voice therapy alone which is again similar to the study conducted by Mc Crory et al, 2001 which showed 76% of patients demonstrated elimination and/or reduction of vocal cord nodules with voice therapy.

According to most of the authors soft nodules are managed by speech and language therapy whilst hard nodules are managed by microlaryngoscopic surgery (Kleinsasser O, 1991) and speech therapy (Harris M, 2008). Our study is also of the same opinion.

Leonard in 2009 commented that voice therapy can be effective in improving voice quality and tissue health but does not necessarily result in complete resolution of pathology.

Pedersen and McGlashan (2012) concluded in their Cochrane database review that there is a need for high-quality randomised controlled trials to evaluate the effectiveness of surgical and non-surgical treatment of vocal cord nodules.

Conclusion :-

In Hard Vocal Fold Nodules phonosurgery is the mainstay of treatment followed by voice therapy. In soft nodules voice therapy is the important treatment which may cure majority of patients. In a well organised voice clinic, voice therapy and/or surgery is effective in improving voice quality as assessed by self rated and observer rated methods.

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The Efficacy of Clonidine Added to Bupivacaine as Compared with Bupivacaine Alone Used in Supraclavicular Brachial Plexus Block for Upper Limb Surgeries

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Abstract :-

This study was conducted to compare the efficacy of clonidine added to bupivacaine with bupivacaine alone in supraclavicular brachial plexus block for upper limb surgeries. Sixty patients were included and divided into two equal groups. First group received 40 ml. of bupivacaine 0.25% plus 0.15 mg. (1 ml.) of clonidine, second group had 40 ml. bupivacaine 0.25% plus 1 ml. NaCl 0.9% respectively. The onset and duration of both sensory and motor block along with haemodynamic changes (heart rate, NIBP, oxygen saturation) were recorded. The level of sedation and side effects were also observed. In this study the addition of clonidine to bupivacaine resulted in faster onset (study group 15.2±1.44, control group 20.4±1.12, $p<0.001$) and longer duration of sensory block (study group 544±31.2, control group 302±34.4, $p=.0363$) as well as analgesia (study group 561.2±30.96, control group 324.4±34.08, $p=.0001$) without any adverse haemodynamic changes. Thus we can conclude that clonidine is an effective adjuvant for improving the quality and duration of supraclavicular brachial plexus block for upper limb surgeries.

Key words : Brachial plexus block, bupivacaine, clonidine, upper limb surgeries.

Introduction :-

Acute postoperative pain is the result of a complex physiological reaction to tissue injury. The dorsal horn of the spinal cord is the site of termination of primary afferents and there is complex interaction between such afferent fibers, intrinsic spinal neurons, descending pain modulating fibers and various associated neurotransmitters such as serotonin, nor epinephrine, acetylcholine, adenosine and glutamate in the dorsal horn[1]. Local anesthetics administered as regional nerve blocks provide postoperative pain relief in many surgical procedures by blocking signal traffic to the dorsal horn. Certain drugs may be used as adjuvant to local anesthetics to lower doses of each agent and enhance analgesic efficacy with reduced incidence of adverse reactions. Tramadol and fentanyl had been successfully used as adjuvants to local anesthetic in brachial plexus block.[2,3]. The concurrent injections of Alpha-2 adrenergic agonist drugs has been suggested to improve the nerve block characteristic of local anesthetic solutions through either local vasoconstriction[4] and facilitation of C fiber blockade[5] or a spinal action caused by slow retrograde axonal transport or simple diffusion along the nerve[6]. Clonidine is a selective Alpha-2 adrenergic agonist with some Alpha-1 agonist property. In clinical studies, the addition of clonidine to local anesthetic solutions improved peripheral nerve blocks by reducing the onset time, improving the efficacy of the block during surgery and extending postoperative analgesia[7,8]. Clonidine possibly enhances or amplifies the sodium channel blockade action of local anesthetics by opening up the potassium channels resulting in membrane hyperpolarization, a state in which the cell is unresponsive to excitatory input[9].

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A number of these studies have focused on the effect of clonidine as adjuvant to either lignocaine[8] or mepivacaine[7]. Further, these studies were done using clonidine 150 mcg, a moderately high dose with adverse drug reactions. We have also compared this moderately high dose of clonidine versus placebo as adjuvant to bupivacaine for brachial plexus block by supraclavicular approach for orthopedic procedures of moderate duration in our study.

Material And Methods :-

The study was conducted in Ramakrishna Mission Seva Pratisthan, Vivekananda Institute of Medical Sciences. Written informed consent was obtained from each patient and the study was approved by the Institutional Ethics Committee.

Sixty patients aged 18 to 60 years, scheduled for elective orthopedic operations in the upper limb, under supraclavicular brachial plexus block, were included in this study. They were of American Society of Anesthesiologists (ASA) Grade I or II physical status. The procedures were of moderate duration and included implant removal, both bone plating, fixation of lower third of humerus and olecranon fixation.

Patients receiving chronic analgesic therapy, those with severe cardiopulmonary disease, thyroid disorders, diabetes mellitus, central or peripheral neuropathies, history of allergy to local anesthetics, or other contraindications to regional anesthesia were excluded from the study.

The study was designed as a prospective, randomized, double-blind, placebo-controlled trial. Participants were allocated to two equal groups of 30 each using a computer generated random number list. Group A (study group) patients received 40 ml of 0.25% bupivacaine and 0.150mg (1ml) clonidine, while group B (control group) received 40 ml of 0.25% bupivacaine and 1 ml of 0.9% sodium chloride through a supraclavicular approach for brachial plexus block. The allocation sequence was generated by the author entrusted with statistical analysis. The anesthesiologist administering the injections and observing the effects received serially numbered sealed envelopes indicating the A or B codes for the anesthetic mixture to be administered. The A and B syringes were loaded with drug by another author not involved in administering the injections and in further evaluation of the patients. All observations (hemodynamic variables, oxygen saturation, level of sedation, time required to achieve surgical block in the operation theatre and the time to rescue analgesic in the post-anesthesia care unit) were also recorded in a blinded manner.

Once a patient was brought into the operation theatre, standard monitoring was set up, including noninvasive arterial blood pressure, heart rate, and pulse oximetry. An 18-gauge IV cannula was inserted in the forearm and an infusion started with lactated Ringer's solution. The surgical procedure was performed by using a standard arm tourniquet inflated to 70 mmHg higher than systolic blood pressure. Hemodynamic variables were measured 10 min before block placement and every 15 min thereafter till the end of surgery.

Nerve blocks were performed, with the aid of a nerve stimulator, by using a 22G short-beveled, insulated (Teflon-coated) 25 mm long stimulating needle. Stimulation frequency was set at 2 Hz, while the intensity of stimulating current was initially set to deliver 1mA and gradually decreased to < 0.5 mA. Negative aspiration was performed while injecting the drug solution to avoid any intravascular placement. The onset

of sensory and motor blocks on the operated limb were evaluated every 5 min after the completion of anaesthetic injection by one of the authors who were unaware of the drug combination administered. Sensory block was assessed by pinprick discrimination (with 22G hypodermic needle) and motor block was evaluated by asking the patient to move the forearm against resistance and to flex the forearm. A pinprick sensation on the contralateral arm was scored as 100 points. Patients were requested to compare pinpricks in the primary innervation areas of the respective nerves in the anesthetized arm with the contralateral arm as reference. The scale ranged from 100 (full sensation) to 0 point (no sensation). Brachial plexus block was considered successful by Vester-Andersen's criteria[10] when at least two out of four nerve territories (radial, ulnar, median and musculo-cutaneous) were effectively blocked. Onset of sensory block was defined as a reduction of sensibility to 30% or less while onset of motor block was defined as reduction of muscle power to grade 3 or less. The time to surgical blockade was defined as the time from the end of anesthetic injection to loss of pinprick sensation along the distribution of the ulnar and radial nerves along with inability to circumrotate the thumb of the concerned limb. When surgical anesthesia was not achieved in a patient even after 30 min from the anesthetic injection, the case was considered as failed block and the operation was then performed under general anesthesia.

Following operation, all patients were observed in post-anesthesia care unit and received rescue analgesic as soon as they complained of any pain. This consisted of tramadol 100 mg IV, repeated if necessary. Patients were given clear instruction to ask for a rescue analgesic as soon as they sensed discomfort caused by pain on the operated hand. The time from the end of anesthetic injection in the operated hand till the first request for postoperative rescue analgesic was recorded in each patient.

The primary outcome measure was duration of analgesia. This was estimated as the time interval from placement of the block till first injection of rescue analgesic. Secondary outcome measures were onset and duration of sensory and motor blockade and any suspected adverse drug reactions.

Noninvasive arterial blood pressure, heart rate and hemoglobin oxygen saturation monitoring was done throughout the procedure. The degree of sedation was evaluated by using the University of Michigan Sedation Scale (UMSS)[11] of 0 to 4.

All patients were clinically assessed during discharge from the orthopedic ward and again after 3 weeks (at the first routine postoperative examination) for occurrence of any neurological complication.

Data were summarized as mean ± standard deviation or as percentages. Statistical analysis was performed by MS Excel 2010 software. Comparison of categorical variables between the two groups was by Chi-square test. Numerical variables were normally distributed and were compared by Student's unpaired 't'-test. All analyses were two-tailed and $P < 0.05$ was considered statistically significant.

Results :-

We recruited 30 subjects per group, more than the calculated sample size. The age, sex distribution, height and body weight in the two groups were found to be comparable (Table1).

Table 2 shows onset and duration of sensory and motor blocks and post operative requirement of rescue analgesia. It was found that the onsets of both sensory and motor blocks were significantly shorter in group A and duration of sensory block was also significantly greater in this group receiving clonidine. Requirement of rescue analgesia was delayed in group A. The mean time from block placement to the first request for pain medication i.e. duration of analgesia was 561 ± 30.96 min in the clonidine group but 324.4 ± 34.08 min in the other group. This difference was highly significant ($p<0.001$) statistically as well as clinically.

No statistically significant difference was observed in heart rate, blood pressure, and oxygen saturation between the two groups at any time.

The sedation score between clonidine and the control group was comparable throughout the study period. All the patients were alert (sedation score 1) in both the groups at all times of observation.

No adverse effect was observed in any of the groups.

The above values are expressed as mean standard deviations.

The p values between the two groups are calculated using student unpaired 't' test.

Table 1. Comparison of the Demographic Data.

	GROUP A	GROUP B
SEX (F/M)	12/18	14/16
AGE (years)	38.8±11.3878	38.6±11.975
HEIGHT (cms)	161.8±7.967	161±5.965
WEIGHT (kgs)	59.8±7.087	57±7.0466

The sex distribution was expressed in fraction but the age, height and weight was expressed as mean ± standard deviation.

Table 2. Comparison of Onset of Sensory and Motor Block, Duration of Sensory Block, Motor Block and Analgesia.

	Onset of sensory block (mins)	Onset of motor block (min)	Duration of sensory block (min)	Duration of motor block (min)	Duration of analgesia (min)
Bupivacaine and clonidine (GROUP A)	15.2±1.44	17.2±1.44	544±31.2	464±39.2	561.2±30.96
Bupivacaine only (GROUP B)	20.4±1.12	22.4±1.12	302±34.4	260±32	324.4±34.08
	$p < 0.001$	$p < .001$	$p = 0.0363$	$p = 0.2946$	$p = 0.0001$

The values of both groups are expressed in minutes.

The values between group A and group B regarding the onset of both sensory and motor

block was found to be clinically earlier and statistically significant. The comparison of duration of sensory block and analgesia between the groups were also statistically significant (<0.05) but the duration of motor block was not statistically significant (>0.05).

Discussion :-

Supraclavicular brachial plexus block is called the spinal anesthesia for the upper limb. The aim of the study was to evaluate the anesthetic and analgesic effect of clonidine when added to the supraclavicular brachial plexus block with injection bupivacaine 0.25%.

The result of the present randomized controlled trial clearly suggests that the patients in both the groups were comparable regarding the demographic data such sex, age, weight and height which was clinically and statistically insignificant (table 1).

Clonidine, as adjuvant to 0.25% bupivacaine for supraclavicular brachial plexus block, prolongs the duration of analgesia as well as sensory block (table 2). The motor block was prolonged clinically but not statistically. Onset times of blocks were also shown to be shortened though the study was not powered to measure these effects.

These findings are at variance with the study by Duma et al which showed no difference in analgesia after addition of clonidine 0.5 ig/kg to levobupivacaine in axillary block.[12] Probable explanation for this inconsistency may relate to inter-patient variations in the anatomy of the plexus sheath and difference in the spread of local anesthetics in the plexus sheath depending upon the block technique. More explanations may be forthcoming when the mechanism of adjuvant action of clonidine in this setting is elucidated.

Bernard and Macarie,[8] evaluating the effects of adding 30-300µg clonidine to lignocaine for axillary brachial plexus anesthesia, reported that the addition hastened the onset of the block and improved the efficacy of surgical anesthesia. There are reported differences in the effects of administration of low-dose clonidine on time of onset and efficacy of nerve block, which may be explained by differences in the type of nerve block, exact mixture injected, and technique used to perform the block (single injection versus multiple injections). In fact, a multiple-injection technique was used, which is known to improve both onset time and quality of nerve block,[13] and this could have reduced the differences in onset time between the two groups.

In a dose-finding study evaluating the minimum effective dose of clonidine required to prolong duration of analgesia after axillary brachial plexus block, Singelyn et al[7] suggested that 0.5µg/kg clonidine should be used. At this dose, significant prolongation of analgesia was achieved without undue sedation, hypotension, or bradycardia. It has been widely demonstrated in different studies that subcutaneous or intramuscular injection of clonidine is not as effective as perineural administration[14] suggesting that the local anesthetic-prolonging effect of clonidine is probably mediated locally at the neuron.[15] This may also explain the variation in response in different types of peripheral nerve blocks, probably related to the rate and extent to which the injected anesthetic solutions penetrate into the nerve.[10] Even though injecting clonidine as the sole analgesic into the brachial plexus sheath does not provide clinically relevant analgesia',[16] it has been demonstrated to inhibit the action potential of A and C fibers in de-sheathed sciatic nerves.[9] Many authors

favor the hypothesis that clonidine exerts its local anesthetic-prolonging effect directly on the nerve fiber, as a result of complex interaction between clonidine and axonal ion channels or receptors.[5,10,14] Peripheral antinociception induced by clonidine has also been related to 2-adrenoceptor-mediated local release of enkephalin-like substances.[17]

We selected a 150 μg dose of clonidine keeping in mind the hemodynamic adversities that could have been produced but in our study no such significant side effects were demonstrated. A similar study by Singh S, Aggarwal A[8] found that clonidine when added to bupivacaine in the dose of 150μg hastened onset of block, improved block efficacy, prolonged postoperative analgesia without causing any significant adverse reaction like hypotension or bradycardia.

But we need a dose finding study to come up with the ideal dose of clonidine as adjuvant to 0.25% bupivacaine for supraclavicular brachial plexus block.

In conclusion, clonidine added to bupivacaine is an attractive option for improving the quality and duration of supraclavicular brachial plexus block in upper limb surgeries.

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The Effect of Intravenously Administered Dexmedetomidine on Perioperative Haemodynamics and Isoflurane Requirements in Patient Undergoing Abdominal Hysterectomy

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Summary :-

After approval from our institutional ethical committe and obtaining written informed consent from the patients, 60 female patients of ASA physical status I & II, undergoing elective abdominal hysterectomy, were selected for the study. They were randomly assigned into two groups, one group receiving dexmedetomidine 1µg/kg i.v. (group D) & the other group saline, the control group (group C). On arrival to operation theatre, baseline parameters (NIBP, heart rate, ECG, Spo_2) were recorded and all patients were given midazolam, glycopyrolate, ondansetron and fentanyl. The dexmedetomidine, diluted in 100 ml saline and 100 ml saline alone were administered 10 minutes prior to induction and general anaesthesia was induced with thiopentone and maintained with O_2, N_2O (40:60) and Isoflurane 0.4% at the beginning. Hemodynamic parameters were recorded and isoflurane concentration was adjusted to maintain blood pressure and heart rate within 20% of preoperative values. Fentanyl was given 50 microgram of incremental dose if isoflurane dial concentration exceeded 3%. In both the groups, blood pressure & heart rate increased after tracheal intubation. The post intubation surge in heart rate and blood pressure were much less in group D compared to group C & the difference was statistically significant ($p<0.05$). The mean dial concentration of isoflurane was significantly less (84.13%) in patients in group D than group C with better preservation of intraoperative haemodynamic stability. Thus a single intravenous bolus dose of dexmedetomidine 1 µg/kg given 10 minutes before induction of anaesthesia reduced increase in heart rate and blood pressure response to tracheal intubation, maintained intraoperative abdominal hysterectomy.

Key words : Dexmedetomidine, Haemodynamic response, Isoflurane, Abdominal hysterectomy.

Introduction :-

Dexmedetomidine, the pharmacologicaly active d-isomer of medetomidine (4, [5] -[1- (2, 3-dimethylphenyl)-ethyl] imidazole), is a highly specific and selective α_2 adrenoreceptor agonist.[1,2] It has been found to have sedative properties and to be well tolerated at the doses studied so far. It causes a dose-dependent decrease in blood pressure and heart rate associated with decreased concentration of plasma epinephrine.[3] It inhibits central noradrenergic transmission and this in turn can reduce the MAC values of volatile anaesthetic.[4,5] However, there are other postsynaptic α_2 mechanisms which are involved in its anaesthetic sparing action.[6] This action of dexmedetomidine can be added to the wealth of material demonstrating a similar action for clonidine, the prototype α_2 agonist.[7,8,9,10]

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Materials & Methods :-

After approval of Ethical Committee, Vivekananda Institute of Medical Sciences, Ramakrishna Mission Seva Pratishthan, the study was done on 60 female patients of ASA physical status I & II aged 30-45 years, undergoing elective abdominal hysterectomy. Double-blind randomized trial was applied. After written informed consent from each patient, they were randomly assigned into two groups, each containing 30 patients. In the evening prior to surgery, 0.5 mg alprazolam was given orally to both groups. On arrival in the operating room, baseline pulse rate, non-invasive blood pressure (SBP, DBP, MAP), ECG and spo_2 were recorded. The study drug diluted in 100 ml saline and 100ml saline alone were administered i.v. slowly for 10 minutes. Study group (group D) received dexmedetomidine (1µg/kg) and control group (group C) received saline. All patients received midazolam 1mg i.v., glycopyrolate 0.2 mg i.v., fentanyl 2µg/kg i.v. and ondansetron 4 mg. Thereafter, induction was done with i.v. thiopental (4mg/kg). Laryngoscopy and intubation was done with succinyl choline 2mg/kg and anaesthesia was maintained with nitrous oxide and oxygen (60 : 40) and isoflurane (0.4% initially). Further relaxation was provided with vecuronium bromide. When haemodynamic parameters increased above acceptable value (20% of baseline value) with lowest possible concentration of isoflurane (0.4%), the dial concentration was increased with an increment of 0.2% up to 1%, then at 0.5% interval. Fentanyl was given in increments of 50µg to supplement isoflurane anaesthesia when dial concentration of 3% isoflurane could not restore blood pressure and heart rate within acceptable value. Isoflurane was terminated at the start of fascial layer closure and nitrous oxide after skin closure. Neuromuscular blockade was reversed with neostigmine 0.05mg/kg and glycopyrolate 10 µg/kg i.v. After adequate reversal assessed by eye opening on request, patients were extubated & sent to post operative recovery area.

Parameters For Evaluation :-

1. NIBP (SBP, DBP, MAP) and Heart rate-
   - Baseline
   - 10 minutes after administration of drug
   - Immediately after intubation
   - 15 minutes interval during rest of operation
   - Postoperatively.
2. Sedation – to be assessed by attending nurse at 2 minutes, 5 minutes and 10 minutes after administration of drugs according to Ramsay sedation score.
3. Isoflurane dial concentration through out the procedure and recorded as 20 minutes interval.
4. Time to awakening – time interval between termination of nitrous oxide and eye opening upon request.

All parameters were recorded and statistically analysed.

Statistical Analysis :-

It was performed using student t test. A p value < 0.05 was considered statistically significant. Statistical analysis was done with MS XL 2007 software.

Results :-

The patient groups were comparable with respect to age, weight, height and duration of surgery. Demographic characteristics of patients are shown in table 1.

Table 1. Demographic Characteristics of Patients and Anaesthesia.

	Control Group	Study Group	p value
Number of patients	30	30	N.A.
Age (year)	39.57 ± 1.38	40.86 ± 1.89	0.999
Weight (kg)	56.87 ± 1.43	56.57 ± 1.65	0.806
Height (cm)	159.27 ± 1.70	159.8 ± 1.34	0.8556
Duration of anaesthesia (min)	101.86 ± 12.60	107.30 ±11.23	0.9343

About 10 minutes after receiving dexmedetomidine, patients were drowsy but arousable (sedation score 2).

Systolic Blood Pressure :-

Before administration of study drugs, the blood pressure values did not differ (p-0.995). After 10 minutes of administration of study drugs, there was no significant (p-0.098) decrease in systolic blood pressure. In both groups there was increase in blood pressure after intubation. The increase in dexmedetomidine group was found to be significantly less ($p<0.0001$) in comparison to control group. The differences were very highly significant up to 30 minutes of drug administration. Thereafter systolic blood pressure though maintained at lower level in group D than group C, but the differences were not statistically significant.

Table 2: Systolic Blood Pressure Response in Two Groups.

	Baseline	10 min	After intubation	15 min	30 min	45 min	60 min	75 min	100 min	Recovery
Group C	128.2 ± 1.78	116.6 ± 1.54	138.4 ± 2.50	137.5 ± 2.06	136.3 ± 2.23	132.8 ± 4.43	143.3 ± 6.02	131.4 ± 3.71	129.2 ± 2.61	126.53 ± 1.94
Group D	130.3 ± 3.38	111.6 ± 3.67	130.3 ± 4.18	128.2 ± 3.18	126.4 ± 2.62	126.5 ± 2.99	139.7 ± 5.30	131.1 ± 4.29	125.7 ± 3.40	122.27± 2.92
p Value	0.995	0.098	<0.0001	0.007	0.0003	0.3026	0.9944	0.4613	0.9999	0.2323

Diastolic Blood Pressure :-

Before administration of study drugs, the blood pressure values did not differ (p-0.2518). Statistically highly significant differences were found after 10 and 15 minutes of drug administration. The difference was significant after intubation. During rest of the intraoperative period and recovery, diastolic blood pressure though maintained at lower level in group D than group C, but the differences were not statistically significant.

Table 3: Changes in Diastolic Blood Pressure in Two Groups.

	Baseline	10 min	After intubation	15 min	30 min	45 min	60 min	75 min	100 min	Recovery
Group C	80.57 ± 1.25	73.53 ± 0.73	96.43 ± 6.75	92.13 ± 5.56	91.13 ± 5.30	85.93 ± 3.46	91.1 ± 4.07	85.2 ± 1.77	78.9 ± 3.42	72.77 ± 1.25
Group D	83.23 ± 1.68	70.73 ± 1.70	73.93 ± 2.38	72.87 ± 1.74	71.67 ± 1.32	70.6 ± 1.30	88.97 ± 0.93	84.53 ± 5.06	75.57 ± 3.52	73.17± 7.24
p Value	0.2518	<0.0001	0.0245	<0.0001	0.1987	0.1524	0.9929	0.6189	0.9997	0.4533

Mean Arterial Pressure :-

Before administration of study drugs, the blood pressure values did not differ (p-0.2169). After 10 minutes of administration of study drugs, there was highly significant (p< 0.0001) decrease in mean arterial pressure. Similar finding was there after intubation. Thereafter mean arterial pressure though maintained at lower level in group D than group C, but the differences were not statistically significant.

Table 4: Mean Arterial Pressure Response in Two Groups.

	Baseline	10 min	After intubation	15 min	30 min	45 min	60 min	75 min	100 min	Recovery
Group C	96.6 ± 0.93	87.8 ± 0.91	110.5 ± 4.63	107.2 ± 3.79	106 ± 3.66	101.6 ± 2.28	108.5 ± 3.31	100.7 ± 1.81	95.77 ± 2.58	91.4 ± 0.95
Group D	99 ± 1.64	84.5 ± 2.11	92.9 ± 2.12	91.3 ± 1.63	89.8 ± 1.39	89.3 ± 1.74	105.7 ± 2.18	99.9 ± 4.29	92.3 ± 2.99	88.4± 4.82
p Value	0.2169	<0.0001	<0.0001	0.2589	0.065	0.3966	0.999	0.6618	0.1764	0.9996

Heart Rate :-

Baseline heart rates between the groups did not differ (p-0.9951). After administration of study drugs there was significant decrease in heart rate in dexmedetomidine group in comparison to control group (p <0.0382). Heart rate increased in both groups after intubation, but in the dexmedetomidine group the difference was significantly less (p< 0.0001). Differences were also very highly significant after 15, 30 even up to 15 minutes of administration of drugs. Thereafter, heart rate was maintained at lower level in dexmedetomidine group, the difference being statistically non-significant.

Table 5 : Heart Rate Changes in Two Groups.

	Baseline	10 min	After intubation	15 min	30 min	45 min	60 min	75 min	100 min	Recovery
Group C	77 ± 2.08	72.2 ± 2.47	93.7 ± 3.77	90.3 ± 2.30	87.6 ± 2.76	89.4 ± 2.95	93.7 ± 6.06	90.1 ± 3.94	82.4 ± 3.38	68.6 ± 2.33
Group D	75.2 ± 3.14	62.1 ± 1.40	80.8 ± 3.21	77.03 ± 3.16	73.4 ± 3.35	83.2 ± 3.85	85.4 ± 5.38	82.8 ± 4.262	72.9 ± 3.36	64± 1.87
p Value	0.9951	0.0382	<0.0001	<0.0001	0.0003	<0.0001	0.1195	0.1482	0.0708	0.1043

Perioperatively 2 patients in the dexmedetomidine group required atropine for bradycardia (heart rate less than 50 beats/min). Bradycardia improved immediately thereafter, and none of the patients required a second dose.

Anaesthetic Requirement :-

The isoflurane dial concentration required during anaesthethic maintainence for hysterectomy was 84.13% less in dexmedetomidine group compared to control group. During 20-40 minutes, 40-60 minutes and 60-80 minutes, differences in dial concentration was very highly significant, but not initially during 0-20 minutes.

Table 6: Isoflurane requirement (dial concentration) in two groups :

	0-20 min	20-40 min	40-60 min	60-80 min	Overall
Group C	0.6267 ± 0.24	1.19 ± 0.53	2.35 ± 0.51	0.837 ± 0.21	1.16
Group D	0.43 ± 0.07	0.55 ± 0.27	0.91± 0.49	0.64 ± 0.13	0.6325
p value	0.8734	0.0003	<0.0001	<0.0001	

Intraoperatively 20 patients in control group and 8 patients in dexmedetomidine group received supplemental fentanyl.

There were no differences among the groups in awakening time during recovery. The oxygen saturation, respiratory rate or incidence of nausea & vomiting also did not differ in two groups.

Even though the study protocol indicates chance of light anaesthesia, during interviews on first postoperative day none of the patient complained of intraoperative awareness.

Discussion :-

Our study was conducted to evaluate whether administration of dexmedetomidine to a commonly administered balanced anaesthetic regimen improves perioperative haemodynamic stability and reduces volatile anaesthetic requirement.

In our study the patients in the dexmedetomidine and control groups were matched for age, body weight and height. There were no significant statistical differences in demographic profile and duration of anaesthesia between the two groups as shown in Table 1.

The major findings in our study were -

Dexmedetomidine at dose of 1 µg/kg i.v. given 10 minutes prior to induction

- Attenuated the haemodynamic response to laryngoscopy and intubation.
- Maintained haemodynamic stability during intraoperative period.
- Reduced intraoperative isoflurane requirement.

In our study fentanyl requirement was also found to be less (67% in group C and 33% in group D required fentanyl).

Dexmedetomidine due to its α_2 adrenergic effect attenuates the sympathetic response to laryngoscopy and intubation decreasing rise in heart rate and blood pressure. Reduction in heart rate is common finding in its use and therefore all patient studied were given glycopyrolate. Bradycardia requiring treatment with atropine was found in 2 subjects in D group.

Sagiroglu AE, Celik M, Orhon Z, et al have demonstrated effect of dexmedetomidine on controlling haemodynamic response to tracheal intubation at different doses ranging from 0.25 to 1µg/kg and found optimal dose was 1µg/kg which is in accordance with our study.[11] Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S also showed that preoperative administration of a single dose of dexmedetomidine resulted in progressive increase in sedation, blunted the haemodynamic responses during laryngoscopy, and reduced opioid and anaesthetic requirements.[12] De Lange S investigated the effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability and found that haemodynamic responses to tracheal intubation and extubation were reduced in the dexmedetomidine group as was intra-operative heart rate variability.[13]

Dexmedetomidine has been widely studied as an anaesthetic adjuvant and its anaesthetic sparing effects are well known. In studies by Aho and colleagues and Aantaa and co-workers, it has been shown to reduce isoflurane requirement dose dependently up to 90%.[14,15] In our study isoflurane requirement was decreased by 84.13% in group D in comparison to control group, in accordance with earlier studies.

In conclusion of our study, it can be stated, that dexmedetomidine may be an attractive adjunctive agent due its haemodynamic stabilizing and anaesthetic sparing effect.

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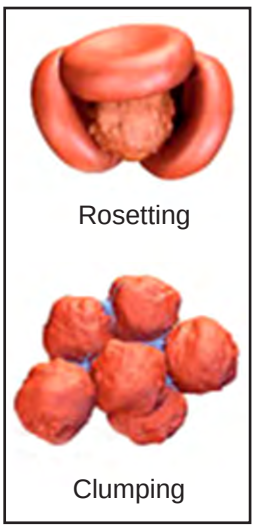
Pathophysiology of Cerebral Malaria : An Insight

Dr. Indrajit Mishra

Cerebral Malaria is a dreadful complication of severe falciparum malaria and frequently leads to death, even when appropriate therapy has been given. Various hypotheses for the pathophysiology of Cerebral Malaria have been postulated over time: alteration of vascular permeability, immuno-pathological mechanism, intra-vascular coagulation, mechanical obstruction of microvessels, or metabolic effects. Each of these hypotheses was in vogue at one time or the other with its more or less well justified therapeutic interventions. This article is an attempt to look into the currently favoured hypothesis which assumes a central role for intracapillary sequestration of infected erythrocytes by cytoadherence to various endothelial receptors.

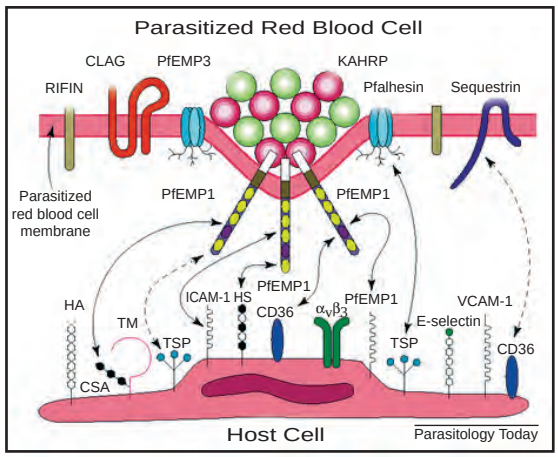
Cytoadherence and Sequestration :-



A consistent histological finding in cerebral malaria in both children and adults is the presence of infected and non-infected erythrocytes packed within cerebral vessels. Sequestration might happen as a consequence of **cytoadherence** of infected erythrocytes to endothelial cells via P falciparum derived proteins on the infected erythrocyte surface attaching to ligands upregulated in the venules. Sequestration can be increased when adherent infected erythrocytes bind other infected erythrocytes **(clumping)** or non infected erythrocytes **(rosetting)** or use platelets to bind other infected erythrocytes (platelet-mediated clumping). Thereafter these adhered erythrocytes sequester out of the microcapillaries and thrive in the perivascular compartment **(Sequestration).**

Parasite binding is mediated by a group of variant surface antigens expressed at the red-cell surface during development. The best described is P falciparum erythrocyte membrane protein-1 (PfEMP1) which is encoded by a family of about 60 variant genes associated with different binding phenotypes.

PfEMP1 is able to bind to many host receptors



on endothelial cells, chief among which are CD36 and the intercellular adhesion molecule 1 (ICAM1). The binding of infected erythrocytes to ICAM1 has been implicated in the pathogenesis of cerebral malaria. Postmortem studies have revealed upregulation of ICAM1

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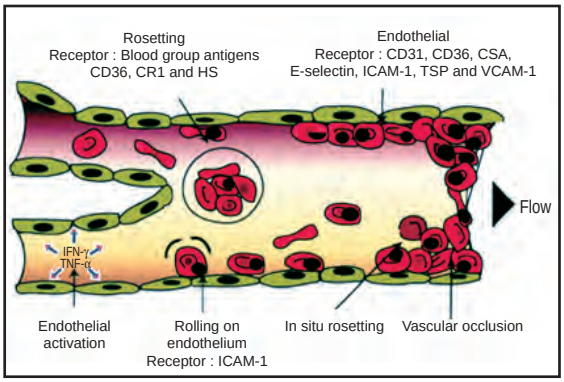
expression on the cerebral vascular endothelium in cerebral malaria, which is localised to areas of parasite-induced sequestration.

Reduction in microvascular flow :-

Sequestration of infected and non-infected erythrocytes within the cerebral vessels reduces the microvascular flow. In addition, the presence of parasites inside erythrocytes decreases the ability to deform (low red-cell deformability) so that erythrocytes have more difficulty in passing through the microvasculature. The rapid reversibility of clinical symptoms suggests that tissue necrosis is unlikely to occur. However, there may be a critical reduction in the supply of metabolic substrate to the brain. This will be exacerbated by increased demand during seizures and fever, and may be worse in patients with severe anaemia or hypoglycaemia. Cerebral blood flow may also be reduced by high intracranial pressure. Inflammatory cytokines can result in inefficient use of substrates.



Inflammatory response :-

P *falciparum* infection results in increases in both proinflammatory and anti inflammatory cytokines. The balance of inflammatory mediators seems critical to parasite control, but their role in the pathogenesis of severe malaria is unclear.

With the rupture of a Schizont there is a pulse release of TNF, IL 1 and gamma INF which inturn induces release of a cascade of proinflammatory cytokines including IL 6, 8, 12 and 18. These Cytokines can induce (mimic) many of the symptoms and signs of a malarial paroxysm (shivering, headache, chills, spiking fever, sweating, vasodilation, hypoglycemia). The cytokines also enhance the second process thought to be responsible for cerebral malaria i.e. sequestration of infected erythrocytes.

Postulated mechanisms for coma in cerebral malaria

Obstruction of cerebral microvascular flow:-

Parasite-induced sequestration of infected and uninfected erythrocytes mediated through cytoadherence, rosette formation, autoagglutination and reduced red cell deformability.

Seizures :-

Overt seizures, Subtle and electrographic seizures, Postictal state.

Impaired delivery of substrate :-

Hypoglycaemia, Anaemia, Hypoxia.

Impaired perfusion :-

Hypovolaemia, Shock, Acidosis.

Raised intracranial pressure :-

Disruption of the blood–brain barrier.

Toxins :-

Nitric oxide, Reactive oxygen species, Excitotoxins, Malaria toxin.

Clotting :-

Intravascular coagulation as a minor mechanism.

Nitric oxide might be a key effector for tumour necrosis factor in the pathogenesis of malaria. Nitric oxide is involved in host defence by killing intracellular organisms, in maintenance of vascular status, and in neurotransmission. Cytokines may upregulate inducible nitric oxide synthase (iNOS) in brain endothelial cells, increasing production of nitric

oxide, which diffuses into brain tissue and disrupts neuronal function. Nitric oxide may rapidly and reversibly reduce the level of consciousness because it is short-lived and can easily diffuse across the blood–brain barrier to interfere with neuronal function.

The associations found between disease and nitric oxide activity, iNOS, or genetic polymorphisms in the iNOS promoter gene have not been consistent. Results have varied with age, endemicity, and geographical location.

Blood–brain-barrier function :-

Because parasites are largely confined to intravascular spaces, one main question regarding the pathogenesis of cerebral malaria is how these parasites cause neuronal dysfunction. There is growing evidence that parasite induced sequestration of infected and uninfected erythrocytes changes blood–brain barrier function.

Post-mortem analysis has shown widespread cerebrovascular endothelial cell activation (increased ICAM1 endothelial staining, reduction in cell-junction staining, and disruption of junction proteins), particularly in vessels containing infected erythrocytes. Perivascular macrophages in these areas expressed scavenger receptor and sialoadhesin—normally expressed only after contact with plasma proteins. However, such disruption of intercellular junctions was not associated with significant leakage of plasma proteins (fibrinogen, IgG, or C5b-9) into perivascular areas or cerebrospinal fluid. ICAM1 binding by infected erythrocytes results in a cascade of intracellular signalling events that disrupt the cytoskeletal-cell junction structure and cause focal disruption to the blood–brain barrier. Focal disruptions in the barrier at sites of sequestration could result in the exposure of sensitive perivascular neuronal cells to plasma proteins and increased concentrations of cytokines and metabolites caused by abnormalities in microcirculation; this may contribute to reduced consciousness and seizure activity.

Raised Intracranial Pressure :-

The most likely cause of raised intracranial pressure is increased cerebral blood volume as a result of sequestration of infected erythrocytes and increased cerebral blood flow from seizures, hyperthermia or anaemia.

Post-mortem studies have provided a wealth of detailed information but they reflect, at best, pathology at a single point after death in the most severely ill patients. Sequestration is extensive, occurring in all parts of the brain to a similar extent, but with substantial variability between individuals and between vessels in an individual. Cut surfaces show petechial haemorrhages. Electron microscopy shows knob-like protrusions on the surface of infected erythrocytes and at sites of attachment to vascular endothelium with high concentrations of extraerythrocytic haemozoin (a product of haemoglobin metabolism by malaria parasites) inside cerebral vessels. Thus, rupture of infected erythrocytes can lead to an inflammatory process within and around brain capillaries. Axonal injury correlates with plasma lactate, cerebrospinal fluid protein and Glasgow coma score. Increased concentrations of the microtubule-associated protein tau (from degenerated axons)—but not neural cell body or astrocyte proteins in cerebrospinal fluid—suggests that most of the brain parenchymal damage is in axons.

Outcome of cerebral malaria :-

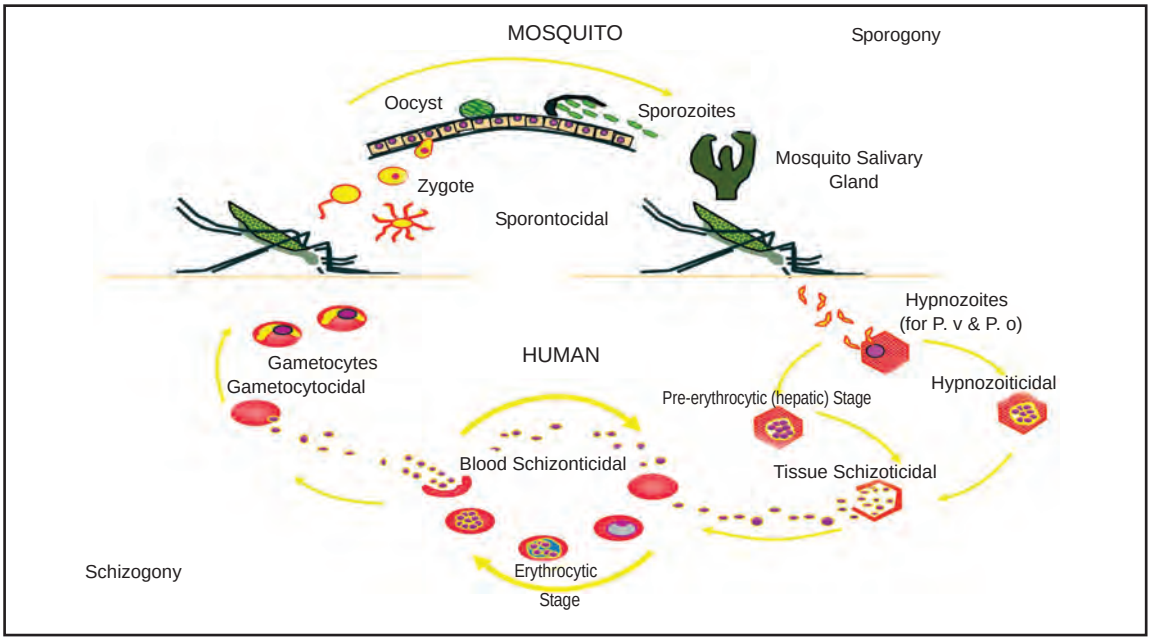
Most patients with cerebral malaria seem to make a full recovery with appropriate and timely management, but neurocognitive sequelae have been increasingly recognised, particularly in children in the past 20 years.

Antimalarials Acting on Different Stages of Life Cycle of Malaria Parasite

Dr. Subhasis Das

Antimalarials are drugs used for prophylaxis, treatment and prevention of relapses of malaria. These are achieved by attacking the protozoal parasite *Plasmodium* at its various stages of life cycle. A schematic diagram is given below showing the stages and forms of malaria parasite at which different types of antimalarials act. Since various stages in the life cycle of malarial parasites show different susceptibility to antimalarial drug, the latter may be classified into the following groups:

1. *Tissue Schizontocides* (used for causal prophylaxis) acting on the pre erythrocytic stages of the parasite and thus completely preventing invasion of the RBCs. Eg., Primaquine and Proguanil.
2. *Hypnozoitocides* (used as antirelapse drugs) acting on the hypnozoite forms of P. vivax and P. ovale and thus able to achieve radical cure of these infections. Eg. Primaquine.
3. *Erythrocytic Schizontocides* acting on the erythrocytic stages of the parasites commonly associated with acute disease. Blood schizontocides may achieve clinical cure or suppression to a subpatent level of infection. These are Chloroquine, Amodiaquine, Quinine, Mefloquine, Halofantrine, Lumefantrine, Atovaquone, Artemisinin, Tetracyclines, Sulfonamides, Pyrimethamine.
4. *Gametocytocides* destroying the male and female gamets of the parasite thus eliminating the transmission to mosquito. These are Primaquine, Quinine, Mefloquine, Chloroquine, Amodiaquine.
5. *Sporontocides* preventing or inhibiting the further development of male and female gamets though not killing them. These are Proguanil, Pyrimethamine and Atovaquone.



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The following table shows the action of antimalarial drugs on the life cycle of malaria parasite :

Drugs	Pre erythrocytic phase		Erythrocytic phase	Hypnozoite	Gametocyte		Sporontocide
	P.fal	P.viv			P.fal	P.viv	
Chloroquine	-	-	+	-	-	+	-
Mefloquin	-	-	+	-	-	-	-
Quinine	-	-	+	-	-	+	-
Primaquine	+	+	±	+	+	+	+
Proguanil	+	±	+	-	-	-	+
Artemisinins	-	-	+	-	+	+	-
Lumefantrine	-	-	+	-	-	-	-
Sulfonamides	-	-	±	-	-	-	-
Pyrimethamine	-	-	+	-	-	-	+
Tetracyclines	+	-	+	-	-	-	-

Properties of commonly used antimalarials :

Drug(s)	Mechanism of action	Antimalarial activity	Toxicity	Remarks
Chloroquine	Inhibits parasite heme detoxification	Acts mainly on large ring-form and mature trophozoite stages.	Nausea, pruritus, dysphopria, postural hypotension, shock, arrhythmias, neuropsychiatric reactions, visual accommodation difficulties, retinopathy (cumulative dose>100g), myopathy.	Still the drug of choice for sensitive malaria parasite (P.vivax, P.malariae, P.ovale). Produces more rapid parasite clearance than quinine, but slower than artemisinins.
Quinine	Inhibits parasite heme detoxification	Acts mainly on mature trophozoite stage. Does not prevent sequestration or further development of circulating ring stages of P.falciparum.	Cinchonism (tinnitus, high tone hearing loss, nausea, vomiting, dysphoria, postural hypotension; ECG-QT_C prolongation; hypoglycemia, diarrhea, visual disturbance, rashes, thrombocytopenia, hemolysis.	As per WHO recommendation, parenteral Quinine is an acceptable alternative in severe malaria if IV artesunate is not available. Oral quinine plus tetracycline or doxycycline or clindamycin combination to be used as 2^{nd} line treatment in uncomplicated falciparum malaria.

Drug(s)	Mechanism of action	Antimalarial activity	Toxicity	Remarks
Artemisinin and derivatives (Artemether, Artesunate)	Inhibits Calcium Adenosine Triphosphatase PfATPase 6	Most rapidly acting of known antimalarials. No action on liver stages. Kills P.falciparum gametocytes. Broadest time window of antimalarial effect (from ring forms to early schizonts).	Reduction in reticulocyte count (but not anaemia); neutropenia at high doses; anaphylaxis, urticaria.	As per WHO recommendation ACT should be used as 1st line treatment for uncomplicated falciparum malaria both in adults and children. For severe falciparum malaria IV artesunate should be used in preference to quinine followed by a complete course of ACT when patient tolerates oral medication.
Primaquine	Inhibits plasmodial dihydrofolate reductase	Eradicates hepatic forms of P.vivax & P.ovale. Kills all stage of gametocytes of P.falciparum.	Massive hemolysis in severe G6PD deficiency, nausea, vomiting, diarrhoea, methemoglobinemia.	Used to prevent relapse in P.vivax and to prevent transmission in P.falciparum. Combined with Chloroquine it causes radical cure in P.vivax and P. ovale.
Mefloquine	As for quinine	As for quinine	Nausea, giddiness, dysphoria, sleeplessness, nightmares, neuro-psychiatric reactions.	Used for oral treatment of uncomplicated multidrug resistant malaria along with Artesunate.
Lumefantrine	As for quinine	As for quinine	None identified	Highly variable absorption related to fat intake. Available only in an oral preparation coformulated with artemether. This ACT is highly effective against multidrug resistant P.falciparum.
Pyrimethamine	Inhibits plasmodial dihydrofolate reductase	Slow acting blood schizonticide. Possibly active against pre erythrocytic stage. Also sporontocidal.	Generally well tolerated. Larger doses may cause megaloblastic anemia, pancytopenia.	Used only in synergistic combination with sulfonamides for treatment or with dapsone for prophylaxis.
Atovaquone	Interferes with cytochrome electron transport	Acts mainly on trophozoite blood stage. Also inhibits pre erythrocytic stage.	Skin rashes, headache, nausea, insomnia, diarrhoea.	Combined with Proguanil for treatment of malaria.
Proguanil	Inhibits plasmodial dihydrofolate reductase	Inhibits pre-erythrocytic stage and is a slow blood schi-zonticide. Also has sporonticidal effect.	Aphthous ulceration and hair loss. Megaloblastic anemia in patients with renal failure.	Causal prophylactic. Not used alone for treatment.

Chronic Pain – Pain Clinics

Dr. Jayanta Bhattacharya

The commonest reason for seeking medical help is pain. It is therefore a big challenge how to manage it even if the exact underlying cause is not determined.

The International Association for the Study of Pain **(IASP)** defines **"Pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage".**

In 1994, IASP classified chronic pain according to specific characteristics;

1. Regions of body involved e.g., Lower limbs, abdomen.
2. Dysfunction of the system which may be responsible for the pain e.g., nervous, gastrointestinal.
3. Pattern and duration of occurrence.
4. Intensity and time of onset.
5. Etiology.

Woolf and others advocated that there are three types of pain : **Nociceptive pain**, **Inflammatory pain** (associated with tissue damage and infiltration of immune cells) and Pathological pain (a disease state caused by damage to the nervous system – **Neuropathic pain**).

Chronic pain is defined as pain that persist beyond the expected term of healing, or more than 3 to 6 months.

Some has advocated that the transition from acute to chronic pain occurs at 12 months.

Others have advocated that-

1. **Acute pain lasts less than 30 days,**
2. **Chronic pain if persists for more than 6 months and**
3. **Subacute pain if lasts from 1 to 6 months.**

Now a days it is seen as a continuum: all pain is acute till it becomes chronic.

According to some - by 3 months pain itself becomes a disease.

Under treatment of chronic pain is a serious public health problem that decreases the patient's quality of life and functional status. So patients suffering from chronic pain should be referred to pain clinics to get an early and aggressive treatment.

A pain clinic is a health care facility that focuses on the diagnosis and management of chronic pain. Pain Clinics vary in the treatments offered and not all hospitals may have a specific pain clinic. Sometimes a consultant with an interest in pain will prescribe drugs or give injections to try to control pain. Other clinics have teams of doctors, psychologists, nurses, physio-therapists, occupational therapists and others. Pain clinics often use a multidisciplinary approach to help people take an active role in managing their pain and regaining control of their life. These programs are focused on the total person, not just the pain.

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Dr. Rovenstine (anaesthetist) established first pain clinic in New York in 1936, solely to treat chronic pain. In 1950s John Bonica introduced the concept of multidisciplinary approach which revolutionized the chronic pain management. In 1970's pain clinics became more widely established.

The pain management service is regarded as a subspeciality of anaesthesiology and the director of services is usually a consultant anaesthesiologist trained in chronic pain management. This relatively new subspeciality has gained rapid popularity and development over the last two decades in the developed countries. In developing countries the concept of pain physician, pain clinics availability and pain management speciality is not well accepted yet by the patients (suffering from chronic pain) and the medical community. This lack of awareness is the main reason for the under treatment of chronic pain.

Chronic pain may be divided into –

A. Nociceptive – caused by stimulation of nociceptors.

1) Superficial – activation of nociceptors in the skin or superficial tissues.

2) Deep -

   a) Somatic – Stimulation of nociceptors in tendons, ligaments, muscles, fascia, bones, blood vessels. It is poorly localized, dull aching in nature.

   b) Visceral – Originates in the viscera. It may be well localized (often difficult to locate). Many visceral regions produce referred pain, where the sensation is located in an area distant from the site of pathology.

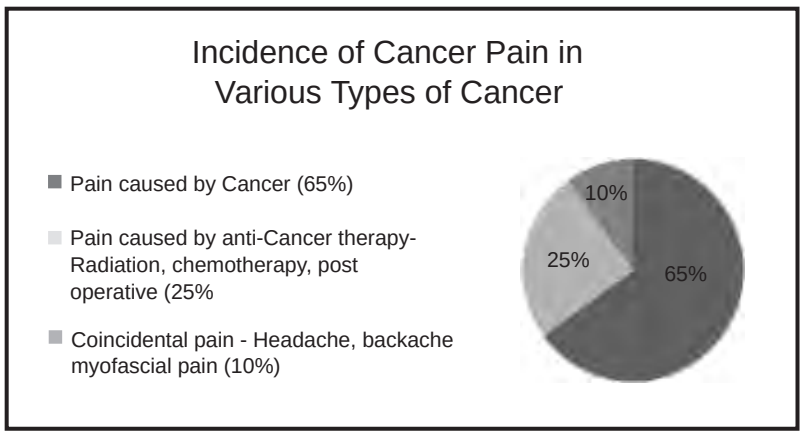
B. Neuropathic – caused by malfunction or damage to the nervous system.

1) Central – originating in the brain or spinal cord.

2) Peripheral – originating in the peripheral nervous system. It is often described as burning, pins and needles, tingling, electrical or stabbing.

Cancer Pain :-

Cancer Pain is due to mixed mechanism. Rarely is it a pure neuropathic, visceral or somatic pain. Usually it is a complex presentation of



Breakthrough Pain :-

Breakthrough Pain - It comes on suddenly, stays for a short duration and is not relieved by the normal pain management of the patient. This type of pain is common in cancer patients who have a background level of pain controlled by medications, but whose pain "breaks through" the medications periodically. The characteristics of breakthrough cancer pain depend upon the cause and the nature of the person (patient).

Neuropathic Pain :-

In 2008, neurology and pain community experts introduced the definition of neuropathic pain (NP). "Neuropathic pain is the pain type arising as direct consequence of a lesion or disease and affecting the somatosensory system."

A group of diverse peripheral nervous system diseases produce NP, including Painful neuropathies, herpetic and post herpetic neuralgias, traumatic neuromas and causalgia (CRPS – II - Complex Regional Pain Syndrome Type II).

Neuropathies include

- Diabetic polyneuropathies
- Sensory neuropathies of AIDS
- Antiretroviral and cancer chemotherapeutic drug induced neuropathies.
- Idiopathic painful polyneuropathy – in elderly subjects.

Pathophysiology – It includes two factors : Sensation and Emotion.

The pain sensation has 2 distinct but continuous processes.

1. Peripheral mechanism comprising Primary afferent nociceptors, Sensitization and Nociceptor induced inflammation.
2. Central mechanism comprising Spinal cord, Ascending pathways and Central pain Modulations.

The pathogenetic mechanisms of NP shows structural changes in 2 sites :

a. Changes affecting intact afferents in partially injured nerves – There is alteration of microenvironment in proximal and distal stumps with increased expression of nerve growth factor (NGF), brain derived neuropathic factor (BDNF), neurotropin 3 (NT3), Cytokines like TNF alpha, IL I beta, IL6. IL 10 - causing increased excitability.

b. Changes in membrane excitability in intact nerves – In intact fibres there is upregulation of ion channels? Mainly Na^{+} channels and some Ca^{+2} channels open up? Crosstalk between nerve fibres. (VGSC, VGCC)

Management of NP – It is often unfruitful, non-rewarding and frustrating. It includes

1. **Management of underlying cause** – Controlling diabetes, abstaining from alcohol, elimination of toxins. But controlling the etiological factors is not sufficient in managing NP.
2. **Pharmacotherapy of NP** – Recently, National Institute for Health and Clinical Excellence (NICE) has published a guideline for treating NP among non specialists.

The summary –

a. First line – Oral Amitryptyline or Pregabalin; Except in Diabetic neuropathy (DPN). For DPN – Duloxeitine, but with hypertension and renal compromise use Amitryptyline.

b. Second line – In unsatisfactory results use Amitryptyline or Pregabalin depending on which was used first.
c. Third line therapy – Consider adding Tramadol.

The table summarizes the pharmacological treatment recommendations that were suggested at the Fourth International Conference of the Mechanisms and Treatment of NP in 2003.

First Line	Second Line	Third Line
Pregabalin	Tramadol	NMDA antagonists
Gabapentin	Strong opioids	Mexiletine
TCA (Tricyclic antidepressants)		Topical Capsaicin
SNRIs (Serotonin-nor-epinephrine reuptake inhibitors)		
Topical Lidocaine for PHN		

Athina Vadalouca,MD,PhD,FIPP; Efklidis Raptis, MD+; Eleni Moka,MD,PhD++; et al Pharmacological Treatment of Neuropathic Cancer Pain: A Comprehensive Review of the current Literature. Pain Practice, Volume 12, Issue 3, 2012: 219-251*

3. **Future of drug therapy** – With better understanding of pathogenesis and consequent therapeutic modulation, more useful management strategies may come up in near future. Till then the rational use of the available drugs can help patients to partially bear this problem.

Significance of Pain Management – *"Declaration of Montreal"*

IASP advocates that the relief of pain should be recognized as a human right, that chronic pain should be considered a disease in its own right, and that pain medicine should have the full status of a specialty.

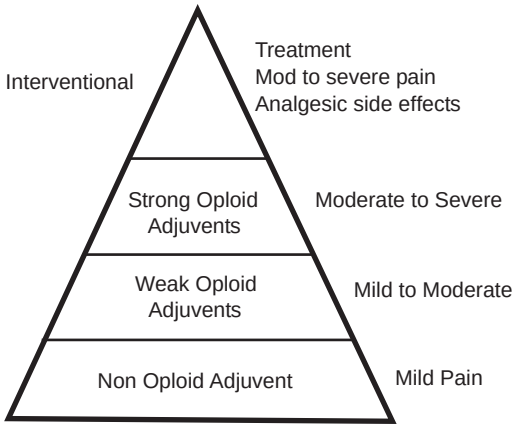
At present it is a specialty in Australia and China only. In other countries pain medicine is a subspecialty under disciplines like Anaesthesiology, Physiatry, Neurology, palliative medicine and Psychiatry.

Impact of Inadequate Pain Relief – As in all intractable pains, it has devastating consequences on the quality of life; not only on the patients daily activities and their ability to manage their disease, but also implies anxiety and distress of the patient and family.

Chronic pain is associated with higher rates of depression and anxiety. Sleep disturbances and insomnia are very common. Substance abuse is quite common in some segments of chronic pain population e.g. chronic headache. Chronic pain also leads to decreased physical activity due to fear of exacerbating pain.

World Health Organization (WHO) Ladder-

The WHO Ladder was first published (1986) in a handbook called *Cancer Pain Relief*. Since then, the Ladder has guided clinicians all over the world in treating cancer as well as noncancer pain.



Interventional Procedures –

Radiofrequency techniques, neuromodulation, direct introduction of medication and nerve ablation may be used to target.

- Either the tissue structures and organ/ systems responsible for persistent nociception.
- Or the receptors from the structures as the source of chronic pain.

Other Modalities of Pain Management -

The WHO analgesic ladder should be followed along with other strategies e.g. Chemotherapy, Radiotherapy and nonpharmacological pain treatment modalities in management of chronic, neuropathic and cancer pain.

Some patients will need interventional procedures. Even though it is classified in step 4 of the ladder, one may consider this at any point of time which seems appropriate.

Myths about Treating Chronic Pain -

Chronic pain is a serious and debilitating condition. Many people suffering with chronic pain are so desperate for help that they're willing to believe anything — and as a result buy into some chronic pain myths that could be unwise and even dangerous **:**

Myths	Facts
To Cure Chronic Pain, Just Treat the Underlying Cause.	Even Mild Chronic Pain Should Be Checked by a Doctor.
Bed Rest Is Usually the Best Cure for Pain.	Chronic Pain Is Connected With Depression.
Increased Pain Is Inevitable as We Age.	There's Rarely a Single Treatment That Will Cure Chronic Pain.
Taking Opioid Pain killers Leads to Drug Addiction.	Even With Good Treatment, Chronic Pain Might Not Go Away.
Taking Opioid Pain Killers Will Completely Cure Chronic Pain.	

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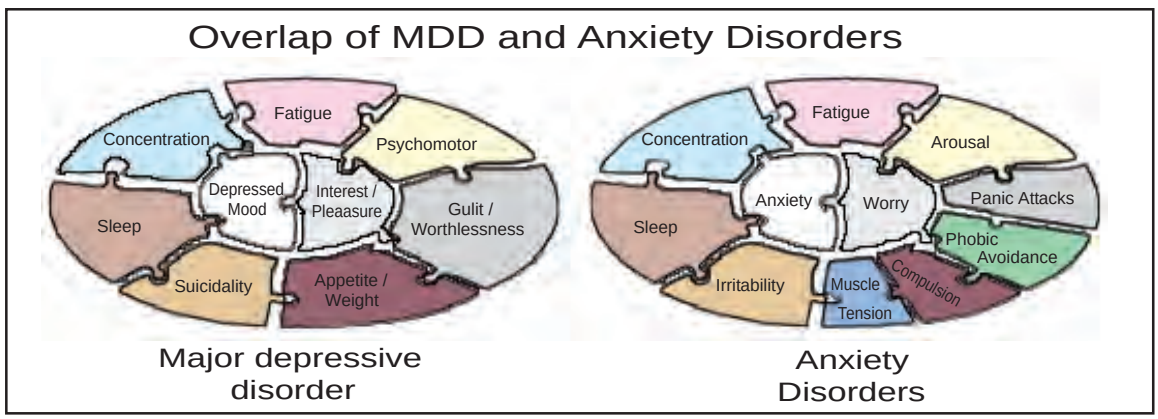
Anxiety Disorders - From Basics to Bedside

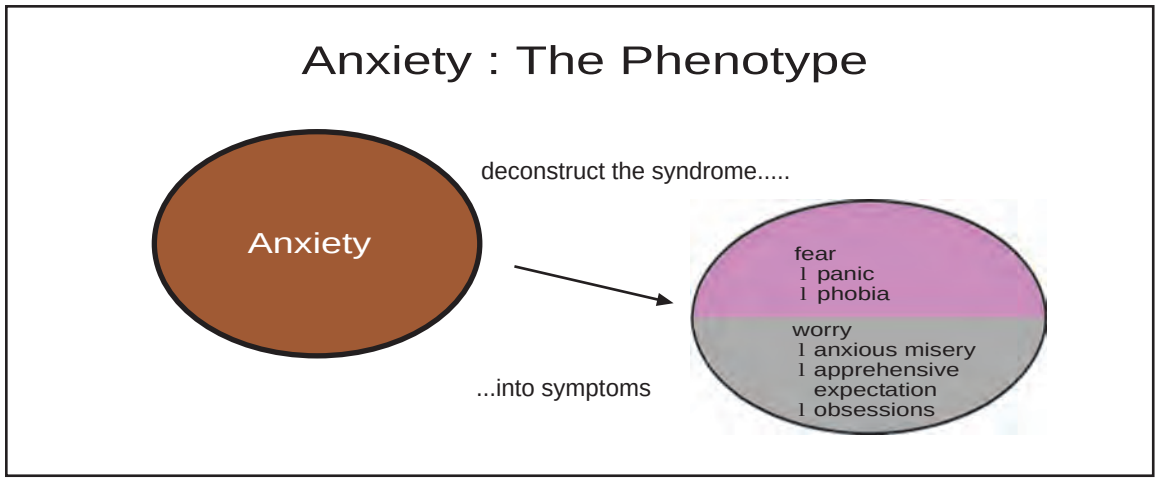
Dr. Uday Chaudhury

Anxiety Disorder :-

Anxiety is a normal emotion under circumstances of threat. It is thought to be part of the evolutionary "fight or flight" reaction of survival. The idea of anxiety as a psychiatric disorder is evolving rapidly. It is characterized by the concept of core symptoms of excessive fear or worry.

In comparison to major depression, which is characterized by core symptoms the depressed mood or loss of interest, anxiety disorder have considerable symptom overlap with major depression symptoms surrounding core features, particularly sleep disturbance, problems concentrating, fatigue and psychomotor and arousal symptoms.





Each anxiety disorder also has a great deal of symptom overlap with other anxiety disorders.

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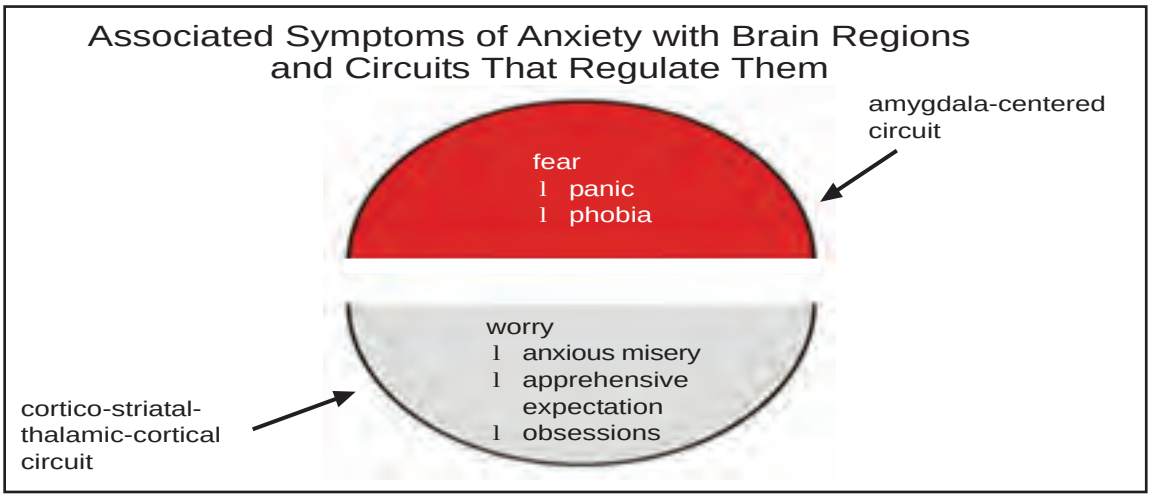
What therefore, is an anxiety disorder?

These disorders all seem to maintain the core features of same form of anxiety or fear coupled with some form of worry, but their natural history over time shows them to morph from one into another, to evolve into full syndrome expression of anxiety disorders symptoms.



Associated symptoms of anxiety with Brain regions and circuits that regulate them.

Anxiety disorders have core features of fear and worry that cut across the entire spectrum of anxiety disorders subtypes, from generalized anxiety disorder to panic disorder, social anxiety disorder, post traumatic stress disorder, and obsessive compulsive disorder.

A great deal of progress has been made in elucidating the role of amygdala is the fear response and the role of cortico – striatal-thalamic -cortical circuits is the symptoms of worry.

Numerous neurotransmitters are involved in regulating those circuits that underlie Anxiety disorders. GABA is a key neurotransmitter, as well as benzodiazepine anxiolytic that act on this neurotransmitter system. Serotonin, norepinephrine, alpha 2 delta ligands, voltage gated calcium channels, are important regulators of anxiety circuits.

Table 1 Symptoms of Anxiety Disorder

Psychological
Apprehension
Fear of impending disaster
Irritability
Depersonalization
Somatic
Tremor
Sweating
Palpitations
Chest pain
Breathlessness
Headache
Dizziness
Diarrhoea
Frequency of micfurition
Initial insomnia
Poor concentration

Table 2 Medical Condition which may mimic Anxiety Disorder
Hyperthyroidism
Phaeochromocytoma
Hypoglycaemia
Paroxysmal arrhythmias
Alcohol withdrawal
Temporal lobe epilepsy

Table 3 Generalised Anxiety Disorder (GAD)	
Signs and symptoms	Excessive anxiety; at least 6 months; difficult to control worry / hypervigilant Associated with 3 or more: Restless / on edge, easily fatigued, concentration problems, irritability, muscle Tension, sleep disturbance causes significant distress often physical complaints like dizziness, tachycardia, tightness of chest, sweating, tremor
Causes	Neurotransmitter dysregulation : NE, 5-Ht, GABA Autonomic nervous system activation; locus caeruleus / NE release / limbic system One year prevalence rate : 1%; lifetime prevalence; 5% Familial association Over half : onset in childhood
Rule outs	Anxiety disorder due to a medical condition (hyperthyroidism; phaeochromocytoma) substance-induced anxiety or caffeine-induced anxiety disorder Other anxiety disorders : panic disorder, OCD, etc. DSM-IV criteria help rule out
Labs/Tests/Exams	Self-rated scales : Beck anxiety inventory (BAI); state trait anxiety inventory Observer-rated scale : Hamilton anxiety rating scale (HAM-A) Physical evaluation Physical examination Routine lab tests; thyroid function tests
Interventions	Pharmacologic : benzodiazepines very effective (diazepam, lorazepam); non Benzodiazepines : buspirone Beta blockers : propranolol CBT Deep muscle relaxation Individual and family therapy Education

Table 4 Obsessive – Compulsive Disorder (OCD)	
Signs and symptoms	Obsessive – recurrent, intrusive thoughts that cause anxiety or compulsions – repetitive behaviours (hand washing, checking) that reduce distress / anxiety and must be adhered to rigidly
	Driven to perform compulsions
	Time consuming (>1 hr/day), interfere with normal routine
	Recognizes thoughts / behaviours are unreasonable
Causes	Genetic evidence
	Neurobiological basis : orbitofrontal cortex, cingulated, and caudate nucleus
	Neurochemical : serotonergic and possibly dopaminergic
	Association between OCD and Tourette's and others
	Lifetime prevalence of 2.5%
	Women > men
	Average onset : 20 years
	Childhood : 7-10 years
Rule outs	Other anxiety disorders : phobias
	Impulse control disorders
	Obsessive – compulsive personality disorder
	Body dysmorphic disorder
	Depression
	Neurological disorder
Labs/Tests/Exams	Yale – Brown obsessive compulsive scale (Y-BOCS)
	Psychiatric evaluation
	Mental status examination
	Neurologic examination
Interventions	Pharmacologic : SSRIs (fluoxentine : higher doses); fluvoxamine; Clomipramine Beta-blockers : propranolol
	Behaviour therapy : exposure and response prevention
	Deep muscle relaxation
	Individual and family therapy
	Education

Table 5	**Post Traumatic Stress Disorder (PTSD)**
Signs and symptoms	Traumatic event (self / family) witness others); threat of harm or death or actual death and helplessness
	Reexperiencing event 'flash-backs' (triggers : sounds / smell)
	Hypervigilance reactions (unaware re-enactment related to trauma)
	Persistent anxiety / outbursts
	Acute (< 3 months); chronic (> 3 months); delayed (> 6 months)
Causes	Rape, torture, child abuse, disaster, murder, war, etc.
	Physiologic / neurochemical / endocrinological alterations
	Sympathetic hyperarousal
	Limbic system (amygdala dysfunction)
	'kindling' : neuronal excitability
	Risk factor : previous trauma
	Lifetime prevalence – 8% (US)
Rule outs	Acute stress disorder
	Obsessive – compulsive disorder
	Adjustment disorder
	Depression
	Panic disorder
	Psychotic disorders
	Substance-induced disorder
	Psychotic disorder due to a general medical condition Delirium
Labs/Tests/Exams	PTSD scale (clinician administered)
	Psychiatric evaluation
	Mental status examination
	CAGE, SMAST
	Physical exam, routine blood studies
	No laboratory test can diagnose
Interventions	Debriefing (rescuers etc.)
	Individual or group psychotherapy
	CBT
	EMDR (eye movement desensitisation and reprocessing)
	Pharmacotherapy : antidepressants – SSRIs, SNRIs, MAOIs, TCAs; antipsychotics; anxiolytics; mood stabilizers
	Family and community support / art therapy / psychodrama

Table 6	**Panic Disorder (PD)**
Signs and symptoms	Excessive panic; at least 6 months; difficult to control worry / hypervigilant
	Associated with 3 or more : restless / on edge, easily fatigued, concentration problems, irritability, muscle
	Causes significant distress
	Often physical complaints : dizziness, tachycardia, tightness of chest, sweating, tremor
Causes	High level of anxiety since childhood
	Autonomic nervous system activation; lacus caeruleus / NE release / limbic system
	One year prevalence rate : 1%; lifetime prevalence; 5%
Rule outs	Medical disorder, substance abuse, misinterpretation of bodily / mental experiences, drug-induced, hypervigilance; chronic worry
Labs/Tests/ Exams	Self-rated scales : Beck anxiety inventory (BAI); state trait anxiety inventory
	Observer-rated scale : Hamilton anxiety rating scale (HAM-A) Psychiatric evaluation
	Physical examination
	Routine lab tests; thyroid function tests
Interventions	Cognitive therapy, SSRIs

Table 7	**Social Phobia (SP)**
Signs and symptoms	Excessive panic; at least 6 months; difficult to control worry, hypervigilant
	Associated with 3 or more; restless / on edge, easily muscle tension, sleep disturbance
	Causes significant distress
	Often physical complaints; dizziness, tachycardia, tightness of chest, sweating, tremor
Causes	Strong genetic loading
	High level of anxiety since childhood
	Autonomic nervous system activation; locus caeruleus / NE release / limbic system
	One year prevalence rate; 1%; lifetime prevalence, 5%
	Familial association

Table 7	Social Phobia (SP)
Rule outs	Schizophrenia
	Patients comfortable with social isolation
	Presence of hallucinations and delusions
	Depression
	Patient does not want face people as he feels inadequate and guilty
	Presence of other symptoms of depression
	Lab tests
	Fear of humiliation in interpersonal situations
Labs/Tests/ Exams	Self-rated scales: Beck anxiety inventory (BAI); state trait anxiety inventory
	Observer – rated scale : Hamilton anxiety rating scale (HAM-A)
	Psychiatric evaluation
	Physical examination
	Routine lab tests; thyroid function tests
Interventions	Cognitive therapy, SSRIs, social skills training

Anxiety disorders are amongst most common psychiatric condition in 15 to 20% of medical clinic patients.

Anxiety as a symptom, can be a part of other psychiatric disorders (particularly depression), or a consequence of physical illness such as thyrotoxicosis or be drug – induced (e.g. caffeine). Anxiety disorders may be associated with a co morbid disorder like substance abuse disorder. Symptoms can be psychological, physical or a mixture of both (Table 1). Intervention is required when symptoms become disabling and interfere with functioning. Certain medical conditions which mimic anxiety disorder are given in Table2. There are several disorders within the overall spectrum of anxiety disorders, each with its own characteristic symptoms, generalised anxiety disorder (GAD), panic disorder, social anxiety disorder (SAnD), obsessive conmpulsive disorder (OCD), and post–traumatic stress disorder (PTSD).

Differential Diagnosis :-

Anxiety is usually transient as a part of 'adjustment disorder' and subsides without treatment. General anxiety (chronic anxiety associated with worry) is an important cause of medically unexplained somatic complaints. Phobic anxiety is characterized by avoidance of feared situation (e.g. social situation, specific situation, public speaking–generalised avoidance in agoraphobia) and it is a common association with panic disorder.

Management :-

It includes a combination of psychological, pharmacological and psychosocial intervention. A holistic approach is required - as it interferes with all three conditions of health : Physical, mental and family education, reassurance, relaxation training, health maintenance activities,

and cognitive behaviour therapy (CBT) are some of the common psychological approaches.

Pharmacological Intervention :-

It involves short time therapy with benzodiazepines (not more than 2-4 weeks) and as and when required a treatment of acute anxiety spell. Long-term therapy with selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) and some tricyclic antidepressants (TCAs) like imipramine and clonipramine.

Buspirone has also got a role in the treatment of anxiety.

Management of Anxiety Disorder Subtypes

Generalized Anxiety Disorder :-

Today, first line treatments include SSRIs (Selective serotonin Reuptake Inhibitors, namely, fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram & Escitalopram) and SNRIs, (selective serotonin and Norpinephrine Reuptake inhibitors, venlafaxine (SNRI) as well as benzodiazepines and buspirone. Some prescribers are reluctant to give benzodiazepines for anxiety disorders in general for GAD in particular owing to the long-term nature of GAD and the possibility of dependence, abuse potential and withdrawal reaction with benzodiazepines. Benzodiazepines can be useful to "top up" an SSRI or SNRI. Benzodiazepines can also be useful for occasional intermittent use when symptoms surge and relief is needed quickly.

If a GAD patient is not doing well after several weeks or months of treatment switching to another SSRI/SNRI or buspirone or anxiolytic with a benzodiazepine can be considered. Failure to respond to first line of treatment can lead to trail of the novel alpha 2 delta ligands, gabapentin or pregabalin. One also can try sedative antidepressants such as mirtazapine, trazadone, or tricyclic antidepressants or even sedating antihistamines such as hydroxyzine.

Adjunctive treatments that can be added to first or Secord line treatment for GAD include hypnotics for continuing insomnia, atypical antipsychotics in low dose for severe, refractory and disabling symptoms unresponsive to aggressive treatment and Cognitive Behavior Therapy.

Panic Disorders :-

Panic attacks occur in many conditions, not just panic disorder, and panic disorder is frequently co morbid with other anxiety disorder and with major depression.

First line treatment included SSRIS & SNRIS as well as benzodiazepines. To note Benzodiazepines are often used as second line options, during treatment initiation with an SSRI/SNRI, for emergent use, during a panic attack, or for incomplete response. Second line treatments include the novel alpha 2 delta ligands, gabapentin and pregabalin as well as tricyclic antidepressants.

Mirtazapine and trazadone can be helpful in some cases as augmenting agents to first line treatment (SSRIs/SNRIs), when there is partial response to treatment. The MAO inhibitors are much neglected in psychopharmacology in general, and for the treatment of panic disorder in particular. However MAOIs, can have purposeful efficacy in panic disorder is specialized setting, where various agents have failed.

Various adjunctive treatments are important in panic disorder. Atypical antipsychotics for severe and treatment resistant cases, cognitive behavior therapy to augment psycho pharmacotherapy and to modify cognitive distortions. To breathe in a paper bag can sometime be useful in panic attacks.

Learning Exercise on Anxiety Disorders

Case Vignette - 1

- A 62 year old man with a history of diabetes mellitus, chronic COPD, hepatitis C, peripheral neuropathy, and a pacemaker for control of cardiac arrhythmia complains of new-onset episodic anxiety occurring over the past 3 weeks. He has no history of anxiety symptoms.
- Episodes of intense anxiety tend to occur in the day time, last for 30 mins to an hour and are accompanied by hyperventilation and a sense of "palpitations" as well as some confusions and disorientation. Of the following, which is least likely to be the diagnosis in this case?
  A. Panic disorder
  B. Episodic hypoglycaemia
  C. Hypoxia caused by COPD
  D. Hypoxia caused by arrhythmia

Case Vignette – 2

- A 36 year-old woman comes to the emergency department with a chief complaint of "I think that I'm going crazy."
- She states that for the past two months, she has been experiencing sudden episodes of palpitations, sweating, trembling, shortness of breath, chest pain, dizziness and feeling as if she is going to die.
- She has been to the emergency department twice in the past weeks, convinced that she is having a heart attack.
- The results of all her physical and laboratory examinations have been within normal limits.
- She states that the first episode occurred when she was walking down the street, not thinking about anything in particular. The episode lasted approximately 15 mins.
- Since that time she had similar episode once or twice a day, everyday. As a result she finds herself worrying almost constantly about when she is going to have another attack.
- She consumes large amount of tea and coffee and smokes, 15-20 sticks per day. She denies drug use and uses alcohol only occasionally.
- Her only medical problem is a one yr. history of hypothyroidism for which she takes 100mcg. of thyronorm.

Diagnosis:-

Investigations:-

Management:-

Case Vignette – 3

- A 28 yrs. old woman comes with a chief complaint of muscle tension. She states that she has experienced a considerable amount of muscle tension during her entire life. It has become increasingly worse over the past seven months.
- She described herself as a worrier and since her first child was born last year, her worrying has increased. She is unable to stop worrying even when she actively tries to do so.
- She worries about a whole host of issues – the status of India's relations with other countries like China, Pakistan, whether or not she and her husband can afford to put their child through college, her husband's health and the stock market.
- She reports the symptoms of restlessness and insomnia. She can fall asleep without a problem but wakes up in the middle of the
  night and cannot fall asleep again.
- She describes her mood as okay and denies any substance use. Both she and her husband work as lawyers, although she had difficulty concentrating on her job since her child was born.

Diagnosis:-

Treatment:-

Organ Endothelium

Dr. Pranab Kumar Das

Oxford Dictionary of Current English writes – an organ is a part of animal body adapted for special vital function. With the word 'organ', one tends to conceive of a mass or collection of tissues within a confinement. Endothelium, the innermost layer of the blood vessels, pervades every nook of the body except lens, cartilage etc. and thereby helps it attain the status of the largest organ of the body.[1] In an individual the endothelial cells (ECS) totaling 1-6 x 10^{13} in number is enough to cover a surface area equivalent to about six tennis courts.[2a]

Arteries are no longer viewed as inanimate tubes. Rudolf Virchow recognized the participation of vascular cells in atherogenesis[3a] and today we have come to admit that ECS are immensely active and their functions are truly protean. Under physiological conditions, these cells control (i) flow of biologically active molecules and nutrients, (ii) vascular permeability, (iii) blood cells interactions with the vessel wall, (iv) inflammatory response, (v) angiogenesis.

The endothelium participates in the local regulation of blood flow and vascular caliber. Under physiologic conditions tonic vasodilatory stimuli are provided by substances endogenously produced by ECS e.g. nitric oxide (NO), prostacycline, hydrogen peroxide, endothelium derived hyperpolarizing factor. ECS also produces potent vasoconstrictor substances e.g. endothelin–1 in a regulated fashion. Under pathologic situations (e.g. excessive exposure to angiotensin II), ECS excessively produce reactive oxygen species e.g. superoxide anion (O_2^-) that can promote local oxidative stress and inactivate NO. Impaired production or excessive catabolism of vasodilators e.g. NO., tilts the balance in favour of the powerful vasoconstrictor e.g. endothelin-I, angiotensin-II and this lead to increased resistance to blood flow. Such things occur in the pulmonary arteries in cor pulmonale, in penile arteries causing erectile dysfunction.

ECS regulates entry of moleculs and cells into tissues in a selective manner, this ability to serve as a selectively permeable barrier fails in vascular disorders e.g. hypertension, atherosclerosis. Such dysregulation of permeability also occurs in pulmonary edema and other situations of 'capillary leak' e.g. in septic shock.[2b]

The endothelial cells of the vascular intima constitutes the crucial contact surface with the blood. The ECS possess many highly regulated mechanisms of capital importance in vascular homeostasis. Endothelium normally present as an antithrombotic surface and maintain blood in a liquid state during protracted contact. This remarkable blood compatibility derives from (i) NO and prostacycline antagonising platelet activation and aggregation (ii) heparin sulphate proteoglycan molecules expressed on the surface of the ECS, serve like heparin as a cofactor for Antithrombin III (iii) Thrombomodulin that binds thrombin molecules and activates protein S & C which in turn inactivate FVa & FVIIIa, combating thrombus formation. In addition to

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the antithrombotic functions, normal ECS possess potent fibrinolytic mechanism, should a thrombus begin to form.[3b] ECS can produce both tissue and urokinase type plasminogen activators that catalyse the activation of plasminogen to plasmin to lyse fibrin in the nascent thrombi. ECS can, on the other hand, substantially produce the major inhibitor of fibrinolysis, Plasminogen Activator Inhibitor (PAI-1). Thus, in pathologic circumstances, the ECS may promote local thrombus accumulation rather than combat it. Inflammatory stimuli can also induce expression of the potent procoagulant tissue factor and important contributor to DIC in sepsis.

ECS play critical role in normal host defense and in pathological states. Normally ECS resists prolonged contact with blood leucocytes; but when ECS is activated by bacterial products e.g. endotoxin or proinflamatory cytokines during infection, an array of leucocyte adhesion molecules are expressed on the surface of ECS to bind leucocytes. Recruitment and for that matter adhesion is selective according to pathologic condition e.g. in acute bacterial infections the granulcytes and in chronic inflammatory states e.g. tuberculosis, athrosclerosis, the mononuclear leucocytes are recruited by ECS adhesion molecules.

In addition to contributing to innate immunity, ECS also participates actively in both humoral & cellular limbs of immune responses. In immune mediated diseases e.g. in TTP, HUS, ECS injury occurs by it through mediation of complement. In solid organ allografts, presentation of foreign histocompatibility complex antigen can trigger immunologic rejection.

Growth of new blood vessels, angiogenesis, results from endothelial proliferation and tube formation[2c]. The stimuli are growth factors e.g. vascular endothelial growth factor (VEGF) and forms of fibroblast growth factor (FGF). These stimuli result from chronic hypoxaemia and tissue ischaemia and give rise to the development of collateral vascular network in ischaemic myocardium. The progenitor cells may reside in the blood vessel wall or home to ischaemic tissues from bone marrow. Similarly tumours to grow larger than a few mm. need angiogenesis. Tumours secrete VEGF that induce proliferation & migration of ECS into tumour e.g. sprouting[2d].

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Primary Cavernous Hemangioma of Thyroid Gland

Dr. Anirban Majumder

Introduction :-

Cavernous haemangioma of the thyroid gland is extremely rare and often escape diagnosis preoperatively. I report a case of a cavernous haemangioma of the thyroid gland.

Case report :-

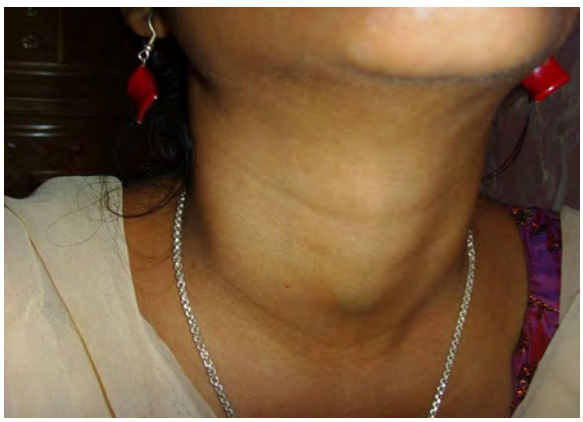
Ms. S. Ghosh, 21yrs. female was presented with swelling in the front of neck for last 6 months without any history of weight loss. Her weight was 47 kg, BMI 21 and regular normal pulse rate. Examination revealed a soft, non-tender, mild to moderate thyroid swelling with bluish discolouration without any bruit. She was clinically in euthyroid state.

Thyroid function tests (TFT) revealed: T3:1.17 ng/ml (0.80–2.10), T4:8.20ug/dl (5.10–12), TSH:1.46U/L (0.70–5) and her anti TPO antibody : 14 IU/ml (normal < 35) was negative.^{99m} Tc pertechnetate scan showed enlarged gland with normal uptake of radiocontrast : 3.4% (normal 0.4- 4%) with some patchy defect in lower portion of right lobe.

Ultrasonogram of thyroid revealed an enlarged gland with inhomogeneous and hypoechoic nodule on right side that was well demarcated from the rest of the gland and hypovascular on doppler ultrasound indicating hemangioma of thyroid gland.

Discussion :-

Haemangioma of the thyroid gland is extremely rare, however reported from India also. Ultrasonography and Computed tomography (CT) are two non-invasive imaging methods to diagnose the condition. Calcified soft tissue mass on imaging study may confuse with papillary thyroid carcinoma, but no calcification was demonstrated in the given case. Ultrasound examination of the lesion is often highly suggestive of the diagnosis and appears hypo-vascular on color Doppler ultrasound. Surgical exploration and histological examination of the surgical specimen may often require to confirm the diagnosis. FNA should be avoided and effort should be made not to rupture these lesions during surgical procedure.



MD, DM., Assoc. Prof., KPC Medical College, Kolkata.

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Young Female with Skin Rash and Heart Failure

Dr. Arghya Chattopadhyay[1], Dr. J. Das[2], Dr. A. K. Ganguly[3], Dr. A. Majumdar[4], Dr. T. J. Sarkar[5]

Abstruct :-

A 26-year-old female presented with gradually changing quality of voice, diffuse pigmentation all over body and lymphadenopathy in upper cervical group. Biopsy of a lymph node showed follicular hyperplasia with a few discrete large cells. Over a period of time she developed purpuric rash over extremities and peri-orbital area, respiratory distress and heart failure. Echocardiography revealed cardiac amyloidosis and rectal biopsy with Congo red staining was positive for amyloidosis. Skin biopsy from hyperpigmented lesion of right forearm was also suggestive of amyloidosis and bone marrow examination showed plasma cell dyscrasia with a small M band in serum protein electrophoresis. Finally it was diagnosed a case of Primary Systemic Amyloidosis.

Key words :-

Primary systemic amyloidosis; Heart failure.

Introduction :-

Primary systemic amyloidosis (AL amyloidosis) is a plasma-cell dyscrasia of unknown cause. Immunoglobulin light chains or fragments of light chains, produced by plasma-cell clones form extracellular amyloid fibrils. Amyloid deposition can occur in any organ in the body, causing features such as congestive cardiac failure, renal failure and hepatosplenomegaly, as well as skin lesions. Both sexes are affected by this disease, with onset most commonly in the sixth decade or after. Although recent advances in therapy are encouraging, the prognosis for primary amyloidosis remains poor.

Case Report :-

A 26-year-old female admitted in the month of June, 2010 with hoarseness of voice, diffuse pigmentation all over body and lymphadenopathy in upper cervical group of lymph nodes for last one year. It was of insidious onset and was progressive in nature. Detailed history taking did not reveal any history of fever, joint pain, joint swelling, bone pain or any other constitutional symptoms. Examination showed only upper cervical lymphadenopathy, diffuse skin pigmentation with thickening of skin of upper limb. There was no history of Raynaud's phenomenon and the tongue was thick but of normal size. Differential diagnosis of collagen vascular disease, malignancy with paraneoplastic syndrome, tuberculosis and lupoid proteinosis were made. Routine blood tests and thyroid profile, Anti nuclear antibody (ANA), double stranded De-oxy-Ribonucleic Acid (ds DNA), Rheumatoid Factor (RA), Hepatitis B surface antigen (HBsAg), Anti Hepatitis C Virus (Anti HCV) antibody and Human Immunodeficiency Virus antigen (HIV) were within normal limit. Mantoux (with 10U tuberculin) was positive

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with 21mm induration and erythema. Chest X-Ray (Posterior-anterior view) showed perihilar lymphadenopathy. Contrast Enhanced Computer Tomography of Thorax confirmed the X-ray findings but failed to specify the nature of the lesions better than Chest X-Ray. Biopsy from the cervical lymph node showed follicular hyperplasia with few discrete large cells and CD 15, CD 30 and Bcl 2 were advised, but the patient sought discharge from hospital for personal reason without undergoing these investigations.

In February, 2011 she got readmitted with complaints of respiratory distress, bilateral swelling of feet, a few purpuric skin rash over extremities and face. The lesion resolved spontaneously and similar purpuric rash in peri orbital region appeared. She also reported pain and tingling sensation in the distal parts of all four limbs and the skin pigmentation has increased remarkably. Physical examination revealed persistence of upper cervical lymphadenopathy, bilateral pitting pedal edema with engorged and pulsatile neck veins and gallop rhythm, orthopnoea, decreased vocal resonance and breath sound over lower zone of right lung.

Considering the new features suggestive of heart failure, skin rash and pigmentation a new set of differentials was considered in addition to the previous ones including the possibility of primary systemic amyloidosis.

Laboratory workup revealed leucocytosis with a positive urine culture of Klebsiella pneumonia. Chest X-ray showed persistence of perihilar lymphadenopathy with right sided pleural effusion. Pleural fluid study was transudative. Serological tests encompassing viral markers and autoimmune profile were negative. Abdominal ultrasonography did not reveal any significant findings. Nerve conduction study was suggestive of entrapment neuropathy of right median nerve at wrist joint and bilateral peroneal neuropathy.

Echocardiography revealed increased ventricular wall thickness with ground glass appearance of myocardium, restrictive left ventricular filling pattern and moderate pericardial effusion posteriorly with borderline left ventricular systolic dysfunction and thickened mitral and tricuspid valves. These features were strongly suggestive of cardiac amyloidosis.

Rectal biopsy with Congo Red staining revealed orangophilia in amorphous deposits around the blood vessels, suggestive of amyloidosis. Skin biopsy was also consistent with amyloidosis.

Bone marrow examination revealed plasma cell dyscrasia, with M band in serum protein electrophoresis. Twenty four hour urinary protein was 440mg. without any light chain on electrophoresis.

A final diagnosis of Primary Systemic Amyloidosis was made. The patient was treated with pulse dexamethasone and cyclophosphamide and thalidomide daily. Patient tolerated the drugs well and was discharged with a plan of bone marrow transplant.

Discussion :-

Amyloidosis is the term for diseases caused by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs. These diseases are a subset of a growing group of disorders attributed to misfolding of proteins.

Polypeptide chain gets folded to form a secondary structure of the protein molecule. Helical structure and pleated structure are two important secondary structures of protein molecule. The amyloid protein has a beta-pleated sheet structure, which makes it highly insoluble and resistant to proteolytic digestion and hence difficult to remove from the tissues. About 25 different proteins are known to produce amyloid fibrils in human, most of them are constituents of plasma. These normally soluble precursor proteins, due to some unknown reason, get mis-folded and forms a beta-pleated sheet structure and becomes amyloid. Inherited amyloidosis is due to mutation in certain precursor protein, which makes them susceptible to mis-folding. In case of primary systemic amyloidosis, the amyloid is derived from monoclonal immunoglobulin light chain and is called as AL amyloid where L stands for light chain of immunoglobulin molecule. In case of secondary amyloidosis, which is associated with many chronic inflammatory diseases, amyloid fibrils are derived from cleavage fragment of the circulating acute phase reactant serum amyloid A protein (SAA), hence this type is called as AA amyloid. Serum amyloid A protein is synthesized in liver during inflammation. In localized cutaneous amyloidosis, amyloid is derived from keratin released from apoptotic keratinocytes. The possible reason that many diverse conditions are associated with amyloidosis is each of these conditions results in excessive production of proteins that are prone to mis-folding. In multiple myeloma-associated AL amyloidosis, precursor light chains of immunoglobulin (Bence Jones protein) are produced in large quantity by malignant plasma cell clone and can be detected in serum or urine by electrophoresis. Multiple myeloma is a malignancy of plasma cell. Amyloidosis develops in about 15% of patients of myelomatosis. Majority of patients of AL amyloidosis do not have obvious B-cell / plasma cell neoplasm hence they are idiopathic amyloidosis. These patients might have underlying B-cell dyscrasia in which production of abnormal protein, rather than production of tumor masses, is the only clinically apparent manifestation. Although different types of amyloid are associated with distinct clinical picture, all amyloid share a certain common features sich as : Amorphous eosinophilic appearance on light microscopy in H and E staining, bright green fluorescence observed under polarized light after Congo red staining, beta-pleated structure on X-ray crystallography, deposition of amyloid in tissues leading to distortion of tissue architecture, organ enlargement (organomegaly) and organ dysfunction. Amyloid deposition can occur in any organ. Primary systemic amyloidosis (AL) is known for highly varied clinical manifestation.

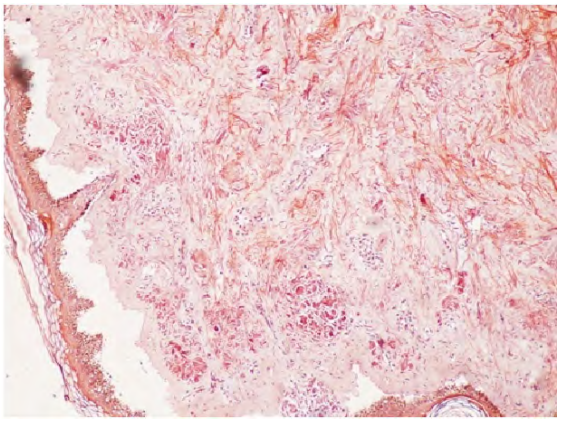
Cutaneous involvement is seen in 40% patients with AL amyloidosis. Cutaneous manifestation depends upon the site of amyloid deposited. Amyloid deposition in superficial dermis produces shiny waxy translucent papules and common sites for predilection are eyelids, retro-auricular areas, neck, axilla. Amyloid deposited around pilosebaceous unit leads to the destruction of hair, producing alopecia. Diffuse infiltration of scalp skin results in the thickening of skin which gets thrown into longitudinal folds resembling cutis vertices gyrata. Diffuse infiltration of large area of skin may simulate

scleroderma. Infiltration of nail matrix by amyloid may produce ridging, splitting and brittleness of nail plate.

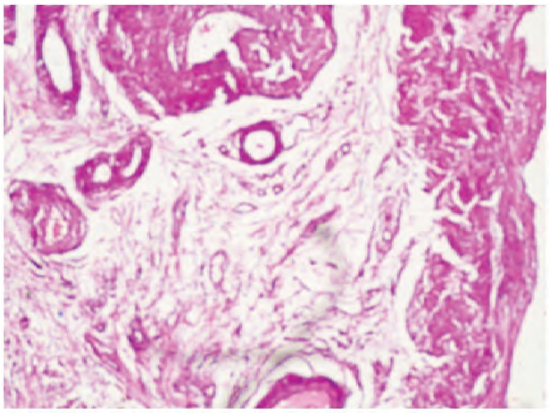
Amyloid infiltration of vessel wall causes capillary wall fragility, which leads to purpura and ecchymosis after a minor trauma or even spontaneously. Periorbital area is one of the common sites of expression of purpura, as evident in this case. The capillary fragility may be demonstrated by pinching the skin. Purpuric lesions with normal platelet count and normal coagulation profile should suggest the possibility of capillary fragility. Amyloid deposition in tongue leads to macroglossia. Tongue is diffusely enlarged and firm and there may be tooth indentation along its lateral border. Amyloidosis is the commonest cause of macroglossia in adults. Macroglossia if severe might lead to dysphagia. Macroglossia was present in our case. Hepatomegaly occurs in 50% of patients and splenomegaly in 10%. Cardiac involvement leads to conduction defects, arrhythmias, congestive cardiac failure and may account for 40% of deaths.Cardiac involvement in terms of cardiac amyloidosis with features of congestive heart failure was present in this case. Carpal tunnel syndrome is seen in up to 25% of patients of primary systemic amyloidosis as was present in our case. Amyloid infiltration might occur in peripheral nerves leading to thickening of nerves and resulting neuropathy often mimicing Hansen's disease. Renal involvement presenting with proteinuria and renal failure, is one of the bad prognostic indicators.

Our patient had plasma cell dyscrasia and M band in serum protein electrophoresis. Diagnosis was confirmed by demonstration of amyloid in rectal biopsy and skin biopsy. Clinically, it is difficult to distinguish primary, secondary or familial form of amyloidosis. Immuno-histochemical staining using commercially available antisera is useful for classifying the type of amyloid deposited in tissues. Biopsy is very important for the diagnosis. Hematoxylin and eosin staining suggests the possibility of amyloidosis but Congo red staining confirms the diagnosis. Congo red staining results in a brick red color of amyloid when seen under ordinary light and under polarized light shows classical green birefringence. Unfortunately, polarized microscopy is not easily available in developing country like India. In systemic amyloidosis, amyloid deposits are seen in dermis, subcutaneous tissue and blood vessels, where as in localized cutaneous amyloidosis, deposits are seen only in papillary dermis; subcutaneous tissues and blood vessels are not involved.

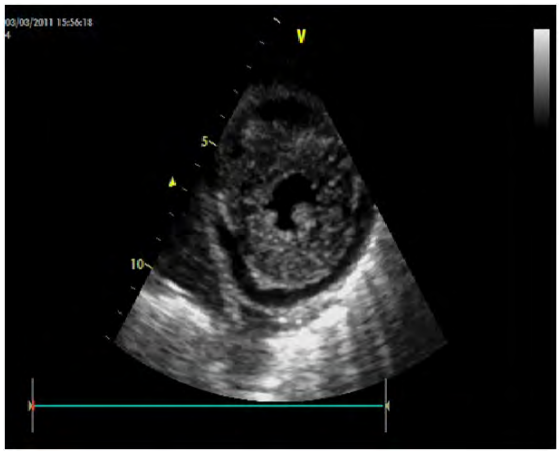
Prognosis in AL amyloidosis is poor and major causes of death are cardiac and renal failure. The median survival of patients with myeloma-associated amyloidosis is five months and for patients with primary systemic amyloidosis is 2.1 years. Prognosis depends upon the extent of involvement. Treatment of amyloidosis is aimed at reducing the supply of precursor proteins.[4] In AL amyloidosis, the precursor is immunoglobulin light chain produced by B lymphocytes/plasma cells hence treatment with cytotoxic agents like melphalan and prednisolone that reduces plasma cell proliferation is useful. Chemotherapy will be useful only when precursors are supplied by plasma cells like AL amyloidosis.



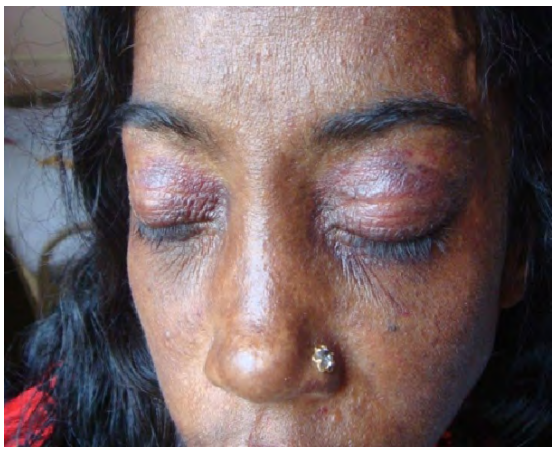
Skin biopsy showing anyloidosis



Rectal biopsy showing anyloidosis



Cardiac anyloidosis ‘‘ground glass appearence’’



‘‘Raccon Eye’’

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Pure Squamous Cell Carcinoma of Gall Bladder – A Case Report

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Abstract :

Primary squamous cell carcinoma (SCC) of the gallbladder is a rare, aggressive malignant condition. While SCC commonly presents as abdominal pain or lump and/or jaundice, some cases with unusual presentations have been reported in literature. SCC of gall bladder is more common with calculous cholecystitis. We report here a rather unusual presentation of a case of a squamous cell carcinoma of the gallbladder in a 65-year-old female presenting as right hypochondrial pain without cholelithiasis.

Introduction :

Primary SCC is well recognised as a separate entity of gall bladder cancer in the World Health Organisation classification of tumour of gall bladder and extra-hepatic bile ducts.[1]

Pathologically, gall bladder carcinoma can be divided into four subtypes: adenocarcinoma (papillary, tubular, mucinous, or signet ring cell-type, accounting for 80 – 95% of all occurrences); squamous cell and adenosquamous cell carcinoma (2 – 10%); undifferentiated carcinoma (2 – 7%) and rare tumours (small cell carcinomas, sarcomas, melanomas, and lymphomas)[1,2] SCC accounts for only 0 – 12.7% of all gall bladder carcinoma.[3] Secondary SCC, wheather directly invading the gall bladder or carried from distant metastasis, is relatively more common than the primary tumour arising from the gall bladder.[3] SCC of gall bladder characteristically presents as an invasive growth with low tendency towards lymph node metastasis and high incidence of local infiltration and hepatic metastasis, presenting a poor prognosis than adenocarcinoma of the gall bladder.[3,4]

SCC of gall bladder is more common with calculous cholecystitis.[5] Most common symptom is pain, which occurs in 66% of patients.[6] Other clinical presentations are abdominal lump and / or jaundice or empyema or acute cholecystitis.[7]

SCC of gall bladder is predominantly occurs among females, in a proportion of 3:1 over males and usually occur between fourth and sixth decades of life.[3,4,8]

Sonography guided fine needle aspiration cytodiagnosis is a very effective and useful less-invasive technique in diagnosis of gall bladder neoplasm in experienced hand.[6]

Here we are reporting a case of gall bladder squamous cell carcinoma without presence of gall stone

Case report :

A 65 years old woman presented with right hypochondrial pain along with anorexia, weight loss and low grade fever for last 1 year. On examination a lump was found at right hypochondrium. Laboratory tests revealed no abnormalities except for an elevation of alkaline phosphatase (723 IU/l) with reduced haemoglobin (9.1 gm %). Serum levels of α-fetoprotein and carcinoembryonic antigen were normal. Abdominal CT scan reveals space occupying lesion suggestive of gall bladder carcinoma with hepatic infiltration but no gall

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stone was seen. Cholecystectomy was performed which revealed distorted gall bladder mass infiltrating mainly the right lobe of liver with no infiltration of common bile duct and porta hepatis.

Gross morphology (Fig-1) of the resected specimen showed, a distorted irregular mass measuring of 11x 9 x 6 cm. Cut section showed multiple focal grayish- brown hemorrhagic and non-hemorrhagic nodular areas. Focal areas of normal gall bladder mucosa were seen. Gall stone was not found.

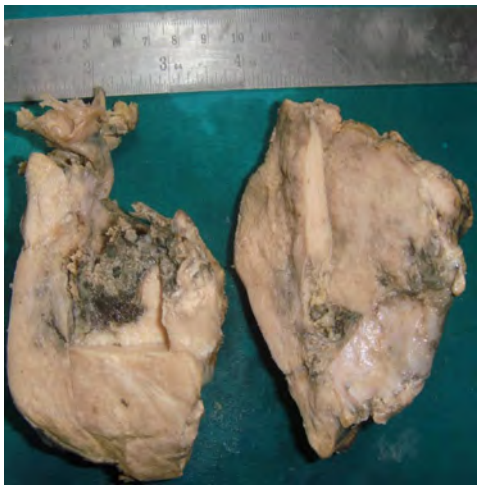

Fig 1: Photograph showing distorted gallbladder mass

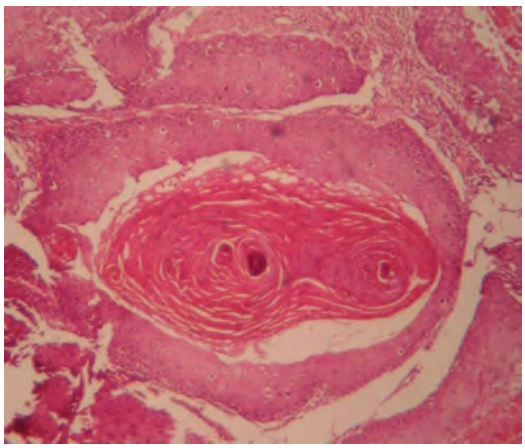

Fig 2: **Low power view** shows pure squamous cell carcinoma with keratin pearl formation

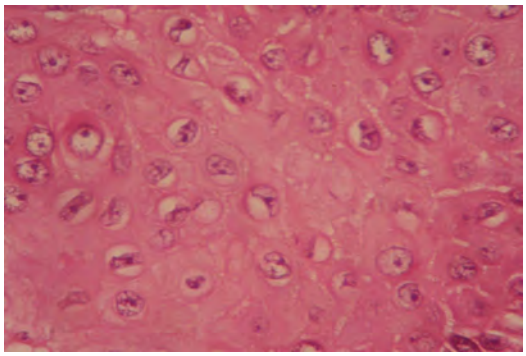

Fig 3 : **High power view** shows pure squamous cell differentiation

Histologically (Fig-2 & Fig-3), moderately differentiated pure squamous cell carcinoma with areas of necrosis was found in multiple sections of gall bladder. Infiltration was present into the hepatic tissue through the serosa. Focal lympho-vascular and perineural invasion was seen. Lymph node showed no malignant invasion.

Discussion :

Mixed adenosquamous carcinoma is an entity where both squamous and glandular elements exist in the same tumour, and reported more frequently than pure primary squamous cell carcinoma variety.[9] Primary squamous cell carcinoma of gall bladder is a rare tumour which we were found in this case.[5]

SCC of gall bladder predominantly found in female and occurs between the fourth and sixth decades of life, [3,4,8] as was found in our case.

Tumours tend to grow early, forming large infiltrative masses and invading the liver and adjacent organs by direct expansion as seen in our case.[3,4] Despite this local infiltration, tumours rarely metastases in lymph nodes or seeding in the peritoneum which were absent in this case.[3,4,8]

Most studies accept that the squamous cells originate from pre-existing metaplastic squamous

epithelium; whereas others believe that SCC of gall bladder originates from squamous differentiation of the adenocarcinoma cells.[3,4,8]

We conclude that SCC of gall bladder usually present with pain abdomen in elderly female with locally invasive lesion.

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