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Journal, Indian Academy of Clinical Medicine • Vol. 19, Number 1, January-March, 2018

Contains 80 pages from 1 to 80 (inclusive of all advertisements)

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Journal, Indian Academy of Clinical Medicine

JOURNAL, INDIAN ACADEMY OF CLINICAL MEDICINE

is edited by

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for the

Indian Association of Clinical Medicine

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E-mail: iacmjournal@gmail.com

ISSN 0972-3560

RNI Regn. No. : DELENG/2000/1686

Indexed in Scopus, IndMED

Listed in UGC Approved List of Journals

"Bibliographic details of the journal available in ICMR-NIC's database – IndMED (http://indmed.nic.in). Full-text of articles (from 2000 onwards) available on medIND database (http://medind.nic.in)."

Published by Dr. MPS Chawla
for and on behalf of the Indian Association of Clinical Medicine
from 4/19 B, Jangpura B, New Delhi - 110 014
and printed by him at Sumit Advertising, 2 DLF (Part) Industrial Area, Moti Nagar, New Delhi - 110 015.

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VIEWPOINT

JIACM 2018; 19(1): 6-7

Weapons of mass destruction

*BM Hegde**

The adverse drug reactions to commonly prescribed drugs by doctors are on the rise!

The following national estimates on well-conducted studies, mainly in the United States suggest that each year, in hospitals alone, there are 28,000 cases of life-threatening heart toxicity from adverse reactions to digoxin, the most commonly used form of digitalis (drug that regulates the speed and strength of heart beats) in older adults. Since as many as 40% or more of these people are using this drug unnecessarily, many of these injuries are preventable. Each year 41,000 older adults are hospitalised – and 3,300 of these die – from ulcers caused by NSAIDs (*nonsteroidal anti-inflammatory drugs, usually for treatment of arthritis*). Thousands of younger adults too are hospitalised for the same. *At least 16,000 injuries from auto crashes each year involving older drivers are* attributable to the use of psychoactive drugs, specifically benzodiazepines and tricyclic antidepressants. Psychoactive drugs are those that affect the mind and/or behaviour.

Each year 32,000 older adults suffer from hip fractures attributable to drug-induced falls, resulting in more than 1,500 deaths. In one study, the main categories of drugs responsible for the falls leading to hip fractures were sleeping pills and minor tranquilisers (30%), antipsychotic drugs (52%), and antidepressants (17%). All of these categories of drugs are often prescribed unnecessarily, especially in older adults.

One example will tell you how we are still groping in the dark about drug toxicity. Digoxin is a good example very liberally prescribed for heart failure. William Withering used this drug as leaves of the plant *Digitalis lanata* more than 300 years ago. We have, of course, refined it – thanks to our technology – as a fine extract, digoxin, digitoxin, etc. So far so good, but we do not know even today the right therapeutic dose for heart failure in the elderly! The safety range between therapeutic and toxic dose is so narrow that we make mistakes always either ways, either too much or too little. There is a group of researchers (Digoxin Investigating Group – DIG group) that has been working on this for decades without much to write home about. Most of the time the drug is over prescribed in the elderly in whom heart failure is a gigantic problem. Poor Withering who had no touch with our hi-tech stuff did not kill as many as we do now.

Even when I was a medical student – half a century ago in the 1950s – we were lucky to use the powdered leaf which had less toxicity and life for us and our patients was easy! In the present *avatar* digoxin gets out of the system very slowly through the kidneys, the latter gets worse in heart failure thanks to slowed renal circulation. Thank God the DIG group has lately come up with a new suggestion to reduce the patient load for digoxin in heart failure which many of us have not read unfortunately! They have shown that only in that small subset of patients in heart failure with atrial fibrillation and NOT in those heart failure patients in normal sinus rhythm! This cuts off nearly half the number of indications cutting drug-related deaths by half. Since the drug gets out so slowly in the elderly, I normally give it from Monday to Friday with two days gap for weekends for its wash out. Exclusion of heart failure in normal sinus rhythms cuts a large chunk of heart failures from dig toxicity. People call me a therapeutic nihilist as I am very, very parsimonious in drug prescribing.

I have seen many digoxin toxicities of all grades from mild anorexia to frank fatal toxicity. My own feeling is that if the patient with heart failure is happy and contented, the outcome is better. Once I had an elderly British lady in heart failure getting in and out of hospital many a time in London.

One day she called me aside and asked me to request the NHS to give her a return ticket to Australia to see her only son who left her twenty years ago to settle there. That was bugging her. That accomplished, she stopped coming back with more failures, the power of a happy mind to heal!

This is the story of only one drug which has been with us for 300 years. Think of other killers like NSAIDs which kill thousands as they are so liberally prescribed by pain doctors for quick relief making them a pain in the neck. Many other commonly prescribed drugs not referred to here add to the burden of mass killers. Prescription drugs kill more people than the street drugs peddled by quacks. While they

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get caught and punished, we sit in our air-conditioned rooms and get all the protection thanks to our patrons – the most powerful drug lobby. Every thinking doctor should read the following book by the former editor of the prestigious *New England Journal of Medicine*, Marcia Angell entitled *THE TRUTH ABOUT DRUG COMPANIES – HOW THEY HARM SOCIETY AND WHAT TO DO ABOUT IT.* This should be every doctor's bible, but since many of us have not read it, I recommend it to patients, to take care of their lives.

The real weapons of mass destruction were not with Saddam Hussain but are with the medical profession! Let us be very parsimonious in drugging patients like the Scots say in their word parsimony.

Avas

ORIGINAL ARTICLE

JIACM 2018; 19(1): 8-12

Effect of Robotic Erigo Tilt Table Exercise on Neurological Parameters in Hemiplegic Patients: A Pilot Study

Ramakant Yadav, Suraj Kumar**, Aafreen***, Sandeep Yadav*****

Abstract

Background: Stroke is the leading cause of chronic disability worldwide. To prevent persistent neurological deficits, rehabilitation may be effective if started early. The aim of this study is to determine the efficacy of Robotic Erigo tilt table exercises on neurological parameters in patients with hemiplegia following stroke.

Material and methods: Thirty subjects were randomised equally in two groups. Group A underwent conventional physiotherapy (control group) and group B underwent Robotic Erigo tilt table exercise (experimental group). Baseline evaluation of neurological parameters was done at the time of randomisation and re-evaluation was done after 30 days. Outcome measures were National Institutes of Health Stroke Scale NIHSS, Mini Mental Scale Examination (MMSE), Glasgow Coma Scale (GCS) and Modified Ashworth Scale (MAS) scores.

Results: Mean age of the 30 patients was 49.7 ± 7.15 years and 13 were females. Training was started on average 8.67 ± 4.02 days after the stroke. Patients demographic parameters and baseline neurological score were similar in both groups. After 30 days of training, both the groups showed improvement in all the neurological parameters, but Robotic Erigo tilt table group showed more improvement.

Conclusion: The study concluded that the Robotic Erigo tilt table exercises were found to be more beneficial in hemiplegic patients for improving neurological parameters.

Keywords: Robotic Erigo tilt table, National Institutes of Health Stroke Scale, stroke, Modified Ashworth Scale.

Introduction

Stroke is a leading cause of acquired disability in the world, with increasing survival rates as medical care and treatment techniques improve[1]. As a consequence of focal brain ischaemia or haemorrhage, stroke can have both immediate and ongoing physical effects. Within 12 months of stroke, one-third of stroke patients will die and another third are left with disability, restricted in performing simple activities of daily living (ADLs) and requiring some kind of assistance[2]. Although physical therapy may be beneficial in limiting the effects of bedridden condition, but mobilising severely impaired or uncooperative patients is often unprofitable[3].

Robots help early mobilisation and can assist the patient with altered states of vigilance, enabling movement repetitions that may induce central nervous system re-organisation processes that lead to functional recovery[4]. Robotic tilt tables may bring the patient to a vertical position while moving their legs to prevent blood pressure drops. Robotic therapy has been safely and successfully used in acute stroke patients in the past[5].

Methodology

Total 30 subjects were enrolled in the study; 15 patients in conventional exercises group, and 15 in Robotic Erigo tilt table group. The subjects were recruited from the indoor and out patients of Department of Neurology, Uttar Pradesh University of Medical Sciences, Saifai, Etawah. The study was approved by institutional Ethics Committee.

Inclusion criteria were hemiplegia after stroke, both ischaemic and haemorrhagic, within 7 to 28 days of onset, either male or females of age group 30 - 60 years. Subjects with metal implant, recurrent stroke, chronic renal failure, cognitive and speech problem, hemiplegia due to non-vascular causes (malignancy, infections, tumours, brain injury, etc.), sensation loss in the lower extremity and poor sitting balance were excluded. Outcome variables such as Glasgow Coma Scale (GCS), Mini-Mental State Examination (MMSE), National Institutes of Health Stroke Scale (NIHSS), and Modified Ashworth Scale were observed by the same physiotherapist supervising the test procedure at base line as well as on day 30 of intervention. Before experimentation, all subjects were well taught about the measurement variables and their outcomes. After group allocations, respective subjects were treated either with conventional exercises or robotic erigo tilt table exercises. Both exercises were given as individual treatment by the same physiotherapist with same intensity and capacity on 30

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regular days .The subjects were also informed about the experimental risks, if any. The duration of each individual training session was about 50 to 60 minutes per day. All subjects were allowed to take treatment for their co-morbid condition like hypertension, dyslipidaemia, hypothyroidism, cardiac problem along with exercises.

Variables

Independent variables were Robotic Erigo tilt table exercises and conventional exercises whereas dependent variables were GCS, MMSE, NIHSS and Modified Ashworth Scale. The cognition was assessed by MMSE, motor and sensory assessment by NIHSS and Spasticity by Modified Ashworth Scale.

The National Institutes of Health Stroke Scale, (NIHSS) is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, each of which scores a specific ability between a 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0[6].

The Mini-Mental State Examination (MMSE) or Folstein test is a 30-point questionnaire that is used extensively in clinical and research settings to measure cognitive impairment. Administration of the test takes between 5 and 10 minutes and examines functions including registration (repeating named prompts), attention and calculation, recall, language, ability to follow simple commands and orientation. Any score greater than or equal to 24 points (out of 30) indicates a normal cognition. Below this, scores can indicate severe (≤ 9 points), moderate (10 - 18 points) or mild (19 - 23 points) cognitive impairment[7].

The modified Ashworth Scale is a 6-point rating scale that is used to measure muscle tone with ratings from 0 indicating no increase in tone to 5 indicating limb rigid in flexion or extension[8].

Glasgow Coma Scale (GCS) is a neurological scale which aims to give a reliable and objective way of recording the conscious state of a person for initial as well as subsequent assessment. The lowest possible GCS is 3 (deep coma or death), while the highest is 15 (fully awake person). Brain injury is classified as severe (GCS < 8 - 9), moderate (GCS 8 or 9 - 12), minor (GCS ≥ 13).

Conventional exercise

All the exercises were done under the supervision of a physiotherapist, which included the following:-

- Full range of motion (ROM) exercises – passive and active assisted range of motion exercises for upper limb includes shoulder (flexion, extension, abduction and adduction), elbow (flexion and extension), forearm (supination and pronation), wrist (flexion, extension, radial and ulnar deviation).
- To prevent spasticity – positioning of the limb, quick icing, brushing, gentle stroking, and gentle tapping.
- The common mat activities include turning from supine to side-lying to prone and vice versa, prone to prone on elbow, prone on elbow to prone on hand; prone on hand to quadripud; quadripud to kneeling; kneeling to half kneeling; half kneeling to standing with support; standing with support to the standing without support.
- Bridging exercises.
- Prolonged and gradually progressive stretching of hamstring, calf, and wrist.
- Gentle and controlled weight bearing exercises.
- Balance and coordination exercises.

Robotic Erigo tilt table exercises

Robotic Erigo tilt table exercises (Fig. 1) for about 40 minutes per session, 6 times per week for 4 weeks[9,10].

Table I: Shows the exercise protocol on Erigo tilt-table.

Phase I (1st week)	At 30° angle for 40 minutes with 1 minute hold after every 12 minutes at 0° angle
Phase II (2nd and 3rd week)	At 50° angle for 40 minutes (approx.) with 1 minute hold after every 12 minutes at 0° angle
Phase III (4th week)	At 75° angle for 40 minutes (approx.) with 1 minute hold after every 12 minutes at 0° angle

The Erigo exercise session was followed by 15 minutes exercise programme for upper extremities which includes range of motion, strengthening and stretching exercises of shoulder, elbow, wrist and fingers.

Data analysis

A priori alpha level of significance was chosen as 0.05 was used for all statistical analyses. Data was summarised using descriptive statistics of mean and standard deviation. All statistical analysis were performed using SPSS 24.0. Scores of the dependent variables NIHSS, MMSE, GCS and Ashworth was compared for the two instances in each group at baseline and after 30 days using paired t-test and the comparisons between both the groups were evaluated using un-paired t-test.

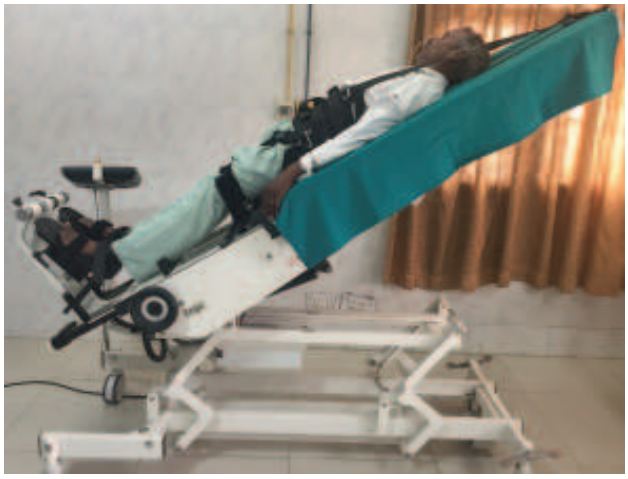


Fig. 1: Robotic Erigo tilt table training.

Result

In this study, total 30 subjects were enrolled on the basis of inclusion and exclusion criteria and randomised equally into 2 groups, conventional exercise group and Robotic Erigo tilt table group (15 in each). Mean age of the patients was 49.7 ± 7.15 years and 13 were females. Training was started on average 8.67 ± 4.02 days after the stroke. Demographic profile and baseline parameters were similar in both the groups (Table II). There was no dropout due to any adverse effects. The baseline scores of impairment (0 day) are presented in graph 1 which shows that there was no significant difference between the scores of the dependent variables NIHSS (p= 0.320), MMSE (p = 0.500), GCS (p = 0.724) and modified Ashworth scale (p = 0.719).

After 30 days of training, both groups showed improvement in all the neurological parameters. The NIHSS, MMSE, and Modified Ashworth Scale score showed more improvement in Robotic Erigo tilt table group than the conventional exercise group. On comparison of all the variables, NIHSS (p = 0.031), MMSE (p = 0.264), GCS (p = 1) and Ashworth (p = 0.433).

Table II: Demographic profile of the patients.

Demographic variables	Conventional group (n = 15)	Erigo tilt table group (n = 15)	Level of significance (P value)
Age (years)	49.53 ± 6.22	49.87 ± 8.41	0.4513
Weight (kg)	61.93 ± 11.1	62.53 ± 7.12	0.4306
Height (metre)	1.59 ± 0.08	1.63 ± 0.06	0.0573
BP systolic (mm of Hg)	1.36.67 ± 17.99	129.07 ± 14.60	0.1072
BP diastolic (mm of Hg)	91.33 ± 12.46	84.67 ± 9.15	0.0530
Pulse (beats per minute)	84.20 ± 6.99	84.40 ± 3.56	0.4610

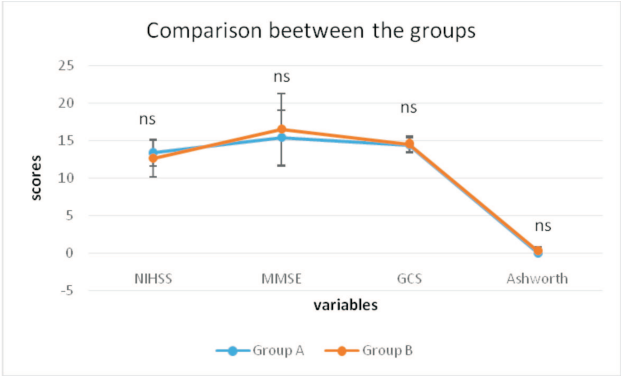
Table III: Comparison (0 versus 30 day) of training among all the variable scores with time.

		Baseline (0 day)	After 30 day training	df	Level of significance P value
NIHSS score	Conventional therapy group	13.40 ± 1.80	6.93 ± 1.87	6.47	0.000*
	Robotic Erigo tilt table group	12.60 ± 2.47	5.20 ± 2.31	7.4	0.000*
MMSE score	Conventional therapy group	15.40 ± 3.64	21.33 ± 2.94	5.93	0.000*
	Robotic Erigo tilt table group	16.47 ± 4.82	22.53 ± 2.83	6.07	0.000*
GCS score	Conventional therapy group	14.40 ± 0.99	15.00 ± 0.00	0.60	0.033*
	Robotic Erigo tilt table group	14.53 ± 1.06	15.00 ± 0.00	0.47	0.110
MAS score	Conventional therapy group	0.07 ± 0.26	0.67 ± 0.62	0.60	0.002*
	Robotic Erigo tilt table group	0.33 ± 0.49	0.47 ± 0.52	0.13	0.433

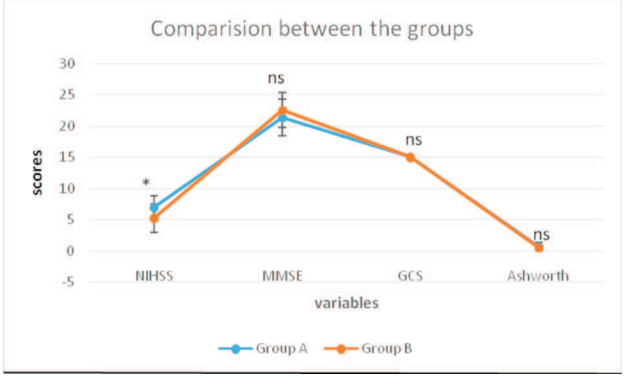
Discussion

The hypothesis that Robotic Erigo tilt table exercises may be beneficial in improving neurological parameters in hemiplegic patients was found to be true in many aspects. Though both the treatments were found to be effective, but Robotic Erigo tilt table group showed more improvement than conventional exercise group.

NIHSS score was found to be improved 12.57% more in Robotic Erigo tilt table group than the conventional group. MMSE score was found to be improved 2.31% more in Robotic Erigo tilt table group in comparison to conventional



***Graph 1:** Shows comparison between group on day 0 (baseline) of neurological parameters.*



Graph 2: *Shows comparison between groups after training (30th day) of neurological parameters.*

group which shows that almost equal improvement was recorded for cognition in both the groups. Glasgow Coma Scale score was improved equally in both the groups as very severe patients were not included in the study so, within one month all the subjects achieved the maximum score of GCS in both the groups. Modified Ashworth Scale score after 30 days of intervention shows that Robotic Erigo tilt table group developed less spasticity when compared to conventional group.

It has been suggested that verticalisation (VT) may play a role in stimulating cortical areas involved in trunk and lower limb control, so that de-afferentation and learned non-use can be contrasted[11]. VT may actively contribute to enhanced cognitive performances through an increase in cerebral blood flow with a consequent induction of cortical plasticity, especially in frontal lobes[12]. Robotic verticalisation induces increased ventilation, increased arousal, improved weight bearing of the lower limbs, and facilitation of antigravity exercise of the limbs[13].

Mobilisation to standing position with a tilt table, has been shown to improve arousal and awareness in small groups of vegetative state and minimally conscious state patients[14-16].

The two primary physical treatments applied to patients with involuntary muscle contractions are electrical stimulation and long-term stretch. When applied to the ankle plantar flexor muscles, the benefits of long-term stretch, seem to be augmented by weight loading[17].This finding, and a personal impression that extensor spasms are sometimes reduced after tilt table standing, prompted a monitored trial of a tilt table standing regimen for a patient with intractable extensor spasms of the lower extremities[18].

Robotic verticalisation maximises the potential for longitudinal weight bearing through the lower extremities in a position of hip-extension, knee-extension, ankle-dorsiflexion, which is difficult to obtain in the conventional physiotherapy setting. Moreover, Robotic verticalisation allows strengthen exercises of body weight shifting from one leg to the other, which are not simply carried out in severe post-stroke patients.

A greater cerebral blood flow modulation during Robotic VT in comparison to physiotherapy VT could further support plastic changes within sensory-motor areas and vestibular system, with the consequent motor and cognitive function amelioration[19-21].

Thus, this study supports the earlier researches on Erigo tilt table effectiveness and safety and clinician can use the Robotic Erigo tilt table in better management of the hemiplegic patients.

Limitations of our study was the small number of patients and short duration of training by the Robotic tilt table.

Conclusion

The study concluded that Robotic Erigo tilt table exercises were found to be effective in improving neurological parameters such as consciousness, cognition, muscle tone, and motor performances in hemiplegic patients.

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ORIGINAL ARTICLE

JIACM 2018; 19(1): 13-16

Correlation of Ankle Brachial Index with Peripheral Vascular Disease in Type 2 Diabetes Mellitus

Tejpal Singh, Manaswi Chaubey**, Praveen Kumar Chaturvedi****

Abstract

Purpose: The aim of this study was to correlate ankle brachial index (ABI) with peripheral vascular disease (PVD) in type 2 diabetes mellitus.

Material and methods: This was a hospital based interdisciplinary prospective study. A total of 100 patients in the age group of 30 to 80 years having peripheral vascular disease with predefined inclusion criteria were included in the study. Patients with other causes of raised blood sugar or peripheral vascular disease were excluded by relevant investigations. Ankle Brachial Index (ABI) was calculated using sphygmomanometer, and Colour Doppler Ultrasound (CDU) was used to diagnose PVD. Both the ABI method and the CDU method were compared for detecting PVD.

Results: In our study, mean age was 60.04 ± 5.03 years, mean body mass index was 27.10 ± 2.67 kg/m^2 and mean duration of diabetes was 7.75 ± 1.50 years. Among the 68 diagnosed cases of PVD on CDU, 70.6% cases were detected to have PVD by the ABI method (true positive) whereas 20 (29.4%) cases remained undiagnosed when ABI alone was used for the diagnosis (false negative). Conversely, among 51 diagnosed cases of PVD by ABI method 5.9% cases were found to be normal on CDU (false positive). The ABI method was found to have specificity of 88.5% but the sensitivity was only 70.6%.

Conclusion: ABI has a very high specificity but the sensitivity is low compared to colour Doppler ultrasound. Therefore, if ABI is abnormal, the diagnosis of PVD is almost certain but in symptomatic cases with normal ABI; colour Doppler should be performed to exclude the PVD.

Keywords: Ankle Brachial Index, peripheral vascular disease, Colour Doppler Ultrasound, type 2 diabetes mellitus.

Introduction

Diabetes, and its complications, have become an epidemic that has become an important and challenging health problem. By 2025, India will have the highest number of diabetes patients (57 million) out of the world total (300 million)[1].

One of the complications of uncontrolled diabetes mellitus is peripheral vascular disease (PVD)[2] . It is also one of the main causes of amputation of lower limb[3] that occurs 12 times more often in diabetics than those without it[4]. PVD is also a risk factor of foot infection[5]. Both PVD and infections are among the major contributors of leg amputations, if a diabetic foot ulcer is present.

Diagnosis of PVD among diabetic patients has its limitation due to diminished clinical manifestations of the disease and diagnostic methods. A high level of specificity (83.3 - 99.0%) and accuracy (72.1 - 89.2%) of the method in detecting ≥ 50% stenosis has been reported for an ankle-brachial index (ABI) ≤ 0.90[6]. ABI is a reproducible and reasonably accurate, non invasive measure for the detection of PVD and the determination of disease severity[7].

Therefore, in 2003, American Diabetes Association (ADA) recommended measuring ABI in all diabetic patients older than 50 years of age, and in younger patients with any other PVD risk factors (e.g., smoking, hypertension, hyperlipidaemia, or duration of diabetes > 10 years)[8]. Most epidemiological studies have used ABI to diagnose PAD[9]. ABI is cheap, reliable and non-invasive method for detecting PVD in type 2 diabetes mellitus. It can be used as an initial screening test for earlier detection of PVD.

Materials and methods

This was a hospital based interdisciplinary prospective study, approved by the institutional review board and informed consent was obtained from each individual.The study followed the tenets of the declaration of Helsinki. A total of 100 randomly selected cases of PVD with type 2 diabetes mellitus (as per American Diabetes 2011 criteria based on consensus opinion from National Data Diabetic

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Group and WHO) having predefined inclusion and exclusion criteria were studied over a period of one-and-half-years.

Patients of age > 14 years with fasting blood sugar ≥ 126 mg/dl (7 mmol/l) and post-prandial blood sugar after a 75 g oral glucose ≥ 200 mg/dl (11.1 mmol/l) were included as cases whereas patients with age below < 14 years, having metabolic syndrome and having other causes of raised blood sugar or PVD as excluded by relevant investigations were not included in the study.

All the cases underwent detailed history and thorough general physical examinations with special emphasis on systemic quantification of PVD symptoms. Anthropometric measurement in the form of height, weight, BMI (Body Mass Index) and ABI were taken and recorded. Biochemical examination with standard laboratory technique in the form of CBC, fasting and post-prandial blood glucose estimation, urine examination, glycosylated haemoglobin estimation, fasting lipid profile, blood urea and serum creatinine estimation, liver function tests were also done to diagnose and quantify the diabetes and its severity.

All the cases with PVD also underwent additional evaluations including Colour Doppler Ultrasound (CDU), ophthalmic examination, ECG, CT scan for cerebrovascular profile and coronary angiography for cardiovascular profile, sphygmomanometric measurement of ankle and brachial artery pressure, Doppler examination to auscultate and record blood flow from dorsalis pedis and posterior tibial and brachial arteries and Treadmill testing to assess functional limitations objectively (decline of ABI immediately after exercise provides further support of diagnosis of PVD).

Ankle brachial index (ABI) was calculated for each leg. The ABI value was determined by taking the higher pressure of the 2 arteries at the ankle divided by the brachial arterial systolic pressure. In calculating the ABI, the higher of the two brachial systolic pressure measurements was used. In normal individuals, there should be a minimal (less than 10 mmHg) interarm systolic pressure gradient during a routine examination. A consistent difference in pressure greater than 10 mmHg between the arms was suggestive of, and a difference greater than 20 mmHg was diagnostic of subclavian or axillary arterial stenosis, which may be observed in individuals at risk for atherosclerosis. ABI < 0.9 was the cut-off used for diagnosis of PVD.

The statistical analysis software SPSS version 17 (IBM SPSS Statistics for windows, SPSS Inc., USA) was used to compare and analyse the data for all the cases.

Results

Among 100 cases included in the study, there were 61 males and 39 female patients with a male to female ratio of 3:2. The youngest patient with type 2 diabetes mellitus was 39-years-old whereas eldest was 80-years-old, with a mean age of 60.04 years (Standard Deviation, SD 5.03). Majority of the cases were older than 50 years (78%) and only 22% cases were below 50 years (Fig. 1).

The mean duration of type 2 diabetes mellitus was 7.75 years (SD 1.50). Among all the cases, 22% cases had diabetes of less than 5 years of duration whereas only 2% cases had diabetes of more than 15 years duration (Fig. 2).

The mean BMI was 27.10 kg/m^2 with standard deviation of 2.67. Among the cases, only 24% cases had BMI in the normal range; 36% of male and 29% of females were overweight, 9% were obese and 3% were very obese (Fig. 3).

Among the cases, 51% were found to have peripheral vascular disease (PVD) detected by ABI method. Majority of the cases with PVD were above 50 years with only 1 case who had PVD in younger age group, i.e., less than 40 years of age. PVD was more common in those who had longer duration of diabetes mellitus, i.e., more than 5 years with majority having 5 to 15 years of diabetes mellitus (Figs. 4, 5 and 6).

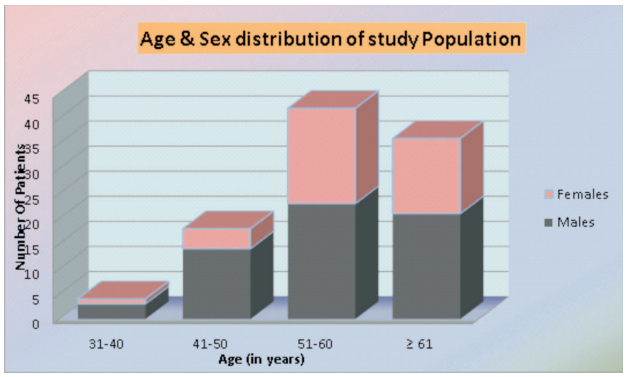

Fig. 1: *Age and sex distribution of cases.*

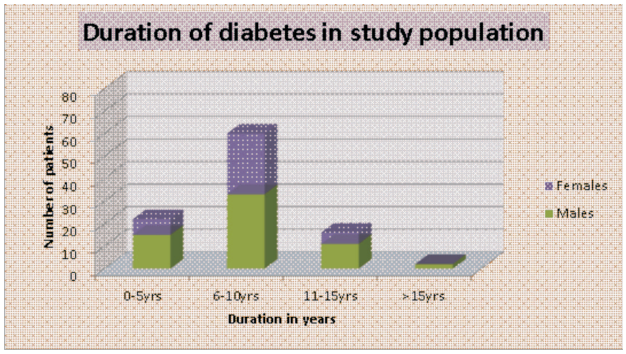

Fig. 2: *Duration of diabetes mellitus in cases.*

Among the cases, 6 subjects were found to have calcification of peripheral vessels detected by colour Doppler ultrasound (CDU) and they were not included while calculating for sensitivity and specificity of ABI. Out of the remaining 94 cases, 68 were diagnosed to have PVD on CDU and 51 cases were detected by ABI method. Among the 68 diagnosed cases of PVD on CDU, only 48 (70.6%) cases were detected by the ABI method (true positive) whereas 20 (29.4%) cases remained undiagnosed when ABI alone was used (false negative). Conversely, among 51 diagnosed cases of PVD by ABI method 3 (5.9%) cases were found to be normal on CDU (false positive). Therefore, ABI was found to have very high specificity, but low sensitivity for detection of PVD (Table I).

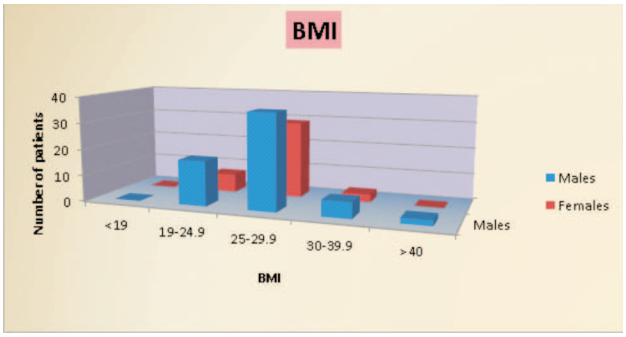

Fig. 3: *Grading of BMI in cases.*

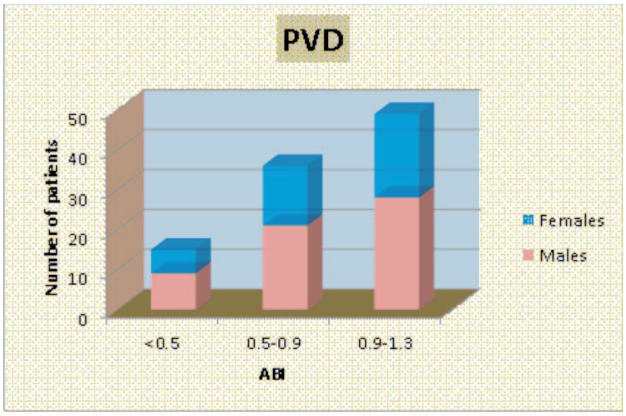

Fig. 4: *Occurrence of PVD in cases using ABI.*

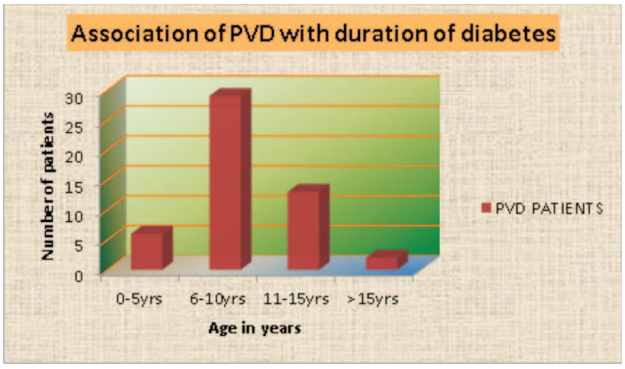

Fig. 5: *Association of PVD with duration of diabetes mellitus.*

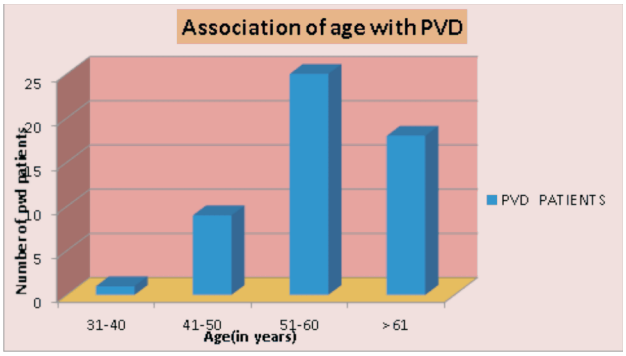

Fig. 6: *Association of age with PVD.*

Table I: Overall sensitivity and specificity of ABI vs colour Doppler ultrasound in PVD cases.

CDU	ABI	
(colour Doppler ultrasound)	Normal	Abnormal
Normal	23 (TN)	3 (FP)
Abnormal	20 (FN)	48 (TP)

TP – True positive, FP – False positive, TN – True negative, FN – False negative.

Study of agreement between ABI values and CDU findings showed a 100% agreement with CDU for the ABI value of less than 0.5 whereas the ABI value of 0.9 or more showed only 47.9% agreement with CDU (Table II).

Table II: Agreement between ABI and colour doppler ultrasound for PVD cases

ABI	CDU		Total
	Normal	Abnormal	
> 0.9	25	23	48
0.7 - 0.9	2	5	7
0.5 - 0.7	0	30	30
< 0.5	0	15	15
Total	27	73	100

Discussion

The mean age of the cases in our study was 60.04 ± 5.03 years and the age range of the cases was from 30 to 80 years. This was comparable with the study of Premalatha *et al*[10].

The present study had more male diabetics (61) compared to females (39) with male to female ratio of 3:2. The mean duration of diabetes was 7.75 ± 1.50 years which is

comparable to the study of Banait *et al*[11]. In our study, the mean BMI was 27.10 ± 2.67 kg/m^2 comparable to the study of Orchard *et al*[12].

As it is difficult to perform CDU in a population based study, ABI method was used in our study and the sensitivity and specificity of ABI was compared to CDU. Earlier studies have suggested ABI as a reliable method for diagnosis of PVD, with ABI value of 0.9 having 95% sensitivity. It is also suggested that a single measurement with peripheral Doppler is ideal for identifying majority of the subjects with PVD. In our study, ABI measurement had 88.5% specificity but the sensitivity was only 70.6%. The low sensitivity indicates that ABI measurement would miss some of the patients with PVD.

Conclusion

ABI has a very high specificity but the sensitivity is low compared to colour Doppler ultrasound (CDU). Therefore, if ABI value is abnormal, the diagnosis of PVD is almost certain whereas if a diabetic has a normal ABI value in asymptomatic cases, PVD is unlikely to be clinically significant and probably no further testing is needed. However, in symptomatic cases of PVD with normal ABI, a CDU should be performed before PVD is definitely excluded.

An additional problem with ABI is that if there is vascular calcification, falsely high pressures would be obtained and if fully calcified, pressure recording is not possible. This is reported to occur common in diabetics and in such cases, only CDU should be used to diagnose PVD accurately.

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ORIGINAL ARTICLE

JIACM 2018; 19(1): 17-21

Dyslipidaemia as a Predictor of Diabetic Retinopathy: A Cross-Sectional Study

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Abstract

AIM and objectives: *To study the association of serum lipid profile with diabetic retinopathy (DR) and also to evaluate its association with diabetic retinopathy.*

Methods: *The study comprised a total of 140 patients with type 2 diabetes mellitus (70 with diabetic retinopathy and 70 without diabetic retinopathy) examined at the Department of Medicine and Ophthalmology LLRM Medical College, Meerut, Uttar Pradesh. Ophthalmoscopic and biomicroscopic examination of ocular fundus was done. Grading of the severity of retinopathy was done according to the ETDRS classification. Serum lipid profile and HbA1c estimation were done. Statistical analysis was performed with Statistical Packages for Social Sciences (SPSS) statistical software (version 20.0 for Windows).*

Results: *There was a significant association of serum total cholesterol and LDL levels with all grades of DR, i.e., mild NPDR, mod. NPDR, severe NPDR and PDR with p value = 0.003 and 0.001 for total serum cholesterol and LDL, respectively. Comparison between the various lipid sub-fractions was done using ANOVA test. Triglycerides and HDL did not show any significant correlation with DR (p = 0.216 and 0.233, respectively).*

Conclusion: *Hypercholesterolaemia and increased LDL levels appears to be a risk factor for diabetic retinopathy. Hence, on the basis of our study, we recommend controlling dyslipidaemia via lifestyle modification and/or medical therapy, to prevent the development, as well as to retard, the progression of diabetic retinopathy in type 2 diabetics.*

Key words: *Diabetic retinopathy, dyslipidaemia.*

Introduction

It is estimated that diabetes mellitus affects 4 per cent of the world's population, almost half of whom have some degree of diabetic retinopathy at any given time[1,2]. In India the prevalence of diabetic retinopathy in the general population is 3.5% and the prevalence of diabetic retinopathy in the population with diabetes mellitus is 18.0% in urban, and 10% in rural, population[3]. Diabetic retinopathy is a very common, potentially preventable, long-term, microvascular complication of diabetes mellitus and a leading cause of visual disability and blindness[4]. While there are multiple risk factors which have been associated with the development and progression of diabetic retinopathy, the duration of the disease and the age of the patient are said to be the strongest predictors; dyslipidaemia, microalbuminuria, BMI and smoking are some of the factors whose role as predictors of diabetic retinopathy are not well established[5,6].The current study is undertaken to determine the association of serum lipid profile with diabetic retinopathy and its severity.

Materials and methods

This study was carried out in the department of Medicine and Ophthalmology LLRM Medical College, Meerut, Uttar Pradesh.

A total of 140 patients of type 2 diabetes mellitus were included in the study. Out of these, 70 patients having diabetic retinopathy served as the study group while other 70 patients, without diabetic retinopathy, formed the control group.

Accordingly, the patients were allocated to one of the following two groups:

Group 1 (study group; n = 70): Diabetic patients, with different stages of retinopathy

Group 2 (control group; n = 70): Diabetic patients, without retinopathy.

Criteria for inclusion

– Patients of type 2 diabetes mellitus within the age

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group of 30 to 80 years

– Duration of diabetes more than 6 months

– Fitness to undergo a dilated fundus examination

Criteria for exclusion

1. Pregnancy
2. Accelerated hypertension
3. Active infection
4. Co-existing ocular disorders like uveitis, opaque or hazy media, retinal vein/artery occlusions, retinitis pigmentosa, vitreoretinal degenerations and dystrophy, high myopia
5. Patients on hypolipidaemic drugs
6. Pupillary abnormalities which prevent adequate dilatation for fundus visualisation
7. Retinal disorder like
8. Recent ocular surgeries (< 6 month)
9. Co-morbid conditions like diabetic nephropathy (grade 3 onwards), chronic liver disease or collagen vascular disease, etc.
10. Psychiatric illnesses and substance abuse

Sampling method and statistical tool:

Patients were selected by stratified random sampling after written informed consent. Ethical clearance was taken from the Ethical Committee of LLRM Medical College.

Data was analysed using SPSS (Statistical Presentation System Software) for Windows (version 20.0). All group data was presented as frequency distribution (proportion) and the average values were presented as means ± SD for the normal distribution data.

Following statistical methods were employed:

1. Descriptive statistics
2. Independent samples t-test
3. One-way ANOVA and post-hoc test
4. Chi-square test
5. Contingency co-efficient analysis

The minimal level of significance was set at $p < 0.05$.

Retinopathy grading was done in the following way:

A. No evidence of diabetic retinopathy

B. Diabetic retinopathy

- Non-proliferative diabetic retinopathy (NPDR)
  1. Mild NPDR
  2. Moderate NPDR
  3. Severe NPDR
- Proliferate diabetic retinopathy (PDR)

Serum lipid profile was done using fasting samples, to analyse total cholesterol, cholesterol components and triglycerides utilising the Dade Dimension Series using photometric enzymatic method. For the purpose of analysis, dyslipidaemia was defined as serum total cholesterol > 200 mg/dl, triglycerides > 150 mg/dl, LDL > 100 mg/dl and HDL < 40 mg/dl for men and < 50 mg/dl for women according to NCEP ATP III guidelines[7].

All the samples were collected after an overnight fast of 10 - 14 hours.

The patients were subjected to following lab. investigations.

1. Complete haemogram
2. Fasting blood sugar and post-prandial blood sugar profile
3. HbA1c
4. Serum lipid profile:
   Serum total cholesterol
   Serum triglycerides
   Serum high density lipoproteins (HDL)
   Serum low density lipoproteins (LDL)
   Serum very low density lipoproteins (VLDL)
5. LFT, KFT, urine analysis including microalbuminuria
6. ECG
7. Other investigations, as per requirement.

Observations and results

Patients were divided into 2 groups as already described, i.e.

Group 1: diabetics with diabetic retinopathy (n = 70)

Group 2: diabetics without retinopathy (n = 70)

Table I shows that mean age in group 1 and 2 was 54.44 ± 9.07 and 50.04 ± 9.74 years, respectively and the difference was significant statistically ($p < 0.001$). The mean diabetic age in group 1 and group 2 was 9.80 ± 5.82 and 5.23 ± 4.48 years, respectively, which was also significantly different from each other ($p < 0.001$). 20% of the patients in group 1 and 34.3% in group 2 had BMI ≥ 25 kg/m^2. Mean BMI value in group 1 and group 2 were 22.84 ± 2.99 kg/m^2 and 23.36 ± 3.82 kg/m^2, respectively which was not significantly different from each other ($p = 0.37$).

Table I: Age, diabetic age and BMI distribution.

Variable	Group 1 (Study group)	Group 2 (control group)	p-value
Age (Years)	54.44 ± 9.07	50.04 ± 9.74	< 0.001
Diabetic age (Years)	9.80 ± 5.82	5.23 ± 4.48	< 0.001
BMI (kg/m^2)	22.84 ± 2.99	23.36 ± 3.82	0.372

Table II shows that in the group 1, mild NPDR was present in 45.7% (n = 32) of patients, moderate NPDR in 25% (n = 18) of patients, severe NPDR in 17.1% (n = 12) of patients and PDR in 11.4% (n = 8) of patients.

Table II: Distribution of diabetic retinopathy in group 1 (study group)

Diabetic retinopathy grade	Frequency (n = 70)
Mild NPDR	32 (45.7%)
Moderate NPDR	18 (25.7%)
Severe NPDR	12 (17.1%)
PDR	8 (11.4%)
Total	70 (100%)

Table III shows that the mean value of total cholesterol was higher in group 1 (186.32 ± 43.92 mg/dl) as compared to group 2 (160.79 ± 30.7 mg/dl). Triglyceride levels also followed a similar trend, with group 1 having mean value of 153.83 ± 50.74 mg/dl and group 2 having 144.21 ± 57.17 mg/dl. HDL levels had very little difference in mean values, with group 1 having mean value of 41.36 ± 8.79 mg/dl and group 2 having 41.04 ± 8.40 mg/dl. Mean values of LDL levels were higher in group 1 (114.08 ± 36.01 mg/dl) as compared to group 2 (90.90 ± 24.90 mg/dl). However, statistically significant difference was found only for total cholesterol ($p < 0.001$), LDL ($p < 0.001$) and not for triglyceride and HDL. Apart from this, statistically significant difference ($p < 0.001$) in the mean value of 1 HbA1c between group 1 (10.40% ± 2.15%) and group 2 (8.96% ± 169%) was also found.

Table III: Mean values of lipid sub fraction and HbA1c in each group.

Variable	Group 1 (n = 70)	Group 2 (n = 70)	p-value
Total cholesterol (mg/dl)	186.32 ± 43.92	160.78 ± 30.77	< 0.001
Triglycerides (mg/dl)	153.83 ± 50.74	144.21 ± 57.17	0.294
HDL (mg/dl)	41.36 ± 8.79	41.04 ± 8.40	0.822
LDL (mg/dl)	114.08 ± 36.01	90.90 ± 24.90	< 0.001
HbA1c (%)	10.40 ± 2.15	8.96 ± 1.69	< 0.001

Table IV shows the mean values of various lipid sub-fractions and HbA1c in sub groups of group 1 (i.e., mild NPDR, moderate NPDR, severe NPDR and PDR) and group 2. Comparison of these mean values were done by ANOVA method which showed that total cholesterol ($p = 0.003$), LDL ($p = 0.001$) and HbA1c ($p = 0.001$) were significantly different between groups. However, triglycerides ($p = 0.216$) and HDL ($p = 0.233$) did not show any significant association between the groups.

Table IV: Mean values of lipid sub-fractions and HbA1c in subjects compared according to severity of diabetic retinopathy

Variable	Group 1				Group 2	P value
	Mild NPDR	Moderate NPDR	Severe NPDR	PDR		
T. cholesterol (mg/dl)	185.12 ± 49.09	182.32 ± 32.53	195.75 ± 49.40	185.87 ± 41.50	160.78 ± 30.77	0.003
Triglycerides (mg/dl)	144.78 ± 43.92	156.61 ± 38.07	149.41 ± 63.24	190.37 ± 71.29	144.21 ± 57.17	0.216
HDL (mg/dl)	41.85 ± 8.54	39.98 ± 8.37	45.38 ± 10.96	36.552 ± 4.40	41.04 ± 8.40	0.233
LDL (mg/dl)	114.31 ± 39.40	110.63 ± 29.07	120.48 ± 38.19	111.27 ± 38.10	90.90 ± 24.90	0.001
HbA1c (%)	10.62 ± 2.44	9.90 ± 2.0	10.43 ± 2.03	10.66 ± 1.37	8.96 ± 1.69	0.001

Discussion

In the present study we found that mean age in the study group was higher than that in the control group. This difference was significant statistically. Dandona *et al*[8] also have found significant correlation between the patient age and diabetic retinopathy.

There may be some bias in estimating the real duration of type 2 diabetes in these patients, as the diagnosis of diabetes could have been delayed due to lack of symptoms and the insidious onset of type 2 diabetes. The mean duration of diabetes in group 1 and group 2 was 9.80 ± 5.82 and 5.23 ± 4.48 years, respectively. The association of longer duration with a higher the risk of DR ($p < 0.001$) was in accordance with previously published reports (like DCCT[9]; Klein *et al*[10]; UKPDS[11]; Larsson *et al*[12]; Wong *et al*[13]; Varma *et al*[14]). It is obvious that patients with retinopathy significantly had a longer mean duration of diabetes. Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR[10]) also found that risk of retinopathy is directly related to the duration of diabetes. In India as well, various studies have

shown an increased prevalence of DR, as the duration of diabetes increases, (i.e., Gupta *et al*[15] APEDS study[16] Agarwal *et al*[17]). The CURES Eye study[18] had found that for every five year increase in duration of diabetes, the risk for DR increased by 1.89 times.

In the present study, most of the subjects in group 1 had poor glycaemic control suggested by raised HbA1c levels. The mean values of HbA1c were higher in group 1 (10.40 ± 2.15 years) than in group 2 (8.96 ± 1.69 years) with p value < 0.001, reinforcing the fact that the development and progression of DR is influenced by the level of hyperglycaemia. HbA1c was also significantly correlated with severity of diabetic retinopathy (p = 0.001). Intensive glycaemic control was effective in substantially reducing the incidence and progression of retinopathy in the Diabetes Control and Complication Trial (DCCT)[19]. The UKPDS (UK Prospective Diabetes Study)[19,11] also showed that intensive glucose control reduced the risk of a two-step change in retinopathy by 21% at 12 years follow-up.

The present study showed statistically significant correlation between diabetic retinopathy and raised total cholesterol level (p < 0.001). The mean values of total cholesterol in group 1 and group 2 were 186.32 ± 43.92 mg/dl and 160.78 ± 30.77 mg/dl, respectively. It was also found that increased cholesterol levels were significantly associated (p = 0.003) with the occurrence of all grades of retinopathy.

The mean triglyceride levels and HDL levels were also higher in group 1 as compared to group 2. However, this correlation was not statistically significant for triglyceride (p = 0.29) and for HDL (p = 0.82).

The mean values of LDL in group1 and group 2 were 114.08 ± 36.01 mg/dl and 90.90 ± 294.90 mg/dl, respectively, which showed significant correlation between DR and raised LDL (p < 0.001). It was also found that increased LDL level was significantly associated with the occurrence of all grades of retinopathy (p = 0.001).

Early Treatment Diabetic Retinopathy Study (ETDRS)[20] had shown that patients with elevated total serum cholesterol levels or serum low-density lipoprotein cholesterol levels at baseline are twice as likely to have diabetic retinopathy as patients with normal levels.

Rema *et al* (CURES eye study)[18] also studied the association of serum lipids with diabetic retinopathy in urban South Indians. The serum triglyceride (p = 0.001) levels and total cholesterol (P = 0.014) were higher in patients with diabetic retinopathy as compared to those without diabetic retinopathy. This association was maintained even after adjusting for age, as age by itself is a significant risk factor for hyperlipidaemia.

Different observations were made by Gupta *et al*[21] who demonstrated that diabetics with raised LDL levels showed higher prevalence of diabetic retinopathy (38%) as compared to diabetics with normal LDL levels (28.3%) (p = 0.05).

Elevated triglyceride levels were found to be a significant risk factor for moderate and severe non proliferative retinopathy and proliferative retinopathy even after adjustment for age, duration of diabetes, HbA1c, and albumin excretion rate in EURODIAB study[22]. In CURES eye study[18] serum cholesterol concentrations were higher in subjects with moderate NPDR compared with subjects without DR (P < 0.05) while triglyceride concentrations were higher in those with mild NPDR compared with those without DR (P < 0.05). In the present study, elevated triglyceride levels were neither associated with overall progression or development of DR nor associated with severity of DR.

Conclusions

Numerous studies have shown an association of lipid fractions with macrovascular complications of diabetes (e.g., coronary artery disease), but relatively few have looked at the association of serum lipids with microvascular complications such as diabetic retinopathy and the available results are conflicting.

On the basis of the present study, we conclude that there is a significant correlation between diabetic retinopathy and patient's lipid profile. Hypercholesterolaemia and high LDL levels are significantly associated with the development as well as the severity of diabetic retinopathy. Hence, on the basis of our study, we recommend controlling dyslipidaemia via lifestyle modification and/or medical therapy, to prevent the development as well as to retard the progression of diabetic retinopathy in type 2 diabetics.

Further studies are required to establish the causal relationship between dyslipidaemia and diabetic retinopathy. If established, these data can lend additional support to current treatment guidelines recommending aggressive lowering of elevated lipids among diabetic patients. Rigorous lipid control, in addition to its known health benefits in preventing cardiovascular disease, may also lessen ocular morbidity and associated health care costs, thereby potentially improving quality of life and vision among people with type 2 diabetes.

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ORIGINAL ARTICLE

JIACM 2018; 19(1): 22-26

Study of Diagnostic Efficacy of Bronchoalveolar Lavage and Bronchoscopic Brush Cytology in Clinico-radiologically Suspected Cases of Lung Malignancies

Prashant Prakash, Pooja Agarwal**, Arup Dasgupta***, Khushboo Gahoi*****

Abstract

***Background:** Fibre-optic bronchoscopy (FOB), along with its guided procedures such as endobronchial biopsy, bronchial brushings, bronchoalveolar lavage (BAL), transbronchial needle aspiration and transbronchial lung biopsy, is the most widely used technique for the diagnosis of lung cancer. This study was undertaken to study the diagnostic efficacy of BAL and bronchoscopic brush cytology in clinico-radiologically suspected cases of lung malignancies, and compare them with biopsy, wherever possible.*

***Methods:** FOB was performed on 130 clinico-radiologically suspected cases of lung malignancy, reporting to our tertiary care centre. The samples obtained were sent for histological and cytological examination.*

***Results:** Bronchoscopic brushing and BAL was done in all the 130 patients and biopsy was performed in 65 cases. Out of these 130 cases, 100 were diagnosed to have lung malignancies giving an overall sensitivity of 76.92% for FOB. Of these 100 cases, 55 patients were detected by BAL alone and bronchial brushing alone diagnosed 80 cases. The most common histological subtype detected was squamous cell carcinoma (57%) followed by adenocarcinoma (24%). Biopsy had a sensitivity of 93.8% as it diagnosed 61/65 cases.*

***Conclusion:** Fibre-optic bronchoscopy – along with its guided procedures – is easy, minimally invasive and is associated with few risks. We recommend that all clinico-radiologically suspected cases of lung cancers should be investigated by BAL, brushings, and endobronchial biopsy wherever possible, since using one or two of the procedures decreases the diagnostic yield of FOB.*

***Key words:** Bronchial biopsy, bronchial brushings, bronchoalveolar lavage, fibre-optic bronchoscopy.*

Introduction

Globally, lung cancer is the leading cause of cancer deaths. Its incidence is rising day-by-day due to increased incidence of smoking and air pollution. By the time patients present to the clinician, the disease has progressed to an advanced stage and curative resection can be offered only in 25 - 30% of cases. Presently, fibre-optic bronchoscopy(FOB) is the most widely used technique for the diagnosis of lung cancer.

A number of bronchoscopic guided procedures have been developed, which include endobronchial biopsy, bronchial brushing, bronchoalveolar lavage (BAL), transbronchial needle aspiration (TBNA) and transbronchial biopsy.

BAL is a simple, safe and rapid lavage procedure by which a sample of peripheral lung tissue, mainly alveoli, is recovered for cellular and biochemical analysis.

Bronchial brushing is a procedure in which cells are taken from the inside of the airway mucosa or bronchial lesions through catheter-based brushing, under direct visualisation or fluoroscopic guidance. Flexible brushes are passed through the bronchoscope, and the bronchial surface is gently abraded to obtain the specimen. Various types of bronchial brush may be used to collect both cellular and microbiological material, using direct vision when collecting from proximal areas of suspicion or fluoroscopic screening when sampling more peripheral sites. A bronchial brushing is used to detect malignancies and changes in cells that may lead to malignancy. It is also used to obtain specimens for microbiologic diagnosis. Both BAL and bronchial brushings have potential to provide information more or less similar to that obtained by lung biopsy. Moreover, these two procedures are simple, safe, economical and the evaluation of the cytologic material requires much less time than the conventional histopathologic techniques. Therefore, this study was undertaken to study the diagnostic efficacy of bronchoalveolar lavage and bronchoscopic brush cytology in clinico-radiologically suspected cases of lung malignancies, and to correlate their findings with biopsy, wherever possible.

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Methods

This study was conducted in the Department of Medicine, S.N. Medical College, Agra, from November 2013 to November 2016, in patients either reporting to hospital or admitted in wards, having clinico-radiological features suggestive of lung cancer. 130 patients with signs, symptoms and radiological features suggestive of lung malignancy were selected. Suggestive symptoms included cough, expectoration, haemoptysis, chest pain, breathlessness, hoarseness of voice, either singly or in combination, and not responding to treatment. Suggestive clinical signs included clubbing, lymphadenopathy, vocal cord palsy, Horner's syndrome, Superior Vena Cova syndrome, lung collapse and recurrent pleural effusion. Suggestive radiological features included findings such as collapse, mass lesion, raised diaphragm, thick walled cavity, rib erosions, unilateral hilar lymphadenopathy, mediastinal widening, parahilar shadow with sunray appearance, features suggestive of obstructive or non-resolving pneumonitis and radiological shadow not responding to antibiotics and anti tubercular therapy. All the selected patients were subjected to a detailed history and clinical examination especially in reference to respiratory system. Routine blood investigations such as CBC, BT, CT, sputum examination for AFB, chest X-rays and CT thorax (if required) were obtained.

FOB was performed in all the 130 cases after taking informed consent and proper preparations, before the procedure. During bronchoscopy, all vital parameters of patients were monitored.

Bronchial biopsy was obtained in 65 patients by fenestrated or toothed forceps from visible lesions (mass or bulging from walls). The tissue obtained was preserved in formalin, and sent for histopathological examination.

Bronchial brushings were taken in all the patients by sheath protected brush introduced through suction channel. Brush was rubbed against the lesion and the specimen obtained was spread over the glass slides and fixed immediately in absolute alcohol.

For collection of BAL, 100 - 120 ml of normal saline was injected in small aliquots and washings were collected in mucous trap via direct suction through FOB. The samples thus obtained were sent to department of pathology for cytological and histopathological examination.

Results

Of 130 cases, 111 (85.38%) patients were males. 88.46% of the patients belonged to the age group of 41 - 70 years, with a mean age of 58.4 years. Majority of the males were smokers (95.5%), and 68.75% had a smoking history of 21 - 40 years. A large bulk of the cases presented to us within 6 months of symptom onset (66.9%) with cough being the commonest symptom, seen in 83.85% patients, followed by breathlessness (69.23%), hemoptysis (26.15%) and chest pain (20.77%). Anorexia and fatigue were the most common constitutional symptoms observed in 61.54% and 58.46% cases, respectively.

The patients had non-specific peripheral signs on general physical examination, with pallor being present in 124 patients, followed by clubbing in 45 patients. On chest X-ray, the most common finding was a mass lesion seen in 30% cases, followed by hilar enlargement in 23.84% and collapse in 18.46%. Other findings included collapse consolidation, superior mediastinal widening, pleural effusion and a solitary pulmonary nodule. Only 3 patients had a normal chest X-ray.

On bronchoscopy, endobronchial growth was the most common finding seen in 50% cases, followed by mucosal irregularity (33.07%), bronchial compression (9.23%) and finally bronchial mucosa hyperemia (7.69%).

Out of these 130 cases, 100 were diagnosed to have lung malignancies giving an overall sensitivity of 76.92% for FOB. Of these 100 cases, 55 patients were detected by BAL (yield-55%). Bronchial brushing could diagnose 80/100 cases of lung malignancies giving a yield of 80%. Biopsy had a yield of 93.8% as it diagnosed 61/65 cases.

Out of the 100 proven cases, 12 cases proved to be malignant on biopsy alone, 16 cases proved to be malignant on brushing alone (BAL was negative and biopsy was not performed), 5 cases proved to be malignant on BAL alone (Brushing were negative and biopsy was not performed, all 5 cases were adenocarcinoma), 29 cases were positive by all three methods, 17 were positive on brushing and biopsy, 3 were positive on BAL and biopsy and 18 cases were positive by BAL and brushings (Table I).

Table I: Comparative analysis of yields of different bronchoscopicaly guided techniques in the diagnosis of lung malignancies (N = 100).

Technique	Number of cases	Percentage
Biopsy alone	12	12
Brush alone	16	16
BAL alone	5	5
BAL + brush + biopsy	29	29
Brush + biopsy	17	17
BAL + biopsy	3	3
BAL + brush	18	18
Total	100	100

In 35 cases, biopsy was not feasible. In the 65 cases where

biopsy was performed, biopsy aided in the diagnosis of 61 cases. In two cases, biopsy was inadequate and in other two cases it was negative for malignancy. Out of 61 cases proven to be positive by biopsy, 12 cases were diagnosed by biopsy alone, 29 cases by all three procedures, 17 cases by brush and biopsy and 3 cases by BAL and biopsy (Table II).

Table II: Comparative analysis of yields of different bronchoscopicaly guided techniques in cases where biopsy was performed (N = 65).

Technique	Number of cases	Percentage
Biopsy alone	12	18.64
BAL + brush + biopsy	29	44.62
Brush + biopsy	17	26.15
BAL + biopsy	3	4.62
BAL + brush	04	6.15
Total	65	100
Total positive by Brush	50	76.92
Total positive by BAL	36	55.38

Squamous cell carcinoma was the commonest cell type found in 57% cases followed by adenocarcinoma in 24% cases and small cell carcinoma in 16% cases. Bronchial carcinoid was seen in 2 cases whereas malignant melanoma was observed in 1 case (Table III). The concordance rate for cyto-histologic diagnosis regarding lung cancer type was 100 per cent in our study, despite these specimens being interpreted independently by different pathologists.

Table III: Incidence of different histopathological types of lung cancers in our study (N = 100).

Histopatholgical type	Number of cases	Percentage
Squamous cell Ca	57	57
Adeno Ca	24	24
Small cell Ca	16	16
Bronchial carcinoid	2	2
Malignant melanoma	1	1
Total	100	100

Discussion

Of the 130 cases studied, 111 patients were males, probably reflecting a greater prevalence of smoking amongst males. Most patients belonged to the age group of 41 - 70 years with a mean age of 58.4 years, probably reflecting a greater exposure to carcinogens in cigarette smoke. Mean age as reported by Gupta *et al*[1] and Singh *et al*[2] was 56.5 years and 57 years, respectively which is in close proximity to our study.

On chest X-ray, the most common finding was a mass lesion seen in 30% cases, followed by hilar enlargement in 23.84% and collapse in 18.46%. Other findings included collapse consolidation, superior mediastinal widening, pleural effusion and a solitary pulmonary nodule. Only 3 patients had a normal chest X-ray. Sharma *et al*[3] and Bhatt *et al*[4] also reported higher incidence of mass lesion, collapse and hilar enlargement in their studies.

On bronchoscopy, an endobronchial growth was the most common finding, which was seen in 50% cases, followed by mucosal irregularity (33.07%), bronchial compression (9.23%) and finally bronchial mucosa hyperemia (7.69%). Similar findings were reported by Rabahi *et al*[5] who found endobronchial mass in 64% cases and mucosal infiltrations in 35% cases.

Out of these 130 cases, 100 were diagnosed to have lung malignancies giving an overall sensitivity of 76.92% for FOB. Karahalli *et al*[6] and Dobler *et al*[7] have also reported high yield of FOB in the figures of 88.9% and 88% respectively. In our study yield of BAL was found to be 55% as it diagnosed malignancy in 55 patients. A similar sensitivity of BAL was reported by Tuladhar *et al* (66.7%)[8], Choudhury *et al* (47.6%)[9], Bodh *et al* (30.14%)[10] and Mlika *et al* (56%)[11]. The causes for varying sensitivity in previous studies could be the use of different techniques for the retrieval and processing of cytological specimens and inclusion of 'suspicious cases' as positive for calculation of sensitivity. The most common histological subtype detected by BAL was squamous cell carcinoma (50.9%), followed by adenocarcinoma (29.1%).

Bronchial brushing diagnosed 80/100 cases of lung malignancies, with the commonest histological diagnosis again being squamous cell carcinoma (55%) followed by adenocarcinoma (21.25%). The sensitivity of bronchial brushing as reported by Matsuda *et al*[12], Piya *et al*[13], Choudhury *et al*[9], Kotadia *et al*[14] and Bodh *et al*[10] were 90.3%,94.6%,80.9%,88.46% and 78.06%, respectively which are comparable to the results of our study. Biopsy had a yield of 93.8% as it diagnosed 61/65 cases. High diagnostic yields of bronchial biopsy have also been reported by Dasgupta *et al* (96%)[15], Piya *et al* (91.3%)[13] and Kotadia *et al* (96.83%)[14].

Out of the 100 diagnosed cases, squamous cell carcinoma was the commonest cell type seen in 57% cases, followed by adenocarcinoma in 24% cases and small cell carcinoma in 16% cases. Bronchial carcinoid was seen in 2 cases whereas malignant melanoma was observed in 1 case.This finding is in concordance with that of Matsuda *et al*[12] who

also found a high incidence of squamous and small cell carcinoma. Sharma *et al*[3] reported squamous cell carcinoma in 42% and small cell carcinoma in 32% cases. Piya *et al*[13] reported squamous cell carcinoma in 64.2%, adenocarcinoma in 18.8%, small cell carcinoma in 13.2% and bronchial carcinoid in 1.9%, whereas Bodh *et al*[10] reported squamous cell carcinoma in 38.7%, small cell carcinoma in 27.1%, adenocarcinoma in 23.87% and bronchial carcinoid in 0.65%. All of these studies reported squamous cell carcinoma to be the commonest type of lung cancer.

Moreover, the concordance rate for cytologic-histologic diagnosis regarding lung cancer type was 100 per cent in our study, despite these specimens being interpreted independently by different pathologists. Hence, we suggest that cytological examination of samples obtained from BAL and bronchial brushings is as reliable as histopathological examination on biopsy samples and hence they should be performed routinely in all cases.

Majority of the previous studies have shown that bronchial biopsy does not provide diagnostic yield in all cases of lung cancer. Chances of missing the diagnosis by bronchial biopsy are more in peripheral lung tumors. In the present study, additional cases on brushing as compared to bronchial biopsy were diagnosed as adenocarcinoma. On bronchoscopic examination, majority of these cases of adenocarcinoma presented with either extrinsic compression or mucosal irregularity of the bronchus, thus there may be a possibility of getting less representative material by bronchial biopsy in such tumours. Furthermore, in mucinous type of adenocarcinoma, bronchial biopsy specimen may contain pools of mucin and very few neoplastic cells with a relative lack of atypia that make the diagnosis of adenocarcinoma more difficult. Hence, in diagnosing adenocarcinoma, BAL and brushings, which are easier to perform and cost effective, play an important role. No collection method is absolutely superior to the others. The choice of bronchoscopic guided procedure is shaped by factors such as the personal preference of the physician, the status of the patient, the location of the lesions, and the differential diagnosis. We recommend that in clinico-radiologically suspected cases of lung cancers, bronchial brushings should be taken in addition to BAL even if no obvious growth is visible on FOB, especially from areas of mucosal irregularities. In our study, only 7 cases of adenocarcinoma could be diagnosed by biopsy whereas with combination of BAL and brushings, a total of 24 cases could be diagnosed further strengthening the aforementioned facts.

In the 65 cases where biopsy was performed, biopsy aided in the diagnosis of 61 cases, out of which 12 cases were diagnosed by biopsy alone, 29 cases by all three procedures, 17 cases by brush and biopsy and 3 cases by BAL and biopsy. 4 cases in which biopsy didn't detect malignancy, BAL and brushings were positive for malignant cells showing the importance of using cytology in addition to histopathological evaluation.

Excessive bleeding after bronchial biopsy was the only complication encountered in 3 cases which was very well controlled by bronchial infusion therapy with adrenaline and cold saline.

Conclusion

We conclude that all clinico-radiologically suspected cases of lung cancers should be investigated by BAL, brushings and endobronchial biopsy wherever possible. Also cytological examination has an added advantage of providing faster results as compared to biopsy. Fiber-optic bronchoscopy along with its guided procedures is easy and has low risk of complications when performed in expert hands. It provides direct visualisation of respiratory tract as well as lesion proper and variety of specimens can be collected. It is imperative that all three procedures be performed when possible since using one or two of the procedures decreases the diagnostic yield of FOB.

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ACKNOWLEDGEMENT

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ORIGINAL ARTICLE

JIACM 2018; 19(1): 27-32

Symptom Index for Detection of Ovarian Malignancy in Indian Women: A Hospital-based Study

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Abstract

Introduction: The current screening modalities (Transvaginal ultrasound and CA-125) for ovarian cancer have not been shown to reduce the morbidity or mortality of the disease. There is emerging evidence that women do experience symptoms of variable duration, even in early stage. An ovarian cancer 'Symptom Index' (SI) is proposed as a tool for early detection. Women reporting pelvic or abdominal pain, bloating, increasing abdominal size, difficulty eating or feeling full quickly, more than 12 times per month, within last one year were considered to have a positive SI.

Aims and objectives: 1. To evaluate and compare the sensitivity and specificity of SI, CA-125 and composite marker (i.e., patient has either a positive SI or positive CA-125) in detecting ovarian cancer. 2. To evaluate Odds ratio of each symptom variable in cancer detection.

Methods: This was a hospital based prospective case-control study. Participants included 90 healthy women at high risk for disease and 45 ovarian cancer patients. Patients with benign and borderline ovarian neoplasm were excluded. Sensitivity, specificity of SI, CA-125 and composite marker was calculated along with 95% confidence interval.

Results: Symptom index had 78% sensitivity and 88% specificity for predicting ovarian cancer. Abdominal pain was the most prevalent symptom, with a sensitivity of 84%. Most of the symptoms appeared within three months of diagnosis of cancer.

Conclusions: Symptom index is cost effective, causes minimal discomfort and can identify women for further investigations such as CA-125 and Trans-vaginal ultrasound, as the first level in a multistep screening programme for ovarian cancer detection, the in general population.

Key words: Symptom index, ovarian malignancy, CA-125, composite marker.

Introduction

Ovarian cancer is one of the most common cancers in women, and accounts for 4% of all cancers. Globally 2,55,000 new cases of ovarian cancer are diagnosed each year. In India, the age-adjusted incidence rates of ovarian cancer vary between 5.4 and 8.0 per 1,00,000 populations in different parts of country[1]. It has the highest mortality rate among gynaecological cancers, causing 1,40,000 deaths per year. The overall five year survival in ovarian cancer is about 35.2%. In early stage, the survival is 80 - 90% compared with 25% in late stages[2]. Earlier clinical diagnosis could shift patients into a more favourable prognostic group. Ovarian cancer is often referred to as a 'silent killer'. A major reason for the high fatality rate is the inability to identify women with early stage disease, due to lack of specific symptoms and inadequate screening tools. The presenting non-specific symptoms are often accepted by women as normal changes associated with ageing, menopause and previous pregnancies. Frequent symptoms recorded at presentation include pain and abdominal swelling, dyspepsia, vomiting, altered bowel habit and urinary symptoms of frequency or retention[3]. Although ovarian cancer meets the World Health Organisation criterion of a disease that would benefit from screening, the current screening modalities have not been shown to reduce the morbidity or mortality of the disease. Screening for ovarian cancer is challenging because it is not a common disease. High-risk women can be identified who would benefit from screening; however, only 10% of ovarian cancer, occur in these women[4]. The use of CA-125 as a first-line screen is a promising approach, but it has been reported that CA-125 is elevated above reference level in only 50% of clinically detectable early stage patients[5]. This lack of sensitivity for early disease, and the fact that CA-125 can be elevated in multiple benign diseases, e.g., fibroid, endometriosis, pelvic inflammatory disease, etc., limits the use of CA-125 for the early diagnosis of ovarian cancer[6]. Transvaginal sonography (TVS) is a very sensitive test, when used as a first line screen, but it is expensive, has low positive predictive value and produces false positive results that lead to high rate of surgeries-per-cancer[4]. TVS is generally taken as a second

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screening tool for women who have positive biomarker results. There is emerging evidence to suggest that women with ovarian cancer do experience symptoms of variable duration, even when disease is in the early stage. Goff *et al* (2007) hypothesised that an ovarian cancer 'Symptom Index' (SI) can be developed as a tool for early detection. Women reporting pelvic or abdominal pain, bloating, increasing abdominal size, difficulty eating or feeling full quickly, more than 12 times per month, within last one year were considered to have a positive SI. Symptom types, frequency, severity and duration were compared between cases and controls. In the confirmatory sample, SI had a sensitivity of 56.7% for early stage disease and 79.5% for advanced stage disease. Specificity ranged from 86 - 90%[7]. CA-125 has a sensitivity of 65% and specificity of 95% for early stage disease[8]. With use of composite marker (either positive SI or positive CA-125 or both) sensitivity for early disease rose to 81%, with specificity of 84%.

Material and methods

This was a hospital based prospective case-control study, conducted from December 2014 to April 2016. The aim of the study was to evaluate symptom index (SI) as a tool for detection of ovarian malignancy. The objectives of this study were to evaluate and compare the sensitivity and specificity of the symptom index (SI), CA-125 (value > 35 U/ml) and composite marker (i.e., patient has either a positive SI or positive CA-125) in detecting ovarian cancer.

$$\text{Sensitivity} : \frac{\text{True positive}}{\text{True positive} + \text{False negative}}$$

$$\text{Specificity} : \frac{\text{True negative}}{\text{True negative} + \text{False positive}}$$

Women were considered to have a positive SI if any of the six symptoms of abdominal pain, pelvic pain, difficulty in eating, feeling full quickly, abdominal bloating and increased abdominal size were present > 12 times per month, within last one year. In the present study, women with an adnexal mass were recruited from outpatient department and data was recorded as per predesigned symptom index proforma. Complete pre-operative evaluation was done. Women with histopathologically confirmed ovarian malignancy were taken as cases (n = 45) and first degree healthy relatives of ovarian cancer patients served as controls (n = 90). Patients with benign and borderline ovarian neoplasms were excluded from the study (Fig. 1). Statistical analysis was performed by using SPSS statistical software version 20. Sensitivity and specificity of SI, CA-125 and composite marker was calculated, along with 95% confidence interval. The symptoms were compared between patient groups using chi-square test/Fisher's exact test. Odds ratio (OR) of each symptom variable for ovarian cancer was calculated by logistic regression analysis. For all analyses, $p < 0.05$ was considered statistically significant.

Observations and results

Majority of patients diagnosed with ovarian cancer were young, less than 50 years, premenopausal (64%) and were of low parity, i.e., ≤ 2 (58%). Amongst the patients diagnosed with ovarian cancer, 33% belonged to early stage (1 and 2) and 67% to late stage. Adenocarcinoma was the most common histopathological type of tumour (82.2%), followed by germ cell tumour (15.2%).

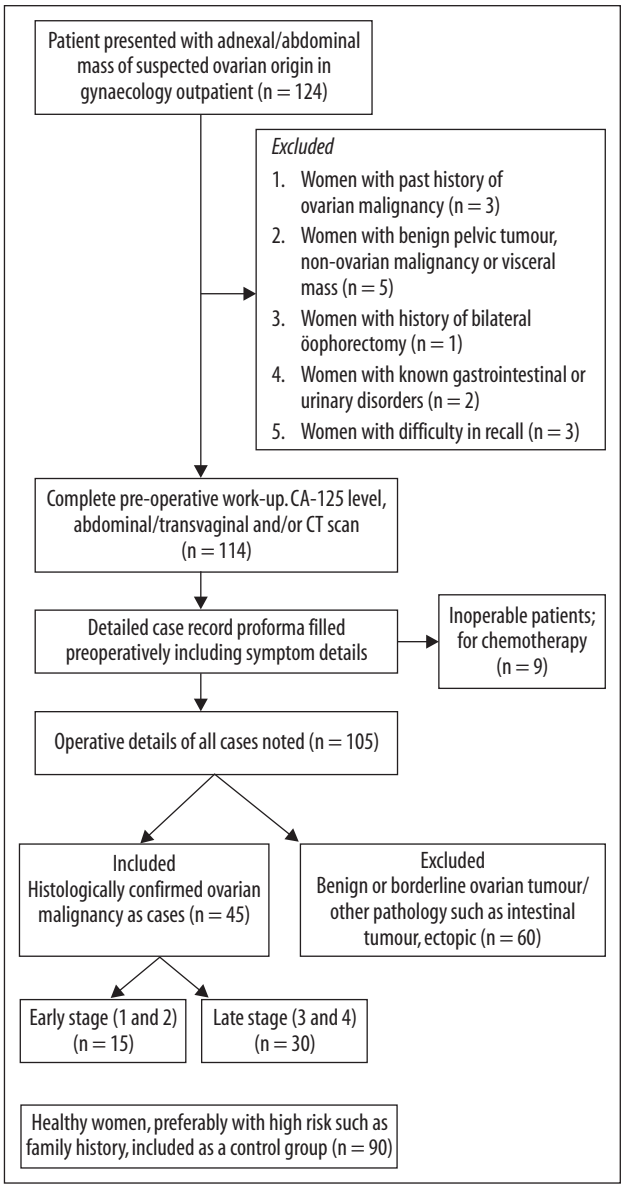

Fig. 1: *Consort flowchart.*

Symptom index had a sensitivity of 78% for predicting ovarian cancer. CA-125 was found to have a sensitivity of 93%, which was better than symptom index; however this difference was not statistically significant (p - value 0.065). Composite marker (either SI positive or CA-125 positive) seemed to be highly sensitive, i.e., 98% for predicting ovarian cancer, even significantly better than symptom index (p - value .004). Amongst the three parameters, symptom index was most specific for ovarian cancer (specificity 88%). CA-125 had a specificity of 79%, which was comparable with symptom index (p - value 0.169). The specificity of symptom index was much higher than composite marker (88% versus 69%), this difference being highly significant (Table I).

Table I: Comparison of sensitivity and specificity of symptom index, CA-125 and composite marker, between cases and controls.

Parameter	Sensitivity	P-value		Specificity	p-value	
		CA-125	CM		CA-125	CM
Symptom index	77.8%	0.065	0.004	87.8%	0.169	< 0.001
CA-125	93.3%	–	0.500	78.9%	–	0.004
Composite marker	97.8%	–	–	68.9%	–	–

Symptom index identified 67% of women with early stage tumour and 83% of those with late stage disease. Sensitivity of symptom index was increased from 67% to 93% when combined with CA-125 (composite marker) for early stage. The sensitivity of CA-125 for early disease was 80%. The late stage sensitivity of CA-125 and composite marker was 100% (Table II).

Table II: Comparison of sensitivity and specificity of symptom index, CA-125 and composite marker, by stage of ovarian cancer.

Parameter	Sensitivity early stage (1 and 2)	p-value		Sensitivity late stage (3 and 4)	p-value	
		CA-125	CM		CA-125	CM
Symptom index	66.7%	0.169	0.125	83.3%	0.063	0.063
CA-125	80%	–	0.500	100%	–	–
Composite marker	93.3%	–	–	100%	–	–

Sensitivity and specificity of individual symptoms was also calculated (Table III); abdominal pain was found to be the most sensitive symptom, with a sensitivity of 84%. Individual symptoms were compared between early and late stages using univariable analysis (Table IV).

Fig. 2 depicts the distribution of symptoms according to time-interval between onset and surgery. Pain abdomen was maximally present within 0 - 3 month interval (58%), which was the most common symptom in cancer patients (85%).

Table III: Sensitivity and specificity of individual symptoms for ovarian cancer.

Parameter	Sensitivity	Specificity
Abdominal pain	84.4%	87.8%
Pelvic pain	6.7%	84.4%
Difficulty in eating	20%	100%
Feeling full quickly	57.8%	96.7%
Abdominal bloating	33.3%	98.9%
Increased abdominal size	48.9%	97.8%

Table IV: Univariable logistic regression analysis of individual symptoms of ovarian cancer in early, late stage *versus* control.

Parameter	Early stage OR	p-value	Late stage OR	p-value
Abdominal pain	28.72	< 0.001	46.68	< 0.001
Pelvic pain	0.84	0.21	0.60	0.56
Difficulty in eating	1.07	0.14	1.36	< 0.001
Feeling full quickly	33.14	< 0.001	43.50	< 0.001
Abdominal bloating	44.50	< 0.001	44.50	< 0.001
Increased abdominal size	50.28	< 0.001	38.50	< 0.001

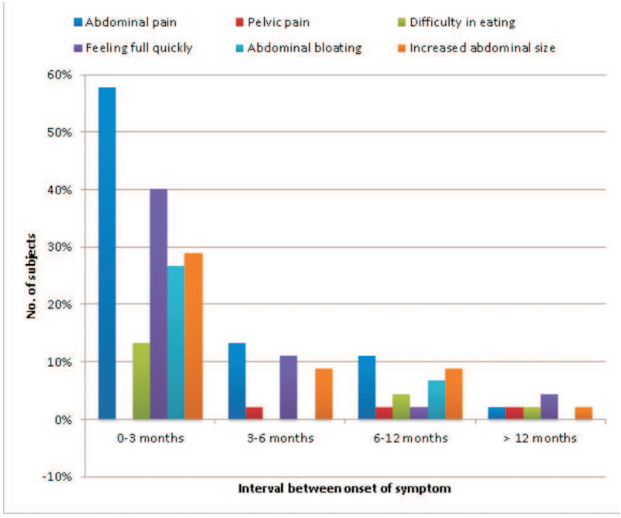

Fig. 2: *Distribution of symptoms, according to time interval between onset of symptom and surgery.*

Discussion

All women with ovarian cancer experience symptoms prior to diagnosis, sometimes even for months. Delayed

diagnosis of ovarian cancer may be attributed to the aggressive nature of tumour, non-specific nature of symptoms, patient's ignorance, social reasons, physician factors and diagnostic delay. Without an effective screening tool for ovarian cancer, early recognition and prompt work-up of symptoms may be critical in improving prognosis by detecting the disease at an earlier stage. This study provides a data source about the type of symptoms, their sensitivity for cancer detection and the time interval between onset of these symptoms till surgery. The current study provides a symptom index in Indian women, based entirely on symptoms that could be used to differentiate undiagnosed ovarian cancer from healthy population. We hypothesised that the symptom index can be used as a part of multistep screening with improved sensitivity and specificity for detection of ovarian malignancy. In our study, majority, i.e., 64% of cancer patients were young and premenopausal (29 out of 45). Goff *et al* in a sample of 2,262 women, found that 48% women were less than 50 years and pre-menopausal[9]. They proposed that ovarian malignancy tends to occur in older (> 50-year-old) women. However, in two different surveys, done in UK by Andersen, only 16 - 18% of cancer patients were less than 50-year-old and majority, i.e., 80 - 82% were more than 50 years[10,11]. Various studies suggest that there may be different pattern of age prevalence for ovarian cancer in Indian women, so screening for ovarian malignancy should be started at early age.

In our study, symptom index had a sensitivity of 78% for predicting ovarian cancer. The sensitivity was 67% for early stage (stage 1 and 2) and 83% for late stage (stage 3 and 4) ovarian cancer (Table I and II). Symptom index also had a high specificity (88%) in detecting disease free women. The greater specificity that we observed in our study reflects a lower occurrence of symptoms in healthy women. The sensitivity of symptom index, reported by Goff *et al* in their analysis was 66.7%, along with a high specificity of 90.0%[7]. Andersen *et al* found that symptom index had a sensitivity of 64% and specificity of 88.2%[10]. They found that the sensitivity for early stage ovarian cancer was 45.2%, and for late stage was 78.0%. A survey done by Rossing reported the sensitivity of symptom index was 67.5% and specificity of 94.9% for all invasive ovarian malignancy[12]. They found that the sensitivity of symptom index for early stage was 62.3% and for late stage, it was 70.7%. Kim *et al* did a case-control study in 116 women with epithelial ovarian cancer; the sensitivity and specificity of symptom index was 65.5% and 84.7% respectively[13]. Their early stage sensitivity was 44.8% and 72.9% for late stage epithelial ovarian cancer. In our study, CA-125 was found to have a sensitivity of 93%, which was better than symptom index (78%), but this difference was not statistically significant ($p = 0.065$). The sensitivity for early and late stage disease was 80% and 100%, respectively. CA-125 had a specificity of 79%, which was lower than SI (88%); again this difference was not statistically significant. Andersen *et al* found that CA-125 had overall 78.7% sensitivity and 95.3% specificity for ovarian cancer[10]. Their sensitivity of CA-125 for early and late stage was 64.5% and 90.2%, respectively. Although CA-125 is a good marker for ovarian cancer, but a large healthy population must be tested in order to detect a small number of cancer cases, which is not feasible and cost-effective. In our study, the accuracy of symptom index as a screening tool for ovarian cancer was found to be comparable to CA-125. In our study, composite marker (either SI positive or CA-125 positive) seemed to be highly sensitive, i.e., 98% for predicting ovarian cancer, even significantly better than symptom index (78%). For early stage its sensitivity was 93.3% and in late stage, it was 100% sensitive for ovarian cancer. However, composite marker had low specificity (69%) for detection of true negatives from healthy population (specificity of SI, 88%). Andersen *et al* found that composite marker had a sensitivity of 89% for ovarian cancer[10]. Their sensitivity for early stage and late stage cancer was 80.6% and 95.1% respectively. However, the specificity was 83% in their analysis. Kim *et al* did a case-control study in 116 women with epithelial ovarian cancer; composite marker had sensitivity of 85.3%, with the specificity of 59.5%[13]. The current analysis suggests that when used in combination with CA-125 as a first line screening tool, the symptom index identifies more women with ovarian cancer than CA-125 alone. However, this increase in sensitivity is achieved at significantly lower specificity, which is the limiting factor. We propose that SI is level one in multistep screening programme for ovarian cancer. Further, all women with positive SI (35 out of 45) were checked for the positivity of CA-125.

In our study, we evaluated the clinical significance of individual symptoms, in terms of sensitivity and specificity. Abdominal pain was the most prevalent symptom amongst the six parameters used in calculating symptom index, with a sensitivity of 84%. Feeling full quickly and increased abdominal size were the next most common symptoms present in ovarian cancer, having a sensitivity of 58% and 49%, respectively. Though all the symptoms had a high specificity in ruling out cancer, difficulty in eating was the most specific followed by abdominal bloating and increased abdominal size (specificity 100%, 99%, 98%, respectively) (Table III). Other rare symptoms with which our patients presented were dysuria, urinary retention and deep vein thrombosis, which were not included in symptom index. Pitta Dda compared the performance of cluster of symptoms in discriminating women with

malignant ovarian tumour from benign[14]. Cluster abdomen (increased abdominal size and abdominal bloating) was most sensitive symptom with sensitivity of 68.3%. The next most sensitive cluster was pain (abdominal pain and pelvic pain), with sensitivity of 55.0%. The most specific symptoms in their study were digestion cluster (indigestion, nausea, vomiting) and back pain, with specificity of 91.4% for both. The current study supports the evidence that women with ovarian cancer more often experience abdominal symptoms. None of the cancer patients had any genital tract symptoms such as abnormal uterine bleeding or vaginal discharge. Both physician and patient tend to underestimate the importance of these non-specific symptoms.

In our study, increased abdominal size was significant in detecting early stage cancer patients, with OR of 50 and p - value < .001. Abdominal bloating, feeling full quickly and abdominal pain also had high OR for early stage cancer (p value < .001) versus healthy population. For late stage cancer, abdominal pain was the most significant symptom variable (OR 46.6, p value < .001). All symptom variables were statistically significant with p value < .001, except pelvic pain (p - value 0.56). Pelvic pain did not have a strong association with malignancy, early or late stage (Table IV). Lurie *et al* studied symptom presentation, duration and analysed symptom frequency according to stage[15]. They compared symptoms of early stage with late stage disease and found that distended abdomen, abdominal pain and bowel symptoms were significant for late stage with OR of 1.6 - 1.7, p - value < 0.05. Rossing *et al* compared symptoms among women with early stage versus late stage invasive cancer[12]. They found that nausea was more commonly reported by women in early stage (OR 1.5); other type of symptoms more frequently presented in late stage.

In our study, out of 45 patients, 85% had abdominal pain, which was the leading symptom of symptom index. Majority of patients with abdominal pain got operated within 3 months, reflecting the importance of abdominal pain as the most important symptom in symptom index, which bothers the patient early. The second important symptom of symptom index was feeling full quickly, which was present in 68% of cancer patients. Out of these, 40% presented within 3 months for surgery, rest 28% probably ignored this symptom initially and got operated late. The least common symptoms in symptom index were difficulty in eating and pelvic pain (Fig. 2). In our study, out of 45 patients of ovarian cancer, symptom index was positive in 35 patients. Out of these, 63% underwent surgery within 3 months of onset of their first symptom. In the current analysis, if 37% patients were diagnosed with in 3 months of onset of their first symptom, this early diagnosis could improve their survival. This delay in reporting for surgery could be attributed to patient's ignorance of symptoms, social reasons and physician's factors, etc. It is plausible that earlier recognition and evaluation of these symptoms may affect disease outcome by decreasing the tumour burden at diagnosis, which has been shown to enhance patient survival.

Conclusion

This study provides clear evidence that ovarian cancer patients do have symptoms, which are non-specific and non-gynaecological in nature and often missed. The 'symptom index' based upon these symptoms, along with their frequency and duration, provides us a simple and useful tool for ovarian cancer detection. Awareness of symptoms in general population can alert women as well as the clinicians to investigate for the underlying catastrophe. Early recognition and evaluation of these symptoms may affect disease outcome by decreasing tumour burden at diagnosis and enhances patient survival. With a good sensitivity and high specificity, symptom index can be applied to general population, causes minimal discomfort, is cost-effective and can identify women for further investigations such as CA-125 and Trans-vaginal ultrasound, where prognosis can be improved with early treatment. Symptom index appears as a promising tool and may serve as the first level in multistep screening programme for ovarian cancer detection in general population.

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INVITATION FOR NOMINATIONS FOR ORATION AWARDS FOR 2018

Suggestions are invited from Fellows/Members for the following Orations for the year 2018 so as to reach Dr.T.P.Singh, Hon. General Secretary, Indian Association of Clinical Medicine, on the official Address given below by **30th June, 2018**:

1. **Prof. B. C. Bansal – Mrs. Uma Bansal Oration**
2. **Dr. G. S. Sainani – Dr. Mrs. Pushpa G. Sainani Oration**
3. **Dr. G. B. Jain Oration**
4. **Founder-President Prof. M. C. Gupta Oration**

- The suggestions are to be made for above Orations to be awarded during IACMCON-2018 (Patiala), Punjab. Nomination form is on page 76.
- The suggestions are to be made only by Fellows/Members of the Association, and must be accompanied with reasons for recommending the particular person showing the value of his/her research and accompanied with eight copies of three of his/her best publications. All the relevant papers in connection with suggestions such as Bio-data, list of publications, etc., should be submitted in **EIGHT SETS** by the proposer.
- The recipient of the above awards should deliver a lecture pertaining to his/her work at the Annual Conference of the Association in October, 2018.

Members of the Governing Body of the Association are not eligible to receive the Orations.

Eligibility Criteria:

1. The Nominee should have a minimum of 3 years standing in the Association as a Fellow (Kindly mention the Fellowship number and date of award).
   i. The member should have a standing of minimum three years in the Association.
   ii. The member should have participated in the annual conferences, scientific programmes, contributed to the *Journal,* and actively engaged in the organisation of the annual conference of the IACM.
   iii. For Founder-President Dr. M. C. Gupta Oration', the subject of Oration should be related to cardiology.

Dr. T. P. Singh, Hony. Gen. Secretary, Indian Association of Clinical Medicine,
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ORIGINAL ARTICLE

JIACM 2018; 19(1): 33-38

Antimicrobial Susceptibility of Gram-Positive Isolates from Neonatal Septicaemia in A Tertiary Care Hospital

Shyam Sunder Keshari, AK Kapoor**, Anudita Bhargava***, Dharmendra Kumar Singh*****

Abstract

Background: The purpose of this prospective study was to determine the antimicrobial susceptibility pattern of Gram-positive bacterial isolates from blood culture in clinically diagnosed neonatal septicaemia cases, and to suggest a viable empirical therapy.

Material and methods: Blood samples (1 - 2 ml) were collected with aseptic precautions from suspected neonates for culture and sensitivity.

Results: Out of a total of 146 cases, 86 (58.9%) specimens showed bacterial growth. Of these, Gram-positive microorganisms were isolated from 35 (40.7%) samples. The most frequent Gram-positive isolates were Staphylococcus aureus in 22 (25.6%) followed by coagulase negative Staphylococci (CONS) in 10 (11.6%). All 22 staphylococcal isolates were 100% sensitive to vancomycin, teicoplanin and linezolid, and were 100% resistant to ampicillin and 90.9% resistant to cotrimoxazole. Four isolates were methicillin resistant Staphylococcus aureus (MRSA), and two of these exhibited primary in-vitro resistance to quinupristin/dalfopristin (9.1 %). Minimum inhibitory concentration (MIC) of quinupristin/dalfopristin by E-test strips in resistant isolates were 25 and 30 mcg/ml respectively. All 10 isolates (11.6%) of coagulase-negative Staphylococcus (CONS) were 100% sensitive to linezolid, vancomycin, teicoplanin, and quinupristin/dalfopristin, and were 100% resistant to ampicillin. The streptococcal isolates were 3 (4.5%) and 100% sensitive to vancomycin, teicoplanin, linezolid, oxacillin, quinupristin/dalfopristin and were 100% resistant to ampicillin and co-trimoxazole.

Conclusion: Linezolid, teicoplanin or vancomycin should be preferred as an empirical therapy for Gran-positive neonatal septicaemia.

Key words: Neonatal sepsis, Gram-positive cocci, CONS, MRSA.

Introduction

Neonatal sepsis is the single most important cause of neonatal morbidity and mortality[1]. The term 'Neonatal Sepsis' incorporates septicaemia, pneumonia and meningitis of the newborn. Neonates are particularly vulnerable to infections because of immature immune systems. Moreover, several risk factors have been identified both in neonates and in mothers, which make them susceptible to infections. Blood stream infection is the commonest infection in this age group. A wide spectrum of organisms like *Klebsiella spp., Staphylococcus aureus, Pseudomonas* and *Salmonella spp.* have been reported as potential pathogens in neonatal septicemia[2]. *S. aureus* has become resistant to most of the recently developed therapeutic agents, hence antimicrobial chemotherapy for this species has always been empirical[3]. Further, methicillin resistant *Staphylococcus aureus* (MRSA) isolates are now becoming multidrug resistant and are susceptible only to glycopeptide antibiotics such as vancomycin[4].

Strikingly, information about antimicrobial susceptibility from most of the developing world, which could potentially benefit neonatal sepsis control programme, is severely deficient though surveillance studies in developed countries are being undertaken at regular intervals. The aim of the study was to determine the culture and sensitivity pattern and, based on these findings, to suggest an initial empirical therapy in cases of Gram-positive neonatal septicaemia.

Material and methods

A prospective study was carried out from January 2006 to December 2006 in 146 neonates of both sexes who were clinically of suffering from neonatal septicaemia and were admitted to the neonatal intensive care unit of Sarojini Naidu Children Hospital, affiliated to M.L.N. Medical College, Allahabad. Both early onset (78) and late onset (68) cases of neonatal septicaemia were included in the study. This research work was duly approved by the ethics committee of the M.L.N. Medical College, Allahabad.

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A written consent to screen and investigate the neonates was obtained from the parents. A neonate was considered well-vaccinated in accordance with his age. The neonate, at the time of admission, presented with one or more of the following clinical features: abnormal temperature, refusal to feed, sluggish movement, jaundice, respiratory distress, diarrhoea, vomiting and seizures. The other required clinical information was obtained from hospital records.

Blood sample (1 - 2 ml) was collected with proper aseptic precautions, inoculated into 5 ml of brain heart infusion broth with 0.025% sodium polyanethol sulfonate and transported to the microbiology department within 2 hours. The specimen was incubated overnight at 37° C. Next day first subculture was done on blood agar, chocolate agar and MacConkey agar. The blood agar and chocolate agar plates were incubated in CO_2 jar and MacConkey agar was incubated aerobically at 37° C overnight. If, no growth was observed in any of the culture media, it was reported as provisionally sterile after 48 hours. The broth was further incubated at 37° C and observed for development of any turbidity. Second subculture was done when turbidity was noticed, or on 7th day of incubation whichever was earlier. If no growth was seen, then specimen was finally reported as sterile. If growth appeared, it was identified to the species level and antimicrobial susceptibility was done.

Antimicrobial susceptibility testing was performed by using Kirby-Bauer Disc Diffusion method[5] following NCCLS guidelines[6]. This technique provides qualitative or quantitative information on the susceptibility of a given microorganism to a particular antimicrobial agent.

Results

The clinical features commonly observed at the time of admission, in suspected cases of neonatal sepsis, were abnormal temperature, sluggish movement, refusal to feed, jaundice, respiratory distress and seizures. It may be noted that one or more signs and symptoms may be observed in a single case of neonatal septicaemia. All these cases were subjected to blood culture examination. Isolates were identified and screened for antimicrobial susceptibility.

Out of a total of 146 blood cultures, 86 (58.9%) cases were culture positive, 53 (36.3%) were sterile and 7 (4.8%) were contaminated samples (3 or more isolates), hence these 60 cases were not pursued further for the purpose of the culture sensitivity study. Neonatal septicaemia was more common in males as compared to female, and M:Fratio was1.7:1.

Out of 86 culture positive isolates cases, *Gram-negative* isolates were found in 51 (59.3%) followed by *Gram-positive* in 35 (40.7%) (Table I). Amongst *Gram-positive* microorganisms, the most frequent bacterial isolates were *S. aureus* in 22 (25.6%) followed by coagulase negative *Staphylococci* (CONS) in 10 (11.6%). (Table I).

Most of the culture positive neonates 48 (55.8%) were more than 7 days old and 38 (44.2%) were of 0 - 7 days. The association between the age groups (0 to 7 days and 8 to 28 days) and culture test (positive/negative) was statistically significant (p - value = 0.0239 and 95% confidence interval ranged 0.48 - 0.88) (Table II). This suggests a higher incidence of late-onset neonatal septicaemia.

Table I: Distribution of isolates in cases of neonatal septicaemia.

Organism	Total No. (%)
S. aureus	22 (25.58%)
Klebsiella spp.	20 (23.25 %)
Escherichia coli	13 (15.12%)
CONS	10 (11.63%)
Acinetobacter spp.	8 (9.30%)
Pseudomonas spp.	6 (6.98%)
Citrobacter spp.	4 (4.65%)
Streptococcus spp.	3 (3.49%)
Total isolates	86 (100%)

Table II: Association between age of neonates and blood culture test.

Culture	Age 0 - 7 days	Age > 7 days	Total cases
Culture positive	38	48	86
Culture negative	36	17	53
Contaminated	04	03	07
Total	78	68	146

p value = 0.0239, 95% Confidence interval: 0.48-0.88

To simplify the interpretation of antibiotic sensitivity testing, both sensitive (S) and moderately sensitive (MS) microorganisms were clubbed together and characterised as sensitive, since moderately sensitive microorganisms when judiciously exposed to higher concentration of antimicrobial drugs became sensitive.

All staphylococcal isolates were sensitive to vancomycin, teicoplanin and linezolid, and were resistant to ampicillin (100%) and cotrimoxazole (90.91%) (Table III). There were four methicillin-resistant *S. aureus* (MRSA) isolates. Of these, two isolates exhibit primary *in-vitro* resistance to quinupristin/dalfopristin by E-test strips (HiComb-test). The MIC was 30 µg/ml and 25 µg/ml respectively. They were labeled as quinupristin/dalfopristin resistant MRSA.

Table III: Pattern of antimicrobial sensitivity in *Staphylococcus aureus* and Coagulase-Negative Staphylococcus (CONS) in septicaemic neonates.

S. N.	Antimicrobials	*Staphylococcus aureus* (n = 22)			CONS (n = 10)		
		S*	MS*	R*	S*	MS*	R*
1.	Ampicillin	0	0	22 (100%)	0	0	10 (100%)
2.	Amoxycillin- clavulanic acid	14 (63.6%)	5 (22.7%)	3 (13.6%)	6 (60.0%)	2 (20.0%)	2 (20.0%)
3.	Cefotaxime	15 (68.2%)	3(13.6%)	4 (18.2%)	7 (70.0%)	2 (20.0%)	1 (10.0%)
4.	Cephalexin	13 (59.1%)	4 (18.2%)	5 (22.7%)	5 (50.0%)	3 (30.0%)	2 (20.0%)
5.	Ciprofloxacin	15 (68.2%)	4 (18.2%)	3 (13.6%)	6 (60.0%)	2 (20.0%)	2 (20.0%)
6.	Clindamycin	17 (77.3%)	2 (9.1%)	3 (13.6%)	5 (50.0%)	4 (40.0%)	1 (10.0%)
7.	Co-trimoxazole	0	2 (9.1%)	20 (90.9%)	8 (80.0%)	0	2 (20.0%)
8.	Erythromycin	10 (45.5%)	5 (22.7%)	7 (31.8%)	4 (40.0%)	4 (40.0%)	2 (20.0%)
9.	Gentamicin	8 (36.4%)	2 (9.1%)	12 (54.6%)	4 (40.0%)	1 (10.0%)	5 (50.0%)
10.	Linezolid	22 (100.0%)	0	0	10 (100.0%)	0	0
11.	Oxacillin	18 (81.8%)	0	4 (18.2%)	7 (70.0%)	3 (30.0%)	0
12.	Quinupristin/ dalfopristin	20 (90.9%)	0	2 (9.1%)	10 (100.0%)	0	0
13.	Teicoplanin	22 (100%)	0	0	10 (100.0%)	0	0
14.	Tetracycline	15 (68.2%)	3 (13.6%)	4 (18.2%)	5 (50.0%)	1 (10.0%)	4 (40.0%)
15.	Vancomycin	22 (100.0%)	0	0	10 (100.0%)	0	0

S = Sensitive, MS* = Moderately sensitive, R* = Resistant.*

All strains of CONS were 100% sensitive to linezolid, quinupristin/dalfopristin, teicoplanin and vancomycin. These isolates were also highly sensitive to cefotaxime and clindamycin (90%), followed by amoxycillin-clavulanic acid combination, ciprofloxacin, co-trimoxazole, cephalexin, erythromycin (80%). All these strains were 100% resistant to ampicillin.

All three streptococcal isolates were highly sensitive to amoxicillin-clavulanic acid, linezolid, oxacillin, quinupristin/ dalfopristin, teicoplanin, cefotaxime and vancomycin (100%), followed by ciprofloxacin and gentamicin (66.66%) each. Resistance to ampicillin and co-trimoxazole was 100% and to erythromycin, 66.6%.

Discussion

A wide spectrum of microorganisms has been described as the cause of neonatal septicaemia, and this varies from place to place. Moreover, the organisms isolated are often resistant to multiple antimicrobials, which make the treatment difficult, sometimes leading to fatality. Neonates are particularly vulnerable to infections, so any delay in initiation of empirical therapy or wrong choice of antibiotic is bound to have adverse repercussions and should be avoided. Moreover, despite development of newer antimicrobial agents, rapid increase in bacterial resistance, even to newer antimicrobial agents, is quite alarming.

Common clinical features of sepsis among neonates at the time of admission were abnormal temperature, sluggish movement, refusal to feed, jaundice, respiratory distress and seizures. These observations were accordance to previous study[7]. Neonatal septicaemia was more common in male neonates; M: F ratio was 1.7:1.

Since developing countries also not have appropriate systems to conduct nationwide studies, institutional or city based studies are the only means, at the moment, to ascertain the current situation of antibiotic-resistance, in order to prescribe adequate therapy for this emergency condition. The present study provides information regarding *Gram-positive* organisms identified from blood culture of neonates, and their antimicrobial susceptibility in a tertiary care hospital.

In the present study, the culture positivity rate was 58.9% and was in accordance with a previous study by Jain *et al*[7] (56.6%) and Ako-Nai *et al*[8] (55%). Various comparable studies have demonstrated widely different culture positivity rates owing to multiple factors. Arora *et al*[9] reported a culture positivity rate of 46.8%, Roy *et al*[10] 47.5%, whereas Agnihotri *et al*[11] observed only 19.2%. A high rate of culture positivity in our study has been attributed to collection of blood specimen before initiation of

antimicrobial agents in septicemic neonates, bedside inoculation of specimen into enrichment broth, good laboratory protocol, and owing to a large number of unattended deliveries.

The age distribution of neonates ranged between 0 - 28 days. Maximum blood culture positive cases 48 (55.8%) were observed in neonates older than 7 days, whereas 38 cases (44.2%) were observed in 0 - 7 days old septicemic neonates, suggesting a preponderance of late-onset neonatal infections. Our findings were contradictory to those of Agnihotri *et al*[11] who reported maximum culture positivity (64.4%) in the first week of life.The high positivity rate in the present study may be due to less exposure to antibiotics at this stage. However, it definitely calls for close monitoring of newborns to find out other risk factors responsible, so that appropriate preventive measures can be undertaken.

Out of 86 culture positive cases, a majority 46 (53.5%) were due to Gram-negative bacteria (mostly of enterobacteriaceae family), followed by Gram-positive 35 (40.7%) and rest 5 (5.8%) cases showed mixed growth. Our findings were in agreement with those of Agnihotri *et al*[11] who reported incidence of Gram-negative (58.5%) and Gram-positive (41.5%). Our findings were in disagreement to other workers who reported a higher incidence of Gram-positive organisms[8,11].

Among Gram-positive microorganisms, *S. aureus* 22 (25.6%) was the commonest isolate, followed by CONS in 10 (11.6%) cases. These findings were in accordance with previous studies done by Ako-Nai *et al*[8] and Agnihotri *et al*[11]. Similarly, Ojukwu *et al*[12] also observed that, in neonatal septicaemia in high risk babies in South-Eastern Nigeria, the most common Gram-positive isolate was *S. aureus*.

However, our findings contradicted the findings of Gaynes *et al*[12] who in their study of nosocomial infections in high risk nurseries observed that infection in neonates with different birth categories ranged between 36% to 49% of all infections and commonest isolate was CONS (51%), followed by *S. aureus* (7.5%) and group B streptococcus (7.9%). Roy *et al*[10] reported that the incidence of CONS was 16.6% and *S. aureus* was 14%. The incidence of *S. aureus*, CONS, and *Streptococci* in our study was 25.6%, 11.6% and 3.5%, respectively. Findings of above studies, particularly in respect to *S. aureus,* showed wide variations in comparison to our observations. Multiple bacterial growth was found in 5 (5.8%) cases, which was in much variance with those of Roy *et al*[10] who observed multiple bacterial growth in four samples (0.54%).

An area-based knowledge of the bacteriological spectrum, in case of neonatal septicaemia, is essential firstly because initial antibiotic administration will not wait for the culture and antibiotic sensitivity results, and secondly due to high rate of morbidity and mortality associated with infections, a rational choice of an empirical therapy is most important. In the Western World, an antibiotic of choice is directed towards group B *Streptococcus* and *E. coli* but in tropical countries like India, the initial neonatal infection, may be caused by multi-drug resistant hospital acquired pathogens. The causative organisms are resistant species of *Enterobacteriaceae* family, *Pseudomonas spp.* and *Staphylococci*, etc. Group B *Streptococcus* is not common in India as is evident by National Neonatal-Perinatal Database Network (NNPD)[15] derived report.

Sensitivity pattern of *S. aureus* in septicemic neonates showed 100% sensitivity to linezolid, teicoplanin and vancomycin, and 100% resistance to ampicillin and 90.9% to co-trimoxazole. Roy *et al*[10] also observed that more than 95% staphylococcal isolates were resistant to ampicillin and none were resistant to vancomycin or teicoplanin. Similarly, Shobha *et al*[16] reported that all isolates of *S. aureus* were sensitive to Vancomycin. Vancomycin is the drug of choice for MRSA[17]. Linezolid is a FDA approved drug for the treatment of infections caused, both by methicillin susceptible and resistant strains of *S. aureus*[18]. No vancomycin-intermediate sensitive Staphylococcus aureus (VISA) has been found in the present study, though reported by others[19]. Shaw *et al*[20], in a study on neonatal sepsis, reported that the Gram-positive organisms displayed a high degree of resistance to most penicillins and cephalosporins but glycopeptides and monobactams were effective. Further, *Staphylococcus* was100% resistant to penicillins while 10 - 25% rate of resistance was also seen with most of the other penicillins and cephalosporins. They were, however, 100% sensitive to vancomycin and imipenem-cilastatin, thus supporting our observations. These studies reported that 25% of *Staphylococci* were resistant to gentamicin, which was contrary to our observations whereas 54.6% of *Staphylococci* were resistant.

Chugh *et al*[21] reported a predominance of Gram-positive isolates (64.71%) in septic meningitis and reveled that both *Streptococci* and *coagulase negative Staphylococci* were highly sensitive (100%) to linezolid, vancomycin and piperacillin-tazobactam. *Staphylococcus* aureus was 100% sensitive to linezolid and vancomycin but was only 87.5% sensitive to piperacillin-tazobactam combination. The *Streptococcus spp*. showed a high degree of resistance to tetracycline 91.67%, co-trimoxazole 88.89% and penicillin 63.89%. *Staphylococcus aureus* showed resistance to the tune of 83.33% each to tetracycline and cotrimoxazole, and 79.17% to penicillin. These findings partially supported our observations.

Quinupristin/dalfopristin combination was found to be

sensitive in 90.9% cases of *S. aureus* and in all cases of CONS. Although this combination is not available for treatment in India and is only available for experimental use (research tool), yet, resistance to quinupristin/dalfopristin was observed in two cases in the present study. These two isolates were MRSA, showing primary *in-vitro* resistance to quinupristin/dalfopristin. The MICs for quinupristin/dalfopristin resistant isolates were 30 µg/ml and 25 µg/ml, respectively[22]. Allignet *et al*[23] reported that Staphylococcal resistance to quinupristin/dalfopristin was always associated with resistance to compounds A, e.g., dalfopristin, but was not necessarily for compounds B, e.g., quinupristin.

CONS showed 100% sensitivity to linezolid, quinupristin/dalfopristin, teicoplanin and vancomycin, and 100% resistance to ampicillin. Our findings were in conformity with Roy *et al*[10] in respect to sensitivity of CONS to vancomycin and teicoplanin but in variance to ampicillin resistance (89%). Shaw *et al*[20] observed that 4 cases (3.05%) of coagulase negative Staphylococcus (CONS) were resistant to all antibiotics, except vancomycin.

All three Streptococcal isolates were 100% sensitive to linezolid, quinupristin/dalfopristin, teicoplanin, vancomycin and oxacillin. Chang *et al*[24] reported that quinupristin/dalfopristin was found active against β and α haemolytic strains of Streptococci, thus supporting our findings.

The limitations of the present study were:

1. The results of *in-vitro* culture sensitivity are not always in concurrence with *in-vivo* observations.
2. Proper culture media and sensitivity facilities are required.
3. Prompt and aseptic techniques are required for the collection of the samples.
4. The present study could not give a clear cut idea about the contribution of nosocomial infections as some of the cases were referred from village hospitals and ill-equipped nursing homes.

In conclusion, the practical implications of the present study for a hospital antibiotic policy are:

- An ongoing review of the causative organisms and their antibiotic sensitivity patterns should be made essential to formulate an empirical antimicrobial therapy relevant to a particular region.
- Irrational and irrelevant use of antimicrobial agents are mostly responsible for the high degree of resistance to antimicrobial agents. This is true even with newer generation of anti-microbial agents.This aspect should be kept in mind.

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ORIGINAL ARTICLE

JIACM 2018; 19(1): 39-41

Rheumatic Heart Disease – A Neglected Giant

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Abstract

Objective: To study the outcome of rheumatic heart disease (RHD) patients admitted to a tertiary care institute.

Patients and methods: This a retrospective study done in Sri Jayadeva Institute of Cardiovascular Sciences and Research, for 515 patients who were admitted with a diagnosis of RHD in our hospital.

Results: Out of the total 515 patients, 294 (57%) were female. Predominant valvular involvement was mitral, followed by aortic and tricuspid valve. Out of 515 patients, 237 were admitted for Percutaneous transluminal mitral commisurotomy (PTMC) and 212 patients were admitted to ICU with various complications viz. congestive heart failure (CHF) in 166 patients infection in 27, anaemia in 10, cerebro-vascular accident (CVA) and peripheral embolism in-8 , acute coronary syndrome in 4, pericardial effusion in 3, prosthetic valve thrombosis in 3 and complete heart block in 1. Out of these 212 patients admitted to ICU, 37 patients (17.45 %) died.

Conclusion: RHD is still a major health problem in developing countries like India and one of the most common causes of mortality, higher than the mortality associated with acute coronary syndrome.

Key words: Rheumatic heart disease,complications, PTMC, death.

Introduction

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) were widely prevalent throughout the world at the beginning of the second half of the twentieth century. However, thanks to industrialisation, during the ensuing decades the disease disappeared in the west but the major impact has now been porne by developing countries like India,which constitute a majority of the world's population. As with so many other health problems, these are countries which can least afford the economic and social costs of ARF and RHD. Particularly frustrating has been the fact that ARF and RHD are, theoretically, preventable if therapy is directed towards eliminating the initial group A streptococcal pharyngitis (GABHS) infection and further repeated infections are prevented or are effectively treated. But this important goal of prevention is neglected by parents, doctors and policy makers. As a result, the poor children suffer because of grave negligence and adults bear the sequelae of rheumatic fever and complications of rheumatic heart disease, including death.

Background

RHD is a condition in which permanent damage to heart valves is caused by ARF.It is estimated that 15.6 million people are affected worldwide by ARF and 3 lakhs, out of 5 lakhs individuals that acquire ARF every year, go on to develop chronic RHD[1]. ARF follows 0.3 to 3% of cases of GABHS pharyngitis. As many as 39% of persons with ARF may develop varying degrees of pancarditis associated with valve insufficiency,congestive heart failure (CHF) and even death. Chronic manifestations due to residual and progressive valve deformity occur in 9 - 39% of adults with previous RHD. Fusion of the valve apparatus resulting in stenosis or combination of stenosis and insufficiency develops 2 - 10 years after an episode of ARF, and recurrent episodes may cause progressive damage to the valves. 3 million patients have chronic heart failure requiring repeated hospitalisation[1,2]. RHD remains a major public health problem in many parts of the world[3,4].Globally,India contributes nearly 25% - 50% of newly diagnosed cases, deaths and hospitalisations due to RHD. As per WHO estimates, nearly 1,33,000 deaths, annually. were attributable to RF/RHD in the Southeast Asia region which includes India, compared with the 10,000 and 30,000 deaths in America and Europe, respectively[3]. Considering a median incidence of 0.5/1,000, approximately 1,31,000 children suffer from ARF every year in India[5]. At least one-third of them develop chronic RHD, i.e., nearly 44,000 patients are added every year. Considering the lowest and the highest reported prevalence of RHD in the population/school children, the number of RHD cases in India could range from 0.44 to 3.37 million[6]. People affected often look and feel healthy again once their outward

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symptoms are resolved, but with further streptococcal infections the ARF returns, worsening their heart damage. Often RHD is only detected when it is so advanced that only expensive and complicated heart surgery can save the person's life. And their life is often cut short by complications associated with RHD, while awaiting surgery or not being able to afford surgery. This article is an attempt to highlight the impact of RHD on Indian society.

Patients and methods

Retrospectively, the records of RHD patients admitted in our hospital (Sri Jayadeva Institute of Cardiovascular Sciences and Research) were assessed. More than 500 patients were included in the study and their records were analysed. Baseline data along with pattern of involvement of valves, main reason for admissions, any procedure done and outcomes were assessed.

Results

Totally 515, RHD patients were admitted in 3 months. 294 (57 %) were females and 221 (43 %) were male. Patients' age group was 8 to 80 years and mean age was 36.94 years. Pattern of valvular involvement is shown in Fig. 1 and Table I.

Total of 303 (58.83%) admitted to wards, out of which 297 (57.7%) patients were admitted for routine Percutaneous transluminal mitral commisurotomy (PTMC) or valve surgeries. Out of 237 patients admitted for PTMC, 60 patients were admitted for valve surgeries and 5 patients for coronary angiography. Out of 515 patients, 212 (41.16%) patients were admitted to intensive care unit for various reason. Out of 237 patients admitted for PTMC all underwent successful PTMC and only 2 patients required emergency mitral valve replacement due to chordal tear and severe MR. Another 5 patients admitted in ICU with pulmonary oedema underwent emergency PTMC,out of which 2 patients died despite the procedure.

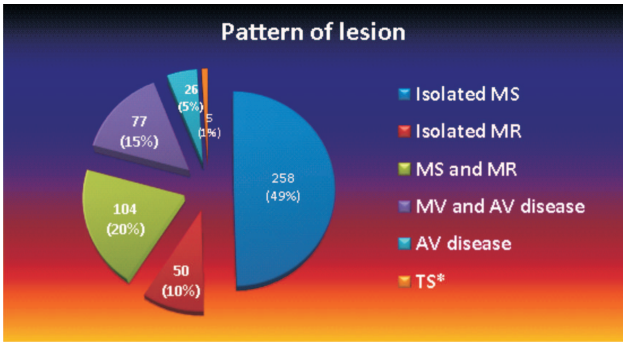

Fig. 1: *More than 2/3 patients had tricuspid regurgitation (TR) and it was difficult to distinguish functional from organic TR.*

Out of 212 patients admitted to ICU, majority (166 patients, 78%) had congestive heart failure (CHF), 27 patients had infection, 10 had anaemia, 8 patients had cerebro vascular accident (CVA) and peripheral embolism, 4 patients had acute coronary syndrome, 3 patients had pericardial effusion, 3 patients had prosthetic valve thrombosis and 1 patient had complete heart block.

Out of these 212 patients admitted to ICU, 37 patients (17.45%) died. Out of these 37 patients who died, 13 patients (35.13%) had undergone some intervention in the past. 6 patients underwent PTMC, 2 patient underwent CMV - Closed mitral valvotomy, 4 patients MVR - Mitral valve replacement and 1 patient DVR - Double valve replacement. Atrial fibrillation was seen in 24 patients (64.86%). The various causes of death are shown in Table II.

Table I: Incidence of various valve lesions in hospital admissions.

Pattern of lesion					
Isolated MS	Isolated MR	Both MS and MR	Both mitral and aortic valve disease	Isolated aortic valve disease (AS and AR)	Tricuspid stenosis/ regur-gitation
258 (50%)	50 (9.7%)	104 (20.19%)	77 (14.9%)	26 (5%)	65 (1%)

Table II: Various causes of death among RHD patients.

Cause of death	Total deaths - 37 cases
CHF	13 (35.13%)
Inefction/sepsis	10 (37%)
Others	13 (35.13%)
CVA	2
CVA + peripheral embolism	3
Peripheral embolism	3
Prosthetic valve thrombus	3
Acute coronary syndrome	1
Infective endocarditis	1

Discussion

RHD is still a major problem in developing countries like India. This study included 515 patients; 57% of them were female. This fact of female predominance is similar to what was mentioned in some studies from South Asia, the Middle East and North Africa[7,8]. Out of total 515 patients, 237 were admitted for routine PTMC and neary all patients underwent successful PTMC except 2 who required emergency MVR, which reflects the experience of the operator working in a high volume tertiary care hospital.

Patient's age group was 8 to 80 years and mean age was 36.94 years. This is more varied and older age group as compared to other studies[9]. The common presenting symptoms were those of RHD complications like congestive heart failure and atrial fibrillation. This is similar to reports from Sudan[9] and Nigeria[10].

Out of these 212 patients admitted to ICU, 37 patients (17.45%) died. Major cause of death was congestive heart failure and infection, infective endocarditis being seen in only one patient. These are different from previous published data[11] which can be explained by older age group of patients and multiple comorbities. Expected mortality in RHD patients, based on previous study is from 1.5%[12-15] to 3.3% per year[16]. Mortality associated with RHD patients admitted to ICU in our study was more than the mortality associated with acute coronary syndrome patients admitted to Kottayam medical college, a large teaching centre in Kerala (17.45/8.04%)[17]. Comparison of causes of mortality from a previous study by EF Bland *etal*[11] is shown in Table III.

Table III: Comparison of causes of mortality from previous studies.

Comparative table	Present study	Study by EF Bland and TD Jones *etal*[11]
Total deaths	37	301
CHF	13 (35.13%)	80% (CHF/RF)
Infection/sepsis	10 (37%)	
Others	13 (35.13%)	60 (20%)
CVA	2	3
CVA + peripheral embolism	3	
Peripheral embolism	3	
Prosthetic valve thrombosis	1	
Acute coronary syndrome	1	
Infective endocarditis	1	30

The prospective stroke registry data from Iran supports that a substantial proportion of strokes in developing countries are due to rheumatic heart disease[18]. In our study, stroke was responsible for death in 5 cases (13.51%).

This data is just the tip of the iceberg as it shows, mortality in patients admitted to a tertiary care hospital. Mortality in small centres expected to be more and some patients may not have access to proper health care system.

Summary and conclusion

RHD is still a major burden in developing countries. This study highlights the mortality contributed by this giant killer. Mortality caused by RHD is more than acute myocardial infarction.

Limitations

It is a retrospective study and there may be bias, as the more sick patients were referred to an tertiary care hospital. Also, because of increased prevalence of RHD, it may be just an innocent bystander.

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ORIGINAL ARTICLE

JIACM 2018; 19(1): 47-51

The Role of Semi-rigid Thoracoscopy in the Diagnosis of Undiagnosed Pleural Effusions in a Tertiary Care Centre in North India

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Abstract

Background: Undiagnosed pleural effusions remain a diagnostic challenge for pulmonologists, even though changes in pleural space are radiologically obvious. Semi-rigid thoracoscopy has the advantage of easy manoeuverability, although the biopsy samples are smaller as compared to those with rigid thoracoscopy. Here our aim was to study the role of semi-rigid thoracoscopy in the diagnosis of undiagnosed pleural effusions in a tertiary care centre in North India.

Methods: A total of 125 patients of undiagnosed pleural effusions were enrolled for the study out of which 104 patients underwent semi-rigid thoracoscopy and biopsy was taken and sent for histopathology.

Results: Out of 104 patients, 75 (72.11%) were male and 29 (27.89 %) were female. Most common thoracoscopic finding was nodules found in 36 patients (34.61%) followed by adhesions in 30 patients (28.84%). On pleural biopsy, the most common diagnosis was malignancy which was found in 43 patients (41.35%) followed by tuberculosis in 32 patients (30.77%). Adenocarcinoma was most common malignancy seen in 27 patients (25.96%). The diagnostic yield of semi-rigid thoracoscopy was 90.39%. There were no serious complications or death during the procedure.

Conclusion: Semi-rigid thoracoscopy is a safe, simple, and accurate tool for diagnosis of undiagnosed pleural effusions with minimal complication rates.

Keywords: Semi-rigid thoracoscopy, undiagnosed pleural effusion.

Introduction

Undiagnosed pleural effusions are those effusions where the diagnosis remain inconclusive even after initial thoracentesis[1]. Approximately 25% of pleural abnormalities remain unexplained after repeated thoracentesis and/or closed pleural biopsies. In the early 90s, the semi-rigid thoracoscope was successfully introduced for the management of patients with pleural effusions of unknown origin. The autoclavable semi-rigid thoracoscope has immense potential in the diagnosis and management of pleural disease. Semi-rigid pleuroscope, which has the combined property of flexibility of the fibreoptic bronchoscope and the rigidity of conventional thoracoscope, overcame the problem of limited view by easy manoeuverability of its nimble tip around the adhesions.

Literature on its utility, from developing countries, is limited, so this study was undertaken to study the role of semi-rigid thoracoscopy in the diagnosis of undiagnosed pleural effusions.

Materials and methods

The study was done from January 2016 to November 2017 on patients with pleural effusion, who were undiagnosed even after one thoracentesis, coming to indoor and outdoors of PG Department of Medicine, S.N. Medical College, Agra. Informed and written consent for the procedure was obtained from all the patients. A detailed medical history, drug history, and physical examination was done. Imaging, such as chest X-ray (postero-anterior, lateral, and decubitus views), ultrasonography, and computed tomography scan was done where indicated. The patients health and respiratory status were assessed by complete blood count, coagulation studies, electrocardiogram, arterial blood-gas analysis, percutaneous oximetry, and pulmonary function tests.

The instrument that was employed in our study was a prototype semi-rigid thoracoscope (model LTF 160Y-1; Olympus, Japan). The patients with contraindications for thoracoscopy (those with a pleural space insufficient for visualisation and mobilisation of the instrument),

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hypercapnia, or severe respiratory distress, uncontrollable cough, coagulation disorder, patients having co-morbid conditions, patients with pleural masses and pneumothorax without the presence of pleural effusion, pregnant and lactating mothers, patients with age < 12 years were excluded from the study.

Patients were kept fasting for 6 - 8 hours prior to the procedure. Vascular access was achieved with intravenous cannula inserted in the upper limb opposite to the side of thoracoscopy. In patients with small pleural effusion, an artificial pneumothorax was created by injecting approximately one litre of air into pleural cavity just prior to the procedure. This allowed lung to collapse and hence reduced the chances of lung being injured by the introduction of trocar. Patients were positioned in lateral decubitus with the affected side upwards. Arm on the side of thoracoscopy was positioned above the patient's head. This allowed better access and widening of the intercostal spaces. Thoracoscopy was conducted under conscious sedation. A single site entry was selected on the mid-axillary line between 4th and 7th intercostal spaces of the chest wall. After infiltration with lignocaine, chest wall was incised and trocar was inserted into the pleural cavity. Pleural fluid was removed via suction. Thoracoscope was then introduced via the trocar. The pleural cavity was visualised thoroughly. Pleural biopsy was obtained from suspicious areas over the costal and diaphragmatic pleura. At the end of the procedure, a chest tube was introduced and connected to underwater seal drainage. This was removed after complete expansion of lung which was confirmed by repeated chest radiographs.

Results

A total of 125 patients with undiagnosed pleural effusion were admitted for semi-rigid thoracoscopy. 21 patients were excluded from our study because they fell in one of our exclusion criteria. Rest of the 104 patients underwent semi-rigid thoracoscopic guided pleural biopsy, and subsequent histopathological examination of the tissue sample was done.

The age of the patients ranged from 14 - 82 years with mean age of 45.87 years. 75 (72.11%) were males and 29 (27.89%) were females. Male: Female ratio was 2.6: 1. Most common symptom was breathlessness seen in 95 patients (91.35%), followed by chest pain in 82 patients (77.89%), fever in 79 patients (75.96%), loss of appetite in 76 patients (72.11%), weight loss in 65 patients (62.5%). 46 patients (44.23%) were smokers and 58 (55.77%) were non-smokers. On chest X-ray, maximum number of patients (55.77%) showed large pleural effusion followed by moderate effusion in 29 patients (27.89%), small in 13 patients (12.5%), and 4 patients (3.85%) had loculated pleural effusion (Table I). Right side was involved in majority of patients, i.e., 56 patients (53.85%). 92 patients (88.47%) had exudative pleural effusion, while 12 patients (11.54%) had transudative pleural effusion.

Table I: Demographic and clinical features of patients undergoing semi rigid thoracoscopy for undiagnosed pleural effusion.

Demographic Characteristic	Result
Total patients	104
Mean age (years)	45.87
Male: Female	2.6:1
Sex	
Male	75 (72.11%)
Female	29 (27.89%)
Smoking status	
Smokers	46 (44.23%)
Non-smokers	58 (55.77%)
Presenting symptoms	
Dyspnoea	95 (91.35%)
Chest pain	82 (77.89%)
Fever	79 (75.96%)
Loss of appetite	76 (72.11%)
Weight loss	65 (62.5%)
Extent of effusion on chest X-ray	
Small (upto 1/3 of hemithorax)	13 (12.5%)
Moderate (upto2/3 hemithorax)	29 (27.89%)
Large (> 2/3 of hemithorax)	58 (55.77%)
Loculated	4 (3.85%)

On thoracoscopic examination, the most common finding was of nodules which were found in 36 patients (34.61%) followed by adhesions in 30 patients (28.84%), plaques in 15 patients (14.42%) and erythema in 12 patients (11.54%). Mixed findings were in seen in 6 patients (5.77%). No obvious lesion was found in 5 patients (4.81%) (Table II).

Histopathologically, overall the most common diagnosis was malignancy which was found in 43 patients (41.35%). Adenocarcinoma was seen in 27 patients (25.96%), squamous cell carcinoma in 5 patients (4.81%), malignant mesothelioma in 4 patients (3.85%), poorly differentiated carcinoma in 2 patients (1.92%) and lymphocytic lymphoma in 2 patients (1.92%). One (0.97%) patient each of papillary mesothelioma, anaplastic carcinoma, and small cell carcinoma was also encountered. Tuberculosis was the most common non-malignant finding on pleural biopsy

found in 32 patients (30.77%) followed by non-specific inflammation in 16 patients (15.39%). One patient (0.97%) had acute inflammatory exudate (Table III). In 4 patients, a diagnosis could not be made as biopsy was not feasible due to the presence of dense adhesions; in 5 patients no obvious lesion was detected during thoracoscopy, while in 1 patient biopsy was inconclusive.

Table II: Thoracoscopic findings on gross examination of pleura.

Thoracoscopic findings	Total no. of cases (N = 104)	
	Number	Percentage (%)
Nodules	36	34.61
Adhesions	30	28.84
Plaques	15	14.42
Erythema	12	11.54
Mixed	6	5.77
No obvious lesion	5	4.81

Table III: Diagnosis based on histopathological examination of semi-rigid thoracoscope guided pleural biopsy specimen.

Type	Total no of cases (N = 94)	
	Number of patients	Percentage (%)
Tuberculous	32	30.77
Adenocarcinoma	27	25.96
Non-specific inflammation	16	15.39
Squamous cell carcinoma	5	4.81
Malignant mesothelioma	4	3.85
Poorly differentiated carcinoma	2	1.92
Lymphocytic lymphoma	2	1.92
Papillary mesothelioma	1	0.97
Anaplastic carcinoma	1	0.97
Small cell carcinoma	1	0.97
Acute inflammatory exudate	1	0.97

Thus, thoracoscopy led to a diagnosis in 94 out of 104 patients, giving a yield of 90.39%.

No serious complication or death occurred during the procedure. The procedure was well tolerated. Total 10 patients (9.80%) developed minor complications. Post-operative fever was encountered in 5 patients (4.81%), 3 patients (2.89%) developed subcutaneous emphysema which resolved spontaneously within 8 days. 2 patients (1.92%) experienced pain at the site of tube insertion which was shortly controlled by analgesics. However, within 30 days of the thoracoscopic procedure, 2 deaths occurred – but they were due to disease itself or comorbidities, and not due to the thoracoscopic procedure.

Discussion

In our study, 104 patients of undiagnosed pleural effusion underwent semi-rigid thoracoscopy.

The age of the patients in our study ranged from 14 to 82 years; mean age was 45.87 years. Male: female ratio was 2.5:1. In study of Mootha *et al*[2] who studied 35 patients, mean age was 48.68 years and male to female ratio was 2:5 which is similar to our study. Mean age was also found to be comparable with the study of Gao *et al*[3] and Prabhu *et al*[4] while the male to female ratio in the study of Dhooria *et al*[5] and Helala *et al*[6] was also close to our study, i.e., 2.21:1 and 2.33:1 respectively (Table IV).

Out of 104 patients in our study, 92 patients (88.47%) had exudative pleural effusion, while only 12 patients (11.54%) had transudative pleural effusion. Other studies Wang *et al*[7], Prabhu *et al*[4], Gao *et al*[3], Nattusamy *et al*[8], Ahmed *et al*[9], Saifullah *et al*[10], and Kumar *et al*[11] have been done in exudative pleural effusions only. Number of patients with exudative pleural effusion was higher in our study showing their predominance. This could be because tuberculosis and malignancy were found as the most common causes of undiagnosed pleural effusions in all the studies.

On thoracoscopic examination, the most common finding was nodules which were found in 36 patients (34.61%) followed by adhesions in 30 patients (28.84%). In the study of Prabhu *et al*[4], nodules were found in 33 (48.60%) patients and adhesions in 26 (38.24%) patients. In the study of Helala *et al*[6], Ahmed *et al*[9] and Dole *et al*[12] the most common finding was pleural nodules seen in 60%, 62% and 40% patients respectively. Dhooria *et al*[5] also found nodules in maximum number of patients (60%). These findings were similar to our study.

In our study, overall the most common diagnosis was malignancy in 43 patients (41.35%). Adenocarcinoma was seen in 27 patients (25.96%). Tuberculosis was the most common non-malignant finding seen in 32 patients (30.77%). Gao *et al*[3] found malignancy in 97 cases (45.12%) followed by tuberculosis in 91 cases (42.33%). Wang *et al*[7] also found malignancy (55.56%) in maximum patients with adenocarcinoma (25.92%) being the most common. These are in concordance with our study. Tong *et al*[13] and Prabhu *et al*[4] found 32 cases (53%) and 24 cases (35.29%) of malignancy respectively with adenocarcinoma as the most common type of pleural malignancy which is similar to our study. Similarly Thangakunam *et al*[14], Mehta *et al*[15], Mootha *et al*[2], Helala *et al*[6], Ahmed *et al*[9], and Bansal *et al*[16] encountered malignancy in maximum patients on

thaoracoscopic pleural biopsy (Table IV).

However some authors; Saifullah *et al*[10], Dole *et al*[12], Kannan *et al*[17], and Dhooria *et al*[5] reported a higher incidence of tuberculosis in their studies followed by malignancy (Table IV).

The diagnostic yield of thoracoscopy in our study was 90.39%. Out of 104 patients, semi-rigid thoracoscopy helped in reaching diagnosis of 94 patients. In 4 patients, thoracoscopic biopsy could not be done due to the presence of dense adhesions; in 5 patients no obvious lesion was detected during thoracoscopy,while in 1 patient biopsy was inconclusive Our study was concordant with most of the studies done with similar diagnostic yield, e.g., Bansal *et al*[16], and Gao *et al*[3], who found diagnostic yield to be 90.2, and 88.4%, respectively. However, lower diagnostic yield was encountered in studies done by Thangakunam *et al*[14] and Nattusamy *et al*[8] 66.7% each, while Mootha *et al*[2], Dhooria *et al*[5] and Mehta *et al*[15], found diagnostic yield to be 74.3% and 73.3% , 80%, respectively. In these studies, they failed to obtain biopsy samples in a considerable number of cases. Ahmed *et al*[9], found a high diagnostic yield of 96% while Kannan *et al*[17], Saifullah *et al*[10], and Prabhu *et al*[4] found diagnostic yield of 96.4%, 96.7% and 97% respectively. They performed successful biopsy sampling in almost all patients (Table 4).

Thoracoscopic pleural biopsy is considered the gold standard in the diagnosis of malignant pleural effusion and tubercular pleural effusion.The diagnostic yield of thoracoscopic pleural biopsy can be as high as 95% in malignant pleural effusions to 99% in TB pleural effusions which is superior to that of pleural fluid analysis and closed pleural biopsy[18]. These findings and various studies including the present study suggest that thoracoscopic pleural biopsy should be considered in all patients with pleural effusions who remain undiagnosed after an initial pleural fluid analysis.

There were no serious complications in our study. A total of 10 patients (9.61%) developed minor complications. Post-operative fever developed in 5 patients (4.81%), and was controlled by antipyretics within a few days. 3 patients (2.89%) developed subcutaneous emphysema which resolved spontaneously within 8 days. 2 patients (1.92%) experienced pain at the site of tube insertion. Within 30 days of thoracoscopic procedure, 2 deaths occurred, but they were due to the disease itself, or comorbidities, not due to the thoracoscopic procedure.The literature describes a variety of complications whose rates are very minimal and are easily manageable: subcutaneous emphysema (0.6% - 4.9%), air leak (0.5% - 8.1%), empyema (0.5% - 2.7%), haemorrhage (0.3% - 0.4%), shock (0.2%), chest wall seeding by malignancy (0.5% - 4.0%).

Table IV: Comparison of thoracoscopic guided histopathological findings and diagnostic yield of our study with other studies.

Studies	Total (T) patients	Mean (M)	Diagnostic yield (%)	Histopathological finding			
				Malignancy (%)	Tuberculosis (%)	Non-specific (%)	Others findings
Our study	T-104	M-45.87	90.39	44 (41.35) (Adenocarcinoma - 25.96)	30.77	15.39	–
Tong *et al*[13]	T-60	–	95	32 (53)	16 (27)	5 (8)	Parapneumonic-7
Kannan *et al*[17]	T-61	–	96.4	20 (32.7) [Adenocarcinoma - 13 (21.31)]	22 (36.07)	12 (19.68)	–
Prabhu *et al*[4]	T-68	M-50.5	97	24 (35.3) (Adenocarcinoma-15)	16 (25.3)	22 (32.36)	Sarcoidosis-1
Gao *et al*[3]	T-215	M-46.5	88.4	97 (45.12)	91 (42.32)	-	Chronic Inflammation-25
Dhooria *et al*[5]	T-45	M-48.8 ± 13.3	73.3	7 (20)	9 (25.7)	17 (48.6)	–
Helala *et al*[6]	T-40	M-51.3 ± 16.3	95	28 (70)	9 (22.5)	–	Empyema-1 (2.5)
Nattusamy *et al*[8]	T-48	M-50.9 ± 14.1	66.7	30 (62.5) (Adenocarcinoma-18)	2 (4.17)	–	–
Saifullah *et al*[10]	T-60	M-42.85 ± 18.22	96.7	26 (43.34) [Adenocarcinoma-25 (41.7)]	27 (45)	5 (8.3)	–
Dole *et al*[12]	T-60	M-45	95	26 (43) [Adenocarcinoma-18 (30)]	28 (47)	–	Empyema-3 (5)
Bansal *et al*[16]	T-102	M-58	90.2	63 (Adenocarcinoma - 61.8)	30 (29.4)	–	–
Kumar *et al*[11]	T-90	M-47	95.5	31 (34.4)	25 (27.8)	28 (31.11)	Sarcoidosis-2 (2.22)

Conclusion

We hereby conclude that semi-rigid thoracoscopy is a safe, simple, and accurate tool for diagnosis of pleural effusions which remain inconclusive even after thoracentesis. Semi-rigid thoracoscopy is an easy outpatient procedure, done under local anaesthesia with lesser duration of hospital stay. It is well tolerated, and is devoid of major complications. Diagnostic delay will be less with the increased use of semi-rigid thoracoscopy.

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REVIEW ARTICLE

JIACM 2018; 19(1): 52-57

Jaundice in Pregnancy

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Jaundice is a clinical manifestation of increased serum levels of bilirubin, either direct or indirect. When serum bilirubin is more than 2 mg/dl, it is clinically manifested as jaundice. Increased serum bilirubin causes yellowish discoloration of sclera, mucous membranes and urine. The incidence of jaundice in India varies from 0.4 to 0.9/1,000 deliveries[1]. Most common cause of jaundice in pregnancy is acute viral hepatitis. The incidence in developing countries can range from 3 to 20%. The course of most viral hepatitis infections is unaltered in pregnancy with the exception of hepatitis E, where pregnant women have very high mortality rates of 10 - 20%[2] . Jaundice in pregnancy is associated with high maternal and perinatal mortality rates.

Physiological changes during pregnancy

Pregnancy is a cholestatic condition. Due to the physiological perturbations of pregnancy, certain changes occur in liver function tests (LFTs). Serum total, and free bilirubin concentrations either remain same or lower, as compared to, non-pregnant women during all the three trimesters. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels remain same during pregnancy, as compared to, non-pregnant levels. Because of the haemodilution which occurs during pregnancy, serum albumin levels fall during the first trimester. Serum globulin levels increase slightly during pregnancy. Albumin to globulin ratio is slightly decreased during pregnancy. Serum alkaline phosphatase (ALP) increases during late pregnancy due to increased production of bone and liver isoenzymes from the fetus. Serum gamma glutamyl transferase activity levels either decrease or remain same during the second and third trimesters and 5'nucleotidase activity increases during last trimester. Total serum bile acid concentration during pregnancy is not different from non-pregnant state. Table I shows the changes in LFTs during pregnancy[3]. Table II depicts the causes of jaundice during pregnancy[4].

Table I: Changes in liver function test during pregnancy.

Physiological changes in pregnancy, pertaining to liver
Increases
• Alkaline phosphatase levels rise three-to four-fold because of placental production
• Clotting factors I, II, V, VII, VIII, X, and XII
• Transferrin level
• Ceruloplasmin level
Decreases
• Albumin and total protein levels
• Antithrombin III and protein S level
• Gall bladder contractility
No change
• Liver transaminase levels (aspartate aminotransferase, alanine aminotransferase)
• γ-Glutamyl transferase (GGT) level
• Bilirubin level
• Prothrombin time

Table II: Causes of jaundice during pregnancy.

Causes of jaundice in pregnancy
Pre-existing liver disease
• Cirrhosis and portal hypertension
• Primary biliary cirrhosis
• Primary sclerosing cholangitis
• Chronic viral hepatitis B and C
• Chronic liver disease
• Wilson's disease
• Autoimmune hepatitis
Liver disease coincidental with pregnancy
• Budd-Chiari syndrome
• Hepatitis - viral hepatitis A, B, C, E, herpes simplex virus, cytomegalovirus
• Alcohol and pregnancy
• Gallstone disease
Liver disease unique to pregnancy
• Preeclampsia, eclampsia
• Hyperemesis gravidarum
• Intrahepatic cholestasis of pregnancy
• HELLP syndrome (haemolysis, elevated liver enzyme levels, low platelet count)
• Acute fatty liver of pregnancy

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Pre-eclampsia, eclampsia, HELLP syndrome

Pre-eclampsia is defined as high blood pressure > 140/90 mmHg on at least two occasions, 4 hours apart, with proteinuria, which occurs after 20 weeks of pregnancy. Eclampsia is defined as seizures that cannot be attributed to other causes in a woman with pre-eclampsia. Pre-eclampsia and eclampsia affect 5% of pregnancies and are more common in primiparous women with multifoetal gestation[5]. Pre-eclampsia and eclampsia are multisystem disorders leading to hypertension, oedema, proteinuria, hyperuricaemia, and liver involvement, leading to HELLP syndrome.

HELLP syndrome stands for haemolysis, elevated liver enzymes, and low platelets, and usually occurs in the third trimester. HELLP syndrome complicates severe pre-eclampsia, and can become life-threatening, both for the mother and baby. It occurs in 0.5% of all pregnancies. The pathogenesis of HELLP involves vasospastic, procoagulant and inflammatory changes in the maternal vascular bed. Segmental vascular spasm in the liver leads to vascular injury, release of thromboplastin with consequent platelet aggregation and fibrin deposition. Decreased liver perfusion leads to endothelial damage, haemorrhage and hepatocellular necrosis.

Signs and symptoms of HELLP syndrome include right upper quadrant pain, epigastric pain, hypertension. nausea, vomiting, generalised oedema. Laboratory investigations suggestive of HELLP syndrome are:-

- Serum bilirubin normal/slightly increased, usually < 5 mg/dl
- Moderate elevation of AST/ALT
- Prothrombin time is usually normal, unless DIC sets in
- Platelets < 1,00,000/mm^3
- Peripheral smear shows signs of haemolysis
- Increased serum lactate dehydrogenase (LDH) level.

Tennessee classification

Complete syndrome: Platelets ≤ 1,00,000/mm^3
AST ≥ 70 IU/L
LDH ≥ 600 IU/L

Incomplete syndrome: Any one, or two, of the above

Mississippi classification

Class 1: Platelets ≤ 50,000/mm^3
AST or ALT ≥ 70 IU/L
LDH ≥ 600 IU/L

Class 2: Platelets between ≤ 1,00,000/mm^3 and ≥ 50,000/mm^3
AST or ALT ≥ 70 IU/L
LDH ≥ 600 IU/L

Class 3: Platelets between ≤ 1,50,000/mm^3 and ≥ 1,00,000/mm^3
AST or ALT ≥ 40 IU/L
LDH ≥ 600 IU/L

Liver histology shows hepatic sinusoidal deposition of fibrin, periportal haemorrhage, liver cell necrosis, and infarction. These changes are due to vasoconstriction[6,7]. Management includes stabilisation of maternal condition, control of hypertension, magnesium sulfate prophylaxis, correction of coagulopathy, steroid administration, and termination of pregnancy, depending on period of gestation.

Hyperemesis gravidarum

Hyperemesis is a condition in which nausea and vomiting occurs to such an extent causing dehydration, ketosis, and electrolyte imbalance leading to liver damage. Nausea and vomiting are common in pregnancy, affecting up to 70% to 85% of pregnant women[8]. Hyperemesis affects between 0.3% and 2.3% of all pregnancies[9].

Onset of hyperemesis usually occurs in first trimester around 10 - 12th week of gestation and resolves by 20th week. In 15 - 20% women, hyperemesis occurs till third trimester. In 5%, patients nausea vomiting persists till delivery[10].

Liver involvement can occur in as high as 50% patients. ALT is a sensitive marker which may increase upto 1,000 IU/L. Mild hyperbilirubinaemia may also occur. The exact aetiology is not known; various risk factors proposed are hormones like hCG, oestrogen, progesterone, leptin, gastrointestinal dysfunction, thyrotoxicosis, serotonin, hepatic abnormalities, autonomic nervous dysfunction, asthma, allergies, nutritional deficiencies, *Helicobacter pylori* infections[11-14]. Hyperemesis is associated with preterm labour, abruptio placenta and pre-eclampsia. Treatment options are lifestyle modification, short frequent meals, intravenous fluids, and antiemetics.

Intrahepatic cholestasis of pregnancy (IHCP)

IHCP affects less than 1% of all pregnancies in the second half of pregnancy. It is more common in multiparous women with twin gestations, advanced maternal age, and history of cholestasis with oral contraceptive use[5]. Oestrogen affects gall bladder function resulting in slowing and stopping of flow of bile, leading to build up of bile acids in liver, which can spill into the blood stream. Proposed genetic factor is mutation in hepatocellular phospholipid transporter MDR3.

Signs and symptoms include pruritus, which is the most disturbing clinical feature, and develops in 70% of patients. It is severe at night and particularly occurs in hands and feet. Jaundice occurs in only 10% patients-usually mild. Pruritus usually disappears within days after delivery. Jaundice disappears within weeks. Biochemical abnormalities usually resolve within 2 - 3 months. Laboratory investigations suggestive of IHCP are:-

- Rise in serum bile acid is the earliest feature. 10-100-fold increase in serum cholic acid occurs. Chenodeoxycholic acid also increases but less than cholic acid.
- Hyperbilirubinaemia occurs in 10 % patients; levels usually are 2 - 5 mg/dl.
- ALT/AST increase mild usually < 250 IU/L.
- ALP increase is non-specific.
- Prothrombin time is usually normal.

IHCP is a diagnosis of exclusion. Liver biopsy is usually not required for the diagnosis. Biopsy shows dilated centrilobular bile canaliculi and bile plugs.The importance of this disorder is the effects on the foetus. It can lead to chronic placental insufficiency which may result in anoxia, prematurity, perinatal death, foetal distress and stillbirth. INCP often recurs in subsequent pregnancies.

Management options are topical emollients, ursodeoxycholic acid, corticosteroids, S-adenosyl methionine, cholestyramine, vitamin K. Pregnancy should be terminated at 37 - 38 weeks[15].

Acute fatty liver of pregnancy (AFLP)

With an incidence of 1 in 10,000 to 1 in 15,000 pregnancies, it has a maternal mortality rate of 18% and a foetal mortality rate of 23%. AFLP is more commonly seen in nulliparous women and those with multifetal gestation[16,17]. AFLP is defined as acute hepatic failure in the absence of other causes like viral hepatitis, or intrahepatic cholestasis of pregnancy. It is also called as acute yellow atrophy of liver and reversible peripartum failure. AFLP is common in primigravidae, also associated with pre-eclampsia, multiple pregnancy and male foetus. The exact aetiology of AFLP is not known. It is linked to an abnormality in foetal fatty acid metabolism. It may be a result of mitochondrial dysfunction. The most common proposed disorder in AFLP is a deficiency of long-chain 3-hydroxylacyl-CoA dehydrogenase (LCHAD) resulting in accumulation of medium and long chain fatty acids. It is an autosomal recessive disorder and the heterozygous LCHAD deficiency has been identified in some women in AFLP. When both parents are heterozygous, the foetus acquires mutant fatty acids. These un-metabolised free fatty acids return via placental circulation to the mother's circulation and strains maternal hepatic activity leading to symptoms of AFLP. During the third trimester, the metabolic demands of the foetus increase, mothers who are heterozygous for a fatty acid oxidation disorder and having homozygous foetus can develop AFLP because of their inability to metabolise fatty acids for energy production and meeting high energy demands of foetus. Because of this inability, fatty acids can deposit in the liver[5]. The foetal complications include failure to thrive, hepatic failure, cardiomyopathy, microvesicular steatosis, hypoglycaemia, and death.

Liver biopsy is necessary for diagnosis. AFLP is characterised by infiltration and microvesicular fat deposition in centrilobular hepatocytes. Delivery of the foetus leads to rapid recovery without sequelae of chronic liver disease.

Signs and symptoms of AFLP are:-

- Polydipsia, with or without polyuria
- Anorexia, nausea, vomiting
- Fatigue, malaise, altered sensorium,
- Up to 90% patients may develop jaundice
- Around 50% patients develop right upper quadrant pain, ascites, pruritus
- Hepatic encephalopathy can develop in later stage

Laboratory investigations suggestive of AFLP are:-

- Hyperbilirubinaemia, up to 5 to 15 mg/dl
- ALT/AST elevation, up to 1,000 IU/L
- ALP may increase, up to 3 - 4 times normal.
- Increased prothrombin time/partial thromboplastin time
- Decreased serum fibrinogen level
- Hypoglycaemia
- Hyperuricaemia
- Increased blood urea, ammonia levels

Swansea criteria for diagnosis of AFLP [18]

Six or more criteria are required, in the absence of another cause:-

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin > 14 µmol/l
- Hypoglycaemia < 70 mg/dl
- Elevated urea > 340 µmol/l

- Leucocytosis > 11,000/mm^3
- Ascites, or bright liver, on ultrasound
- ALT/ AST > 42 IU/L
- Elevated ammonia > 47 µmol/l
- Renal impairment; creatinine > 150 µmol/l
- Coagulopathy; prothrombin time > 14 seconds or partial thromboplastin time > 34 seconds
- Microvesicular steatosis on liver biopsy.

Liver biopsy is the gold standard investigation for diagnosis, though it is rarely done. or required. Management of AFLP is mainly supportive. Optimal management is prompt delivery. Correction of coagulation profile should go hand-in-hand. Normoglycaemia should be maintained by high carbohydrate diet and intravenous glucose. The patient should be managed in a high dependency unit (HDU), under care of a multidisciplinary team.

Haemolysis

Haemolytic jaundice leads to unconjugated hyperbilirubinaemia because of excessive destruction of red blood cells. Causes of haemolytic anaemia could be thalassaemia, sickle cell anaemia, hereditary spherocytosis, etc. There are no changes in serum transaminase levels. Usually, there is worsening of jaundice during pregnancy.

Acute viral hepatitis

Acute viral hepatitis is a common cause of jaundice in the reproductive age group.

Hepatitis A

Hepatitis A is a Picornavirus and is transmitted by faeco-oral route. Incubation period is 15 - 40 days. It is a self-limiting condition characterised by fever, anorexia, nausea, vomiting, malaise and weight loss. Jaundice usually appears in the second week of disease. Hepatitis A is not transmitted vertically. Liver function tests are abnormal, characterised by elevated ALT/AST. Treatment is supportive.

Hepatitis B

Hepatitis B is caused by a hepadnavirus. It is tran by blood, blood products and sexual contact. It leads to acute hepatitis and may also lead to chronic hepatitis, cirrhosis, and hepatocellular carcinoma in later life. The importance of hepatitis B during pregnancy is related to its role in the perpetuation of chronic infection through vertical transmission. Maternal-foetal transmission of hepatitis B virus is responsible for most cases of chronic hepatitis B[2]. The vertical transmission is mainly in the peripartum period with infected vaginal secretions as well as breast milk. The risk of perinatal transmission is 10 to 50%. HBsAg positivity suggests high infection rates and increased transmission to

Table III: Liver diseases unique to pregnancy.

Disease	Symptoms	Lab values	Jaundice	Trimester	Treatment	Prevalence
Hyperemesis gravidarum	Nausea, vomiting, weight loss	ALT/AST < 1,000 IU/L	Mild jaundice	1st trimester	IV fluids, Thiamine, Pyridoxine, Promethazine	< 2%
Pre-eclampsia/eclampsia	Hypertension, oedema, proteinuria, neurological deficit	Uric acid elevated, ALT < 500 IU/L, proteinuria, DIC in 7% of cases	Develops late, 25% of cases	2nd, 3rd trimester	Beta-blockers, Methyldopa, Magnesium Sulphate, delivery	5%
HELLP syndrome	Abdominal pain, nausea, vomiting, oedema, hypertension, proteinuria	Platelet count < 1,00,000/mm^3, haemolysis, elevated liver enzymes, AST/ ALT - 70 - 6,000 IU/L, raised LDH, DIC	Develops late, 25% of cases	Beyond 22 weeks	Prompt delivery	0.5%
AFLP	Pruritus, jaundice, fatigue, abdominal pain, steatorrhoea	AST/ALT > 1,000 IU/L , PT elevated, DIC	Common	3rd trimester	Delivery	<0.1%
IHCP	Pruritus	ALT/AST<1,000 IU/L, bilirubin < 6 mg/dl, PT normal	Develops 1 - 4 weeks after pruritus, 20 - 60%	2nd trimester	UDCA, delivery	<1%

HELLP: Haemolysis, Elevated Liver enzymes Low Platelets; AFLP: Acute fatty Liver of Pregnancy; IHCP: Intrahepatic Cholestasis of Pregnancy; UDCA: Ursodeoxycholic Acid; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; DIC: Disseminated Intravascular Coagulation; PT: Prothrombin Time.

foetus, upto 70%[2]. Active and passive immunisation should be given shortly after birth, to babies of HBsAg positive mothers.

Hepatitis C

The risk for vertical transmission of Hepatitis C virus (HCV) is about 5 - 10%. The risk of perinatal transmission of HCV is associated with the presence of HCV RNA in maternal blood at the time of birth and co-infection with human immunodeficiency virus (HIV)[19]. HCV has a high-risk of chronic infection.

Hepatitis E

Hepatitis E also has faeco-oral transmission. Acute hepatitis E during the third trimester of pregnancy is a cause of fulminant hepatic failure and has a mortality rate of up to 20%[2]. Maternal hepatitis E virus infection also has been associated with intrauterine fetal death[20,21]. The risks of intrauterine death and abortion in any trimester are greater in pregnant women with hepatitis E, than they are in their uninfected counterparts. There is high vertical transmission through transplacental route, up to 50%. Maternal medical complications of HEV are coagulation failure, hepatic encephalopathy, and acute liver failure. Obstetric complications include intrauterine death, antepartum haemorrhage, premature rupture of membranes and postpartum haemorrhage. Foetal complications are prematurity, foetal growth restriction, still birth and foetal demise[22]. The high mortality rates in pregnancy are because of associated hormonal and immunological changes during pregnancy. Hepatitis E has high incidence of a severe course in pregnant women in some geographical areas such as northern India[23,24].

Cholelithiasis

Pregnancy promotes lithogenesis due to biliary cholesterol saturation and inhibition of the hepatic synthesis of chenodeoxycholic acid. Pre-pregnancy obesity, sedentary lifestyle, low serum leptin levels, and a history of gallbladder disease are risk factors for gallbladder disease. Gallstones regress in the postpartum period. Laparoscopic cholecystectomy for symptomatic cholelithiasis is particularly safe, when performed during the second trimester.

Budd-Chiari syndrome

It is a syndrome in which occlusion of hepatic veins leads to sinusoidal congestion and necrosis of hepatocytes around the central vein. It is characterised by abdominal pain, hepatomegaly, and ascites. Predisposing conditions are factor V Leiden, antithrombin III, protein C/S deficiency, or the presence of antiphospholipid antibodies. Complete anticoagulation throughout pregnancy and the puerperium is required[25].

Chronic liver disease/cirrhosis, portal hypertension

The prevalence of cirrhosis is 0.45 cases per 1,000 deliveries. The most common causes are viral hepatitis B and C, autoimmune and alcohol induced. Cirrhosis can lead to infertility. However, there is an increased risk of premature delivery if these patients become pregnant. Oesophageal varices can be treated by banding, octreotide, or beta-blockers in second trimester[5]. Portal hypertension leads to increased maternal complications, including variceal haemorrhage, hepatic failure, encephalopathy, jaundice, malnutrition, and splenic artery aneurysm[26]. Bleeding from oesophageal varices has been reported in 20 - 25% of pregnant women with cirrhosis[27]. It is recommended to have caesarean section to avoid increased straining and consequent rupture of oesophageal varices.

Autoimmune hepatitis

Autoimmune hepatitis can occur in any age group. There is an increased risk of prematurity, low birth-weight infants, and foetal loss. There is a 20% risk of flare during intrapartum period, and 30 - 40% during postpartum period. Immunosuppressive therapy, in the form of prednisone and azathioprine can be given, with reduced doses during pregnancy. Recent guidelines recommend prednisolone monotherapy for pregnant ladies[28,29,30].

Primary biliary cirrhosis

Primary biliary cirrhosis and primary sclerosing cholangitis are autoimmune diseases. There is a high risk of prematurity, stillbirth in foetus, and liver failure in mother. The magnitude of rise in serum bilirubin depends on the type of disease and presence of anti-nuclear, anti-smooth muscle, anti-liver-kidney microsomal antibodies or antibodies to soluble liver antigen/liver pancreas antibodies. Diagnosis is same as that in the non-pregnant woman[5]. Ursodeoxycholic acid (UDCA) can be given safely.

Wilson's disease

Wilson's disease causes amenorrhoea and infertility in women of reproductive age group. Pregnant patients with Wilson's disease should remain on medication because discontinuation of therapy may cause sudden copper release, haemolysis, acute liver failure and death[31]. D-penicillamine – a copper chelator – is potentially teratogenic[32]. Trientine is safe in pregnancy. Zinc is also not teratogenic and can be used as a copper chelator[33].

Conclusion

The incidence of jaundice, in India, ranges from 0.4 to 0.9/ 1,000 deliveries.

The most common cause of jaundice in pregnancy is acute viral hepatitis. The incidence in developing countries can range from 3 to 20%.

Jaundice in pregnancy is associated with high maternal and perinatal mortality rates. General public should be made aware regarding the routes of transmission of viral hepatitis.

Proper sanitation measures, imparting health education, routine antenatal checkups and screening for viral markers can help in reducing the burden of liver diseases in pregnancy.

The overall morbidly and mortality due to liver disease has reduced, over the past few years, because of a better understanding of physiological changes, and early recognition of clinical and laboratory abnormalities during pregnancy.

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REVIEW ARTICLE

JIACM 2018; 19(1): 58-61

Pulmonary Tuberculosis Versus Pulmonary Non-Tuberculous Mycobacterial Infection

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Abstract

The prevalence of disease caused by Mycobacterium species, other than Mycobacterium complex, like Non-Tuberculous Mycobacterium (NTM) resulting in a disease similar to human tubercular disease is on the rise. NTM are ubiquitous in the environment and naturally prevalent in water and soil. Everyone can come in to contact with them in everyday life. NTM lung infection occur when a person inhales the organism from the environment. Usually this infection occurs in patients with pre-existing lung disease such as chronic bronchitis, cystic fibrosis or healed cavities from old TB infection and amongst smokers. Signs and symptoms of pulmonary infection caused by MTB or NTM often resemble, and their differentiation through acid-fast stain is incomprehensible. This demonstration of Mycobacteria after ZN staining will be for Mycobacterium tuberculosis as well as for Non-Mycobacterium tuberculosis, i.e., NTM. As a result, cases of NTM can be misdiagnosed as pulmonary tubercular infection and may also be mistreated subsequently with ATT. Moreover, NTM pulmonary infection should be considered in the differential diagnosis of MDR TB pulmonary infection. The mainstay of treatment of NTM is use of macrolide. NTM lung disease can have a significant impact on quality of life of an individual.

Key words: Tuberculosis, NTM, MPT64, mycobacterium, MTBC.

Introduction

Tuberculosis is an ancient disease caused by *Mycobacterium tuberculosis*. It is estimated that approximately 9.6 million new TB cases are reported each year globally, out of which 2.2 million are from India. According to the World Health Organisation (WHO) Global Tuberculosis Report 2015, TB remains one of the world's deadliest communicable disease. India accounts for 23% of the global burden of TB[1]. In 2016 the incidence cases of TB in India are 211 and MDR-TB was estimated to be 11 per lakh population as per Global TB Report 2017[2].

The Mycobacterium tuberculosis complex (MTBC) is a known agent for infectious pulmonary tuberculosis (TB). On the other hand, Mycobacteria Other Than Tuberculosis (MOTT) can also cause disease similar to tuberculosis.

The prevalence of disease caused by Mycobacterium species other than Mycobacterium complex, like non tuberculous mycobacterium (NTM), resulting in a disease similar to human tubercular disease is also on the rise. NTM is now more prevalent than tuberculosis (TB) in the United States[3]. It has been observed that while the rates of TB are decreasing across the United States, rates of NTM are on the rise[4]. NTM are ubiquitous to the environment and naturally prevalent in water and soil. Everyone can come in to contact in them everyday life. NTM lung infection occur when a person inhales the organism from environment.

NTM can cause pulmonary disease resembling pulmonary tuberculosis, lymphadenitis, skin lesions and some time disseminated disease. Usually, this infection occurs in patients with pre-existing lung disease such as chronic bronchitis, cystic fibrosis or healed cavities from old TB infection and amongst smokers. Non tuberculosis mycobacteria (NTM) are ubiquitous organisms responsible for opportunistic infections with varied degree of virulence. The incidence and prevalence of NTM lung disease continues to increase worldwide, leading to an emerging public health problem.

Exposure to environmental sources can lead to NTM entering the lungs. In most individuals, these NTM organisms are cleared from the lung naturally and do not cause any disease. NTM are capable of causing the disease but pathogenicity varies among the species. In some people, the organisms infect the airways and lung tissues leading to disease, especially among diseased lungs and causes inflammation in the respiratory system. Without treatment, many people, but not all, will develop a progressive lung infection characterised by cough, shortness of breath, fatigue, and often weight loss.

Signs and symptoms of pulmonary infection caused by MTBC or MOTT often resemble, and their differentiation through acid fast stain is incomprehensible. Identification and speciation of the Mycobacterium becomes essential for the appropriate management and treatment of the

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affected individuals[5,6]. There are about 50,000 to 90,000 people with NTM pulmonary disease in the United States, with a much higher frequency among older adults.However, NTM can affect any age group. In some people, NTM infections can become chronic and require ongoing treatment. Severe NTM lung disease can have a significant impact on quality of life. But, death directly related to NTM lung disease is rare[7].The gold standard diagnostic tool for the diagnosis of pulmonary infection caused by *M. tuberculosis* continues to be demonstration of acid fast bacteria under direct microscopy after Ziehl-Nelsen staining of sputum specimen at peripheral health institutions (PHIs). This demonstration of Mycobacteria after ZN staining will be for *Mycobacterium tuberculosis,* as well as for NTM. As a result, cases of NTM can be misdiagnosed as pulmonary tubercular infection and may be mistreated subsequently with ATT. Whereas, the mainstay of treatment of diseases caused by NTM warrants use of a macrolide.

More reliance on this diagnostic tool (Direct Microscopy after ZN Staining) may render such patients to be labelled as cases of MDR TB.This is possible as the sputum specimen continues to be positive for AFB even after treatment.

Patients with structural lung disease, such as bronchiectasis, COPD, cystic fibrosis (CF), and asthma are at greater risk of being infected with NTM. Up to 50% of patients with bronchiectasis may have active NTM lung infections at the time of diagnosis[8,9]. In COPD patients, the risk of getting an NTM infection has been reported to be 15.7-folds higher than in patients without COPD[10].

Middle-aged or older patient may present with a history of chronic cough, fatigue, and generalised weakness. Patients with co-morbid conditions (such as: Bronchiectasis, asthma, COPD, cystic fibrosis, emphysema and immuno-compromised individuals) and/or lack of response to previous courses of antibiotic treatment, are likely candidates for this disease[11-14].

Diagnosis of NTM infection

Diagnosis of NTM infection should be based on (a) patient complaints, clinical symptoms, (b) radiological picture of lungs and of pulmonary HRCT scan, and (c) confirmed by the detection of NTM species by culture and PCR based molecular methods. For the diagnosis of NTM lung disease, patients suspected to have NTM lung disease are required to meet all clinical and microbiologic criteria. The development of molecular methods allows the characterisation of new species and NTM identification at a subspecies level.The possible presence of NTM lung disease often arises clinically when NTMs are identified on sputum culture from a patient under evaluation for tuberculosis. The laboratory findings used to confirm the diagnosis of NTM infection in this setting will be reviewed here.

The radiographic findings of non-tuberculous mycobacterial (NTM) lung disease are variable, depending partly upon the underlying species. Findings consistent with NTM pulmonary infection on chest radiograph or high-resolution computed tomography scan include infiltrates (usually nodular or reticulonodular), cavities, multifocal bronchiectasis, and/or multiple small nodules. The radiographic pattern of disease can usually be separated into predominantly cavitatory versus nodular/ bronchiectasis lesions.

Cavitatory disease in the upper lung zones, similar to pulmonary tuberculosis, is seen in approximately 90 per cent of patients with *M. kansasii* infection and perhaps 50 per cent of those with Mycobacterium avian complex (MAC) infection. Radiologically, cavities caused by these organisms tend to have thinner walls and less surrounding parenchymal opacity than those caused by *M. tuberculosis*[15,16]. At least 50 per cent of patients with MAC lung disease have radiographic abnormalities characterised by nodules associated with bronchiectasis or nodular/bronchiectatic disease.The nodules and bronchiectasis are usually present within the same lobe and occur most frequently in the right middle lobe and lingual regions of the lung[17].

Differentiation between *Mycobacterium tuberculosis* and NTM

1. AFB staining cannot differentiate between *M. tuberculosis* an NTM. Nucleic acid amplification test (NAAT) for the detection of *M. tuberculosis* is needed. Several commercial tests such as the Xpert MTB/RIF assay (Xpert assay; Cepheid. Sunny vale, CA, USA), the Cobas TaqMan MTB test (Roche Diagnostic, Rotkreuz, Switzerland), and amplified *M. tuberculosis* direct test (Hologic Inc., Scan Diego, CA, USA), are widely used. Compared with AFB smear microscopy, NAA testing has a greater positive predictive value (> 95%) for *M. tuberculosis* with AFB smear-positive specimens in settings in which NTMs are common.

2. MPT64 Ag is one of the major culture filtrate protein (24 kDa)[18,19]. Encoded by the RD2 region genes[20] and has been shown to be a specific antigen that clearly differentiates *M. tuberculosis* complex from mycobacteria other than tuberculosis (MOTT) species[21,22].

Capilia™ TB Neo-assay: a new tool for rapid distinction between tuberculous and non- tuberculous mycobacteria. This rapid assay has sensitivity 97%, specificity 100%, positive predictive value 100%, and negative predictive value 96%[23] and is easy to perform and interpret, and does not require

any sample preparation, trained technicians, or expensive equipment.

Method: The Capilia TB Neo-assay can be performed according to manufacturer's instructions.This IC assay uses a nitrocellulose membrane with specific anti-MPB64 Ag mouse monoclonal antibody immobilised on it. Briefly, 100 ul of the positive broth culture was applied directly into the Capilia well without any manipulation. In positive cultures in solid media, a few colonies from the medium were scraped using a loop (1 up) and suspended in 0.2 ml of extraction buffer (TAUNS). The suspension was vortexed and approximately 100 ul of this suspension was added to the sample well thereafter. The results are available 15 minutes after inoculation of the test cartridge. Results were read as positive for MTBC by observing the presence of purple-red lines on the MTBC area as well as on the test area of the internal quality control.

Capilia TB Neo is a good screening method for rapidly identifying MTBC and distinguishing between MTBC and NTM in AFB-positive cultures. With a reduction in the laboratory turnaround time, this could reduce transmission and rapid IC confirmation test is important in TB control.

Treatment of NTM Lung disease

The management of NTM lung disease is a challenge that should be undertaken by experienced clinicians at centers equipped with reliable laboratory services for mycobacterial cultures and *in vitro* dng susceptibility testing, as it requires prolonged use of costly combinations of multiple drugs having significant potential for toxicity.The diagnosis of NTM lung disease does not obligate the initiation of therapy against NTM species and a decision must be made based on the potential risks and benefits of therapy for individuals patients[24]. NTM are relatively resistant to antibiotics and can become more resistant if only one antibiotic is used to treat the infection. Effective treatment requires two to three drugs: the exact drugs and combination of drugs depends on the NTM species involved, how bad the infection is, and results of drug susceptibility testing. Treatment should continue until the respiratory culture results have been negative, for at least 12 months.

The current strategies for the most common species of NTM lung infections, MAC, are dictated by severity of disease and patient type. Treatment of MAC and *M. kansasii*, the most common causes of pulmonary NTM disease, requires three drugs given either 3 days a week or on daily basis, depending on severity of disease.Treatment of *M. abscessus* is more complicated and associated with poorer treatment outcomes compared with MAC and *M. kansasii*. Patients require several months of treatment with one to two intravenous (IV) drugs in combination, along with oral and sometimes inhaled antibiotics.

Side-effects of drug treatment are common, but most people can complete treatment as prescribed. Thus in summary, NTM treatment is a challenge, should be undertaken by the experienced clinician at centres equipped with reliable laboratory services for mycobacterial cultures. It require prolonged use of costly combination of costly drugs with a significant potential for toxicity. A decision must be made on the potential risk and benefits of therapy on individual basis. However, once the clinician decides to start the treatment, the goal of curative therapy in NTM lung disease is 12 months of culture negativity, therefore frequent sputum sampling, i.e., at every 1 - 2 month interval is needed.

Macrolides (azithromycin/clarthromycin) are the corner-stone of treatment. The standard treatment regimen includes rifampicin, ethambutol, and a macrolide for 18 to 24 months, including 12 months of sputum culture negativity. If eradication of NTM is not achieved by 6 to 9 months of therapy despite an appropriate choice of drugs, consider the option of surgery; and if surgery is not possible, the goal of treatment including the decision on the duration of treatment should focus on symptoms control, short course pulse treatment (oral/ parental/inhalation) to suppress mycobacterial growth.The clinician should consider quality of life and patient centred approach, rather than solely expecting microbiological eradication.

Some patients will need surgery to remove damaged areas of the lung. However, this should only be considered after consultation with experts in NTM and surgery. In most cases, surgery can be performed using VATS (video-assisted thoracoscopic surgery).

Defining treatment success

Although symptomatic improvement is important, it can be complicated by the progression of underlying co-morbidities (if any). Similarly, radiographic improvement can be difficult to document because of underlying lung disease and damage already caused by NTM. Goals of NTM therapy vary for each patient depending on clinical presentation and patient needs. For some, both microbiologic and clinical improvements are important and attainable; while suppressive treatment strategies are appropriate for others.

Conclusion

NTM belongs to the group of orphan diseases, still the demographic changes in western society might probably lead to further increase in the incidence of NTM disease. At present, clinical decisions affecting the patient with NTM heavily rely on expert opinion rather than on good clinical

evidence.There is likely an under-reporting of NTM, because it is not modifiable and in most of the countries, diagnostic procedures are not optimised for isolation of different NTM species. Due to the large number of NTM species, the challenge in identification of species in few laboratories is difficult to meet and sometimes NTM pulmonary infection is treated as MDR TB pulmonary infection. Microbiologists should be available for consultation by the clinician, for the interpretation of laboratory results.

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CASE REPORT

JIACM 2018; 19(1): 62-64

Granulomatous Disease of Bone Marrow: Case Report and Review of Literature

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Abstract

Evaluation of prolonged pyrexia remains a challenge even to an astute clinician. Despite meticulous historical and clinical evaluation, pyrexia may remain undiagnosed and may occasionally resolve on its own.

Infectious diseases, noninfectious inflammatory diseases, immunological diseases, and haematological malignancies account for most of the cases of prolonged pyrexia.

Biochemical, microbiological, and radiological investigations form the baseline of evaluation of prolonged pyrexia. Tissue biopsy, including bone marrow biopsy in the evaluation of prolonged pyrexia has been highlighted in medical literature the world over. However, granulomas in the bone marrow as a cause of prolonged pyrexia are infrequently reported.

Chronic infections, sarcoidosis, HIV, and haematological malignancies are implicated in bone marrow granulomatosis; however, they are not specific and rarely demonstrate typical morphological features so as to make a definitive histopathological diagnosis.

We report the case of a 57-year-old Indian male who had fever for more than three months, and was finally diagnosed as having granulomatous disease of bone marrow.

Key words: Granuloma, bone marrow, tuberculosis, sarcoidosis, lymphoma.

Introduction

Despite great progress in the practice of medicine in the last half century, diagnostic methodology of prolonged pyrexia still remains the same. Bone marrow examination is still regarded as a mandatory test in the evaluation of prolonged pyrexia. In fact, many diseases manifest with histopathalogical changes in bone marrow. Bone marrow granuloma is infrequently reported in bone marrow biopsy. The aetiological spectrum varies, from viral/bacterial infections to haematological diseases. However, the histopathological features in bone marrow seldom point to a specific diagnosis. Finally it is clinical, microbiological, radiological and histopathalogical correlation which helps the clinician in formulating a treatment guideline.

Case report

A 57-year-old male presented to us in July 2016 with history of fever of three months duration. Fever occurred daily with multiple spikes of 101° to 102° Fahrenheit. He also reported weight loss of approximately five kilograms over last three months. Clinical examination revealed normal vitals. There was mild pallor and hepato-splenomegaly. He had no rash, joint pains, oral ulcers, genital ulcers, sternal tenderness, gum hyperplasia, cough or chronic diarrhoea. Routine biochemistry and haematology reports are enumerated in Table I.

Table I: Routine haematology and biochemistry reports.

Haemoglobin	8 gm% (13 - 17gm%)
Total leucocyte count	5,000/mm^3 (4,000 - 10,000/mm^3)
Differential leucocyte count	$P_{69} L_{11} M_{18} E_2$
Peripheral blood film	Microcytic hypochromic red blood cells
Blood urea	40.3 mg/dl (10 - 50 mg/dl)
Serum creatinine	1.05 mg/dl (0.7 - 1.2 mg/dl)
ALT	20.8 U/L (1 - 41 U/L)
AST	29.4 U/L (0 - 40 U/L)
Bilirubin	1.047 mg/dl (0 - 1.1 mg/dl)
Alkaline phosphatase	566 U/L (40 - 130 U/L)
Serum albumin	2.18 g/dl (3.97 - 4.95 g/dl)
Serum globulin	6.01 g/dl (3 - 3.7 g/dl)
ESR	22 mm in 1st hour (1 - 14)
C - reactive protein (CRP)	182 mg/dl (upto 6 mg/dl)

Blood and urine cultures were sterile. Chest X-ray was normal and ultrasound whole abdomen revealed hepatomegaly (15.6 cm) and splenomegaly (19.5 cm). He

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was euglycemic and HIV was non reactive. CECT chest and abdomen revealed hepato-splenomegaly. Mantoux test revealed anergy. Serology for brucella was negative. Serum lactate dehydrogenase (LDH) was 169 U/L (135 - 225 U/L). Serum ACE levels were 254 U/L (8 - 65 U/L), however, there was no hypercalciuria [24-hour urinary calcium: 144.4 mg/24 hours (100 - 321 mg/24 hours)]. Anti-nuclear antibodies, dsDNA, rheumatoid factor and anti-CCP were negative. Anti myeloperoxidase (MPO/pANCA) antibodies were 1.15 U/ml (< 9 U/ml) and serine proteinase 3 (PR-3/cANCA) was 1.17 U/ml (< 3.5 U/ml).

Serum ferritin was 575.78 ng/ml (21.8 - 274.6 ng/ml). β-2-microglobulin was 12,936 ng/ml (800 - 2,200 ng/ml). Serum protein electrophoresis revealed presence of restricted band in γ-globulin region along with hypoalbuminaemia and reduced α_2-globulin fraction. 24-hour urinary protein was 45.6 mg (< 150 mg). Serum immunofixation electrophoresis revealed a faint monoclonal band in the gamma region in the reference lane corresponding to IgG and Kappa light chain immunoglobulins along with normal polyclonal immunoglobulins in the background. There were no skeletal lesions on bone scan and whole body PET-CT with contrast was also unremarkable except hepato-splenomegaly.

Bone marrow aspirate revealed cellular reactive bone marrow. Bone marrow biopsy revealed epithelioid cell granuloma with Langerhan's giant cell with negative stains for acid-fast bacilli and fungus (Fig. 1).

Haematologist opinion was also taken and considering the prolonged history and laboratory investigations, four-drug weight based anti-tuberculous therapy was started. Patient remained very apprehensive regarding the course of his illness as he stayed in hospital for around two weeks, remained febrile and was discharged in febrile phase.

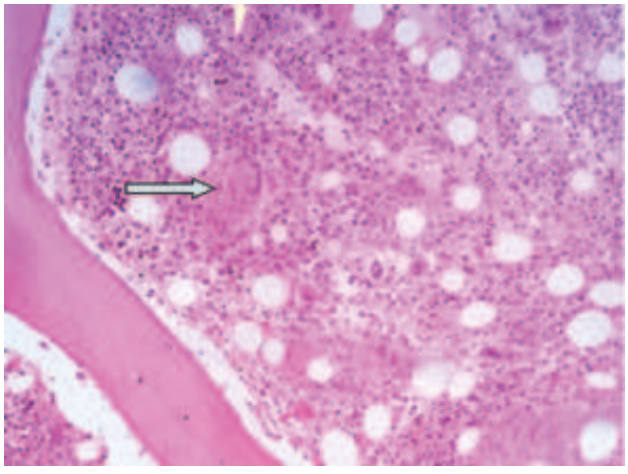

Fig. 1: *H and E stain (10x) of bone marrow biopsy showing epitheloid cell granuloma with Langerhan's giant cell.*

However, he was thoroughly counselled regarding comprehensive and interdisciplinary evaluation and was assured of a positive outcome. He was followed-up every two weeks. He became afebrile at around the third week of anti-tuberculous therapy and there was considerable decrease in the size of liver and spleen. During his last follow-up in November 2016, he was asymptomatic, gained weight, and was clinically unremarkable.

Review of literature

Bone marrow granulomas are infrequently reported in bone marrow biopsy (0.3% to 2.2%). Differential diagnosis of bone marrow granulomas incude viral, bacterial, fungal and parasitic infections, autoimmune diseases, sarcoidosis, and certain types of haematological malignancies. There are certain pathological findings which may point towards a specific disease entity, e.g., caseation necrosis in tuberculosis, Reed-Sternberg's cell in Hodgkin' lymphoma and poorly organised granuloma in HIV infection[1].

Infections which frequently cause bone marrow granulomas include Tuberculosis, Brucellosis, Typhoid fever, Q-fever, Leishmaniasis, CMV, and EBV infections, etc.

Tuberculosis is the most frequently encountered cause of bone marrow granuloma in clinical practice. The incidence ranges from 6% to 48%, world wide. Granulomas are more frequently encountered in miliary tuberculosis for obvious reasons. Disseminated Mycobacterium avium-intracellulare rarely can also produce granulomas in bone marrow. There are anecdotal case records of development of bone marrow granuloma after BCG vaccination also. Caseation necrosis is an uncommon finding in bone marrow granulomas associated with tuberculosis[1,2,3].

Histoplasmosis is the leading cause among fungal infections, giving rise to granulomas in bone marrow, particularly in immunocomprimed settings. In fact, in various studies, bone marrow was the best specimen to recover histoplasma. Caseation necrosis is typically absent in fungal infections[4].

EBV and CMV are the most frequently reported viruses causing bone marrow granuloma. The incidence ranges from 10 - 48%. There are no histopathological characterstics which constitute a pathological hallmark of granulomas caused by viral infections[5].

Bone marrow granulomas are frequently encountered in advanced HIV infection, particularly due to disseminated mycobacterial and fungal infection. Histopathologically granulomas in HIV are subtle, poorly organised and difficult to detect. In a study done by Nicholas *et al,* 80% of granulomas in AIDS were infectious – particularly mycobacterial and fungal (64%). 20 % of granulomas in HIV

infection may remained undiagnosed[4].

Typhoid fever, a commonly encountered infection in India is also associated with development of granulomas in bone marrow. The most important finding on marrow is haemophagocytosis with a chronic inflammatory granulomatous background[1].

After tuberculosis, sarcoidosis is the most frequent cause of bone marrow granuloma. The incidence ranges from 3% to 32%. Pathologically, granulomas are non specific and diagnosis is a combination of clinical, laboratory (serum ACE levels, 24-hour calcium) and radiological findings. A point worth noting is that raised serum ACE level are frequently found not only in sarcoidosis but also in various other conditions, notably, tuberculosis[6].

Hodgkin's and non-Hodgkin's lymphoma are the leading cause of bone marrow granulomas among haematological malignancies. A bone marrow granuloma in patients with Hodgkin's lymphoma can be due to the invasion of the bone marrow or, more frequently, a nonspecific immunologic change. Its presence has been associated with a good prognosis. The finding of a Reed-Sternberg's cell within the granuloma is rare. Distinguishing between sarcoidosis and Hodgkin's disease granuloma can be difficult, if based on pathological criteria only. It is rare for a non-Hodgkin's lymphoma to present initially as a bone marrow granuloma. In non-Hodgkin's lymphoma, especially with follicular small cleaved cells, mixed small cleaved cells, and large cells, granulomatous lesions are sometimes observed. Such lesions consist of a large cell centre surrounded by small cells and clusters of epithelialised histiocytes, giving the appearance of a granuloma. Distinguishing this lesion from a true epithelioid granuloma can be difficult. Immunophenotyping can be helpful in such cases[1,7].

Various drugs are also implicated in development of bone marrow granuloma. Of particular importance are: Penicillamine, Phenytoin, Methyldopa, Allopurinol, Ibuprofen, and Sulfonamides, etc.

Finally, as many as 13% of the cases of bone marrow granuloma are of undetermined origin[8].

To summarise, the histological findings of a bone marrow granuloma are rarely pathognomonic. Still, the importance of bone marrow examination in a case of undiagnosed fever cannot be undermined. Tuberculosis, sarcoidosis, histoplasmosis, typhoid fever, and lymphoma are the most important causes of granulomas in bone marrow and the differential diagnosis can be narrowed down by an astute clinician by thorough clinical examination and interdisciplinary (laboratory and histopathological) evaluation.

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CASE REPORT

JIACM 2018; 19(1): 65-66

Antibiotic-associated Encephalopathy: A Case of Cefepime-induced Myoclonic Encephalopathy

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Abstract

Antibiotics are known to have neurological side-effects, affecting either the central nervous system, peripheral nervous system, or both. Predominant and troublesome central nervous system side-effects are seizures, myoclonus, encephalopathy and peripheral neuropathy. We report a case of myoclonic encephalopathy in a middle-aged diabetic patient with normal renal function, on treatment with cefepime, for Enterobacter cloacae foot infection. Neurological symptoms resolved completely with withdrawal of the drug.

Key words: Myoclonus, encephalopathy, antibiotics, cefepime.

Introduction

Antibiotics are known to have neurological side-effects affecting either the central nervous system, the peripheral nervous system, or both. Predominant and troublesome central nervous system side-effects are seizures, myoclonus, encephalopathy and peripheral neuropathy. Distinguishing a causative drug from endogenous aetiologies in hospitalised patients can reduce morbidity and the cost of treatment. We report a case of cefepime induced myoclonic encephalopathy, which subsided with withdrawal of the drug.

Case report

A 61-year-old female diabetic under treatment for the past 10 years with associated peripheral neuropathy and peripheral vascular disease was admitted to our hospital with non-traumatic, non-healing ulcer on the right sole over the first metatarsal head. Investigations revealed normal liver and renal functions, and elevated total leucocyte counts. Surgical debridement of the wound was done. Pus c/s showed growth of MRSA and *Enterobacter cloacae*. Patient was initated on therapy with cefepime and vancomycin, based on culture and sensitivity of the organism.

After 4 days of therapy, the patient developed jerky movements of all 4 limbs suggestive of myoclonus with delirium. There was no focal neurological deficit. MRI brain was normal, as shown below. EEG showed diffuse slowing suggestive of metabolic encephalopathy. However, all metabolic parameters were normal.

At this juncture, the prescription of this patient was reviewed to rule-out a drug-induced myoclonus. Cefepime induced myoclonus was considered, the drug was discontinued and replaced with injectable meropenem. Myoclonus subsided in 3 days, and the patient recovered uneventfully.

Discussion

Central nervous system complications secondary to antibiotics have been recently termed and classified as antibiotic-associated encephalopathy. They are classified into

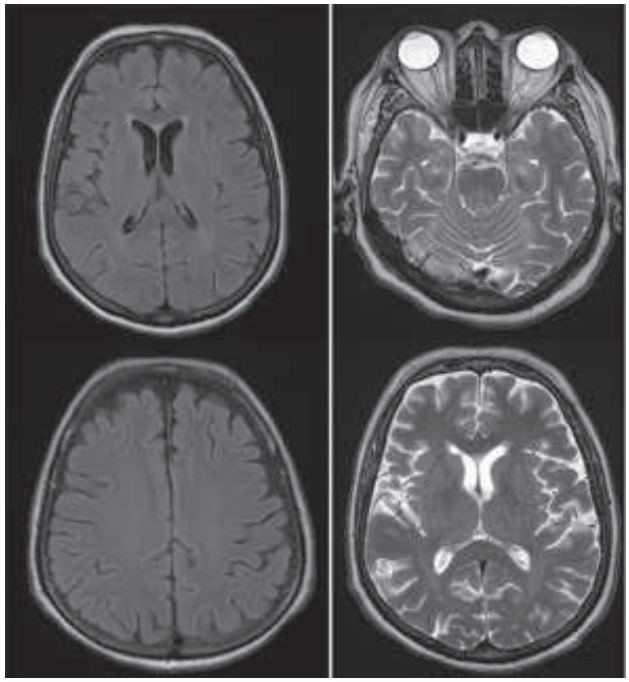

Fig. 1: *T2 and FLAIR sequences of MRI brain showing normal brain image.*

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three groups predominantly, encephalopathy with seizures/ myoclonus, encephalopathy with psychosis and encephalopathy with cerebellar symptoms. Most common antibiotics associated with these complications are pencillins, cephalosporins, macrolides, quinolones, and metronidazole[1].

Mechanisms explaining cephalosporin neurotoxicity are two-fold. One is by reducing GABAergic activity in central nervous system by inhibiting the binding of GABA to GABA-A receptors, resulting in neuronal hyperexcitation and epileptogenicity. The other is by induction of endotoxins and the release of cytokines causing neurotoxicity[2].

In a study by Fugate *et al*, cefepime-related neurotoxicity was observed in 15 of 100 patients treated for various indications with cefepime in ICU, depressed level of consciousness (n = 13), myoclonus (n = 11), disorientation (n = 6), and NCSE (n = 1) patients. Symptoms were seen at a median of 3 days of treatment, mean age group of 69 years, mean dose of 2.5 gm per day and predominantly with renal dysfunction (72%)[2]. Similarly in various case reports on cefepime-related neurotoxicity published previously, renal impairment and age above 65 years were predominant risk factors[3-7].

Cefepime is eliminated predominantly by glomerular filtration; serum levels rise with decrease in renal function. Additionally, in patients with underlying kidney injury, increased permeability of the blood-brain barrier secondary to increased urea predisposes patients to neurotoxicity[2]. Multiple co-morbidities, underlying infection, and drug polypharmacy might contribute to the clinical picture[3-8].

Our patient had diabetic nephropathy (serum creatinine of 1.2 mg/dl), and was treated with normal dose of cefepime. Age was probably her only risk factor. Symptoms were observed after 4 days of treatment with cefepime, establishing a temporal correlation to the introduction of the drug.

Antibiotic-induced myoclonus is probably more common with the widespread use of these drugs for treating various infections. Early identification of the causative drug, and discontinuation will reduce morbidity and prolonged hospitalisation in patients.

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CASE REPORT

JIACM 2018; 19(1): 67-69

A Young Hypertensive with a Neck Mass with Pyrexia of Unknown Origin (PUO)

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Abstract

Takayasu arteritis is a rare auto-immune disorder involving large vessels and mainly affecting young adults. It has idiopathic origin as the exact aetiopathogenesis is not known.It is more common in Asians than other racial groups and can present with varied clinical presentations. Herein we present the case of a 21-year-old male who presented to our OPD with a large neck swelling and primary/idiopathic hypertension with PUO, and later turned out to be a case of Takayasu arteritis.

Keywords: Takayasu arteritis, tuberculosis, vascuilitis, PUO.

Introduction

Takayasu arteritis is an idiopathic, rare autoimmune disorder which results in chronic granulomatous inflammation of medium and large arteries, mainly aorta and its branches, hence also called aortic arch syndrome. It can involve all layers of the arterial wall.This chronic inflammatory process leads to a sequelae of fibrosis, thrombosis, stenosis, and aneurysm formation. It usually affects young female adults in their 2nd and 3rd decade of life[1]. Its aetiopathogenesis is poorly understood, with autoimmune as the most widely accepted aetiology. However, genetic and environmental factors also play some role. A few studies have shown that among the environmental factors, *Mycobacterium tuberculosis* might have some role in the aetiopathogenesis of Takayasu arteritis as both diseases have similar pathological picture with formation of granulomas in the arterial wall[2].

Case report

A 22-year-old young male presented to us with the chief complaints of a large swelling on left side of neck with low grade fever since the last 1 month. Fever was low-grade, continuous, with no diurnal variation, was associated with chills, rigors, night sweats and weight loss, and was relieved on taking medications. It was also associated with headache, and a feeling of spinning of the head.There was no history of breathlessness, chest pain, palpitations, pedal oedema, claudication, or Raynaud's phenomenon. No history of any joint pains, rashes, head injury, blurring of vision, haemoptysis, loss of consciousness or any syncopal episode could be elicited. There was no past history of a similar episode or any history of diabetes, hypertension, tuberculosis in self or family. He was a non-alcoholic and a non-smoker. No history of any other substance abuse or any high risk behaviour could be elicited. The family history was also not significant. Routine and special investigations including typhoid, dengue, and malaria serology were unremarkable. Bone marrow aspiration, chest X-ray, and ultrasound of abdomen were non-contributory. He was advised FNAC of left neck mass in ENT clinic considering it as lymphadenopathy. Initial FNAC revealed blood only; however, a repeat FNAC revealed occasional few giant cells granulomas. Patient was given some antibiotics and NSAIDs but to no relief. His head spinning slowly became troublesome and later for the management of high blood pressure, he was referred to medical OPD. He had hypertension since the last 11 months and was on amlodipine, losartan and hydrochlorthiazide prescribed by a private practitioner. His initial work-up for the cause of hypertension at a private clinic was non-contributory, and hence, he was labelled as a case of essential hypertension.

On examination, the patient was conscious and oriented to time, place, and person. His pulse was 92 beats per minute, regular, normal in volume, with no special character, no radio-radial or radio-femoral delay and all peripheral pulses were comparable and palpable. No bruit was present.The blood pressure was178/100 mmHg in both upper limbs and was 158/110 mmHg in bilateral lower limbs. The respiratory rate was 16 breaths per minute and regular and the patient was afebrile. There was no pallor, icterus, cyanosis, pedal oedema, clubbing or skin rash and JVP was not raised. There was a large neck swelling (Fig. 1) on left side just below the angle of jaw measuring 2 x 2 cm, firm in

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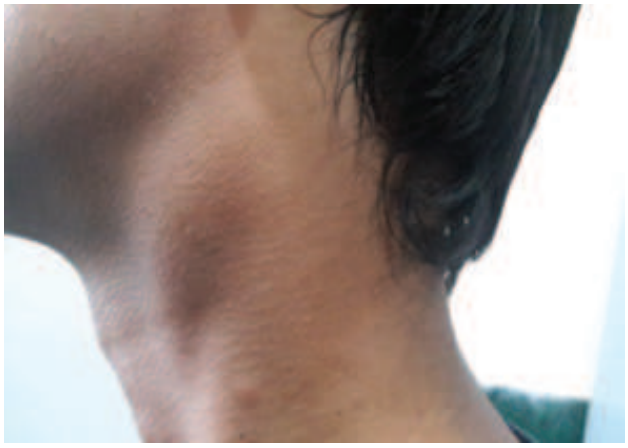

Fig. 1: *Neck swelling.*

consistency, pulsatile and mobile side to side. No surrounding erythema, rash, or discharging sinus was seen. No other lump or swelling was palpable anywhere else.The rest of systemic examination was within normal limits.

His routine investigations were normal except markedly high ESR and CRP. His HIV/ HBsAg/anti-HCV was negative. However, Mantoux test was strongly positive (19 x 20 mm) and IGRA (TB Gold) was also positive. Chest X-ray, USG abdomen and 2D Echo were normal. Patient had a Hb of 9.0 gm/dl, TLC - 7,700/mm^3, platlet count - 3.6 l/mm^3, PCV - 31.2%, CRP - 20 mg/dl, RBS - 94 mg/dl, blood urea - 16.9 mg/dl, s. creatinine - 1.1, s. uric acid - 3.0, T. BIL - 0.5 mg/dl, s. sodium - 135 meq/l, s. potassium - 3.2 meq/l, T. cholesterol - 137 mg/dl, triglyceride - 80 mg/dl, TSH - 1.67, ANA was negative.

Serum renin, serum aldosterone and 24 hour urinary vanillyl mandellic acid (VMA) levels were not increased. However, his bilateral renal artery Doppler showed significant increase in diastolic flow, with *parvus tardus* waveforms in right renal artery suggestive of medical renal disease secondary to right renal artery stenosis with compensatory hypertrophy of left kidney which showed normal Doppler study. Unilateral renal artery stenosis and significant hypertension in a young male, not responding to 3 anti hypertensive drug treatment, pointed towards some vasculitis and hence a CECT neck chest and abdomen was adviced which showed circumferential wall thickening of left common carotid, proximal external and internal carotid artery along with involvement of arch of aorta, circumferential thickening of descending aorta from level T4 vertebrae involving coeliac trunk, superior mesenteric, inferior mesenteric, and common iliac artery along with marked dilatation of descending aorta (8 cm) suggestive of takayasu arteritis (type 3), shrunken right kidney (7.0 x 3.1 cm) with maintained corticomedullary differentiation with hypertrophied left kidney (12.2 x 6.7 cm). MRI renal

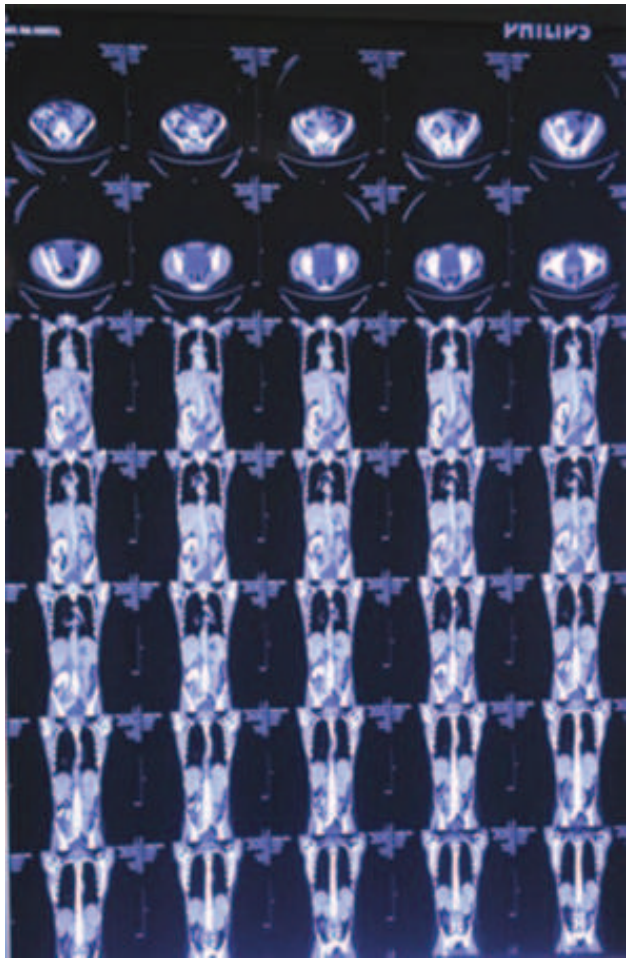

Fig. 2: *CT Aortography showing occlusion in descending aorta.*

angiography was suggestive of right renal artery stenosis. Ultrasound of neck showed diffuse circumferential intimal wall thickening in left carotid artery more marked at the region of bulb. Doppler ultrasound of neck arteries showed diffuse circumferential concentric thickening of left-sided common carotid artery (111 cm/s), external carotid artery (86 cm/s), internal carotid artery (80 cm/s) and vertebral artery (44 cm/s) with anterograde flow. Right common

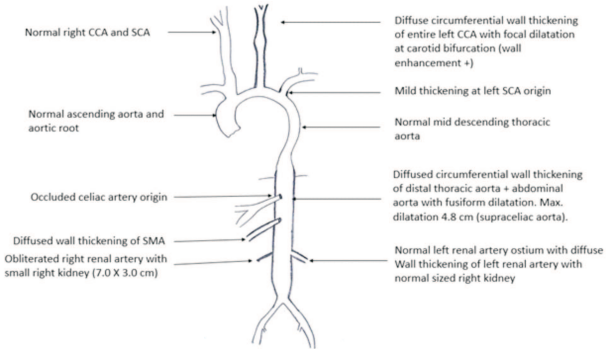

Fig. 3: *Diagram showing widespread aorto-arteritis.*

carotid, external carotid , internal carotid and vertebral artery showed normal wall with no evidence of any plaque or stenosis.

Hence, a diagnosis of large vessel vasculitis (Takayasu arteritis) with probable infective arteritis (tuberculous) was made and the patient was started on steroids along with anti tubercular therapy. Patient's general condition improved. His fever abated and appetite improved. There was a significant reduction in the size of neck swelling and his blood pressure normalised with 5 mg amlodipine twice daily and 12.5 mg hydrochlorthalidone once daily. He was referred to department of cardiology for renal stenting and department of CTVS for management of carotid obstruction, and has since been monitored regularly.

Discussion

Takayasu arteritis a.k.a aortic arch syndrome, a.k.a pulseless disease, a.k.a Martorell syndrome, is an inflammatory and stenotic disease of large and medium sized arteries characterised by chronic inflammation leading to thickening of vessel wall, fibrosis, stenosis, and thrombosis. It has strong predilection for the arch of aorta and its branches. The aetiology of Takayasu arteritis is unknown. Autoimmunity has been the most widely accepted aetiology of Takayasu arteritis; however, there have been studies which suggest other causes such as tuberculosis[2]. Both the diseases share similar pathological changes in the form of chronic inflammatory lesion, occasionaly granulomas on arterial walls. The exact genetic relationship between these two diseases have not been established yet, but both the diseases have been found to be associated with human leukocyte antigen (HLA) alleles[3], cold agglutinins and cryoglobulins during the acute phase of illness[4]. It has also been speculated that *Mycobacterium tuberculosis* can be the triggering factor in inducing vascular damage through production of super antigens, which is thought to act via stimulation of auto – reactive T cells which further cause vascular damage[5]. The initial presenting symptomatology is also quite similar in both diseases which include night sweats, fever, loss of appetite, joint pains, malaise, weight loss which may occur months before vessel get involved. Later vascular compromise and organ ischaemia may happen. As in our patient, the presenting complaint was a neck swelling which was initially thought to be cervical lymphadenitis. However, ultrasound neck and Doppler proved it to be vessel wall thickening. In our patient presence of high erythrocyte sedimentation rate (ESR) (90 mm in 1st hour) , strongly positive Mantoux test (19 x 20 mm), TB gold, and constitutional symptoms like low-grade fever suggested tuberculosis. But, young hypertensive along with the presence of symptoms like spinning of head, headache, vessel wall thickening suggested another aetiology. Our patient was a male and had comparable peripheral pulses and blood pressure in all 4 limbs which is very rare in Takayasu arteritis.

In our case, we could not demonstrate definite active tuberculosis; however, the diagnosis of tuberculosis was presumptive based on high ESR, Mantoux, TB gold and clinical symptoms which resolved promptly with anti-tuberculous therapy, and steroids. The literature also hypothesises the auto-immune basis and not a direct role of mycobacterium. Arnaud *et al* failed to detect mycobacterium in arterial lesions of either active or inactive TA but it did not exclude the possibility of cross-reactivity between mycobacterium and arterial antigens[6]. Recently, Soto *et al,* identified in a case control study, a higher frequency of IS6110 and hupB gene sequences of *Mycobacterium tuberculosis* and bovis in aortic tissue of patients with Takayasu arteritis and in TB compared to patients with atherosclerosis with important statistical differences suggesting that arterial damage could occur due to previous infection with MTB[7]. Finally, the exact pathogenic sequence between Takayasu arteritis and tuberculosis remain to be elucidated.

Conclusion

This case report highlights the atypical presentation of Takayasu arteritis with probable tuberculous arteritis in the form of neck swelling with hypertension and PUO, but with normal peripheral pulses with laboratory evidence of tuberculosis which responded well to ATT in our case.

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CASE REPORT

JIACM 2018; 19(1): 70-73

Guillaine Barré Syndrome Presenting Unusually as Bilateral Claw Hand

Aanchal Arora, Manasa Mudalagiri**, Deepali Sharma**, YC Porwal****

Abstract

Guillaine Barré syndrome (GBS) is an immune mediated acute neurological illness affecting the peripheral nervous system and leading to significant morbidity. It has been classified into demyelinating and axonal forms on the basis of electrodiagnostic techniques. AMAN (acute motor axonal neuropathy) variant is a distinct subgroup of GBS as it may present as weakness of finger extensors apart from causing symmetrical weakness, thus presenting as claw hand. However, prognosis is good with rapid recovery. We present a young male with acute onset weakness of small muscles of both hands, abnormal flexion deformities along with gradually progressive weakness of all four limbs. On the basis of electrodiagnostic studies and CSF analysis, a diagnosis of GBS (AMAN variant) was made. The patient experienced complete recovery four weeks after treatment with intravenous immunoglobulin. Thus, early recognition of atypical forms of GBS can lead to specific treatment.

Key words: Guillaine Barré syndrome, AMAN, claw hand.

Introduction

Guillaine Barré syndrome (GBS) is an acute neurological illness affecting the peripheral nervous system. It affects 1-4 per 1,00,000 of the population, annually throughout the world[1]. It can lead to significant morbidity and mortality. It has been classified electrophysiologically into ADP (acute demyelinating polyneuropathy, AMAN (acute motor axonal neuropathy) and AMSAN (acute motor-sensory axonal neuropathy)[2]. AMAN and AMSAN varieties may follow infection with *Campylobacter jejuni*. AMAN is a distinct subgroup in GBS, commonly seen in the paediatric and young age group. Patients typically have high titres of antibodies to gangliosides (i.e., GM1, GD1a, GD1b). It is generally characterised by rapidly progressive symmetrical weakness and ensuing respiratory failure. It shows certain distinguishing features, the most notable being predominant weakness of finger extensors and paucity of cranial nerve involvement. One-third of patients with AMAN may actually be hyperreflexic. We present the case of a young male who presented with bilateral claw hand as an unusual presentation of GBS (AMAN variant). Prognosis is often quite favourable in AMAN and recovery for many is rapid as was also seen in our case.

Case report

A 20-year-old male presented to our hospital in the first week of June 2017 with acute onset weakness of small muscles of both hands for past two days. A day before, the weakness was preceded by pain and abnormal tingling sensation in both lower limbs. He was unable to button and unbutton his clothes and perform other fine movements of the hand. He also developed abnormal flexion deformities of fingers of both hands. On the day of admission, he had difficulty in wearing and holding his slippers, which gradually progressed to inability to walk without support. On day 3, the weakness ascended to involve his upper limb as he was also unable to lift his arm overhead. However, he was able to feel the clothes and slippers he wore.

There was no history of difficulty in breathing, speaking, or swallowing. There was no complaint of abnormal facial deviation, double vision, or head dropping. There was no history of bladder or bowel involvement, palpitations, diaphoresis, or postural giddiness. There was no back pain, root pain, or abnormal band like sensation. There was no history of fever, vaccination, sore throat, diarrhoea, or skin rash. No significant chronic medical illness was found. No history of drug abuse, addictions or toxin exposure.

On examination, he was conscious, oriented, and afebrile to touch. He was normotensive with normal pulse and respiratory rate. Single breath count (SBc) was 38. General physical examination was normal (Fig. 1). Neurological examination revealed normal higher mental function. Cranial nerve examination was normal. Muscle tone and power was reduced at all joints in all four limbs. Power was grade 2 at ankle and wrist joint, respectively and grade 3 at knee, hip, elbow and shoulder joint, respectively. On testing the small muscles of hand, there was more weakness of finger extensors as compared to flexors, thus demonstrating clawing or the finger drop sign bilaterally (Fig. 2).

In the light of the above findings, a provisional diagnosis of

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acute motor polyneuropathy – probably Guillaine Barré syndrome (GBS) with bilateral claw hand was made. Routine investigations were sent on day 1. Complete haemogram, random blood sugar, liver, kidney function tests including serum electrolytes were within normal limits (Table I). Nerve Conduction Study (NCV) and cerebrospinal fluid (CSF) examination was performed on day 2 to confirm the diagnosis.

Fig. 1: *Figure showing the 20-year-old male.*

Fig. 2: *Figure showing bilateral complete claw hand on admission.*

Compound motor action potential (CMAP) amplitude were decreased in bilateral ulnar, tibial, and right common peroneal nerve. Sensory nerve conduction was normal. Absent F waves in all sampled nerves .These findings were consistent with Acute Motor Axonal Neuropathy (AMAN) variant of GBS. CSF examination revealed albumino-cytological dissociation (Table I).

Table I: Table showing laboratory investigations of the patient.

Investigations	Value
Hb	13.2 g/dl
TLC	8,600/mm3
ESR	17 mm/hr
Platelets	2,80,000/mm3
RBS	91 mg/dl
Bil/SGOT/SGPT/ALP	0.3/31/17/126
BU/Creat	37/0.4 mg/dl
Na+/k+	140/3.5 meq/l
Ca++/PO4++	9.5/5.0 mg/dl
Albumin/Globulin	3.6/3.4 g/dl
CSF cells	5/mm3
Albumin	120 mg/dl

In view of disease progression on day 3, the patient was treated with Intravenous; Immunoglobulin (IVIg) at a dose of 400 milligram/kg body weight daily for five days. Simultaneously exercises were advised for physical rehabilitation of the patient. SBC was monitored daily and weakness did not progress further. Further, his stay was uneventful as he showed signs of recovery after five days of IVIg treatment. At day 7, he was able to walk without support, hold his slippers, and comb his hair. However, lifting objects overhead and fine hand movements could not be completely performed as clawing had only partially improved (Fig. 3). Plantar reflex was flexor, and all deep tendon reflexes were 2+. Thereafter he was discharged and followed up 3 weeks later when he showed complete recovery and clawing improved (Fig. 4).

Discussion

GBS is an acute neurological illness affecting the peripheral nervous system. It can lead to respiratory failure

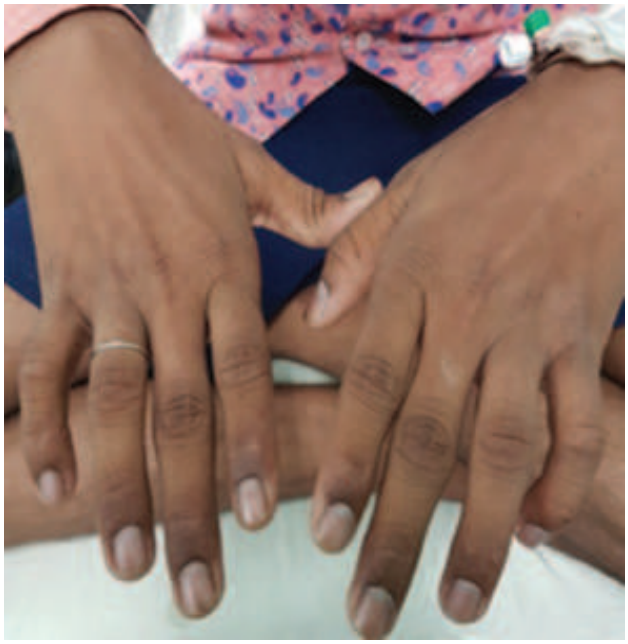

Fig. 3: *Figure showing partial recovery of claw hand at 1st week.*

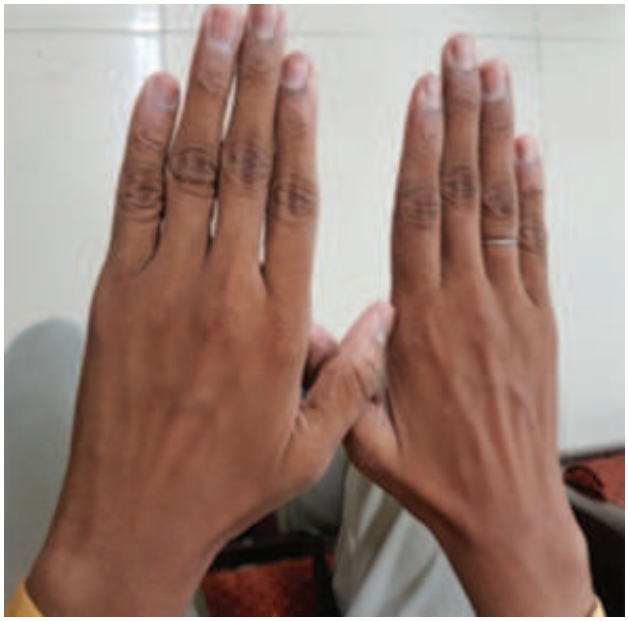

Fig. 4: *Figure showing complete recovery of claw hand at 4 weeks.*

requiring ventilation in approximately 25%, death in 4 - 15%[3,4,5], persistent disability in approximately 20%[6] and persistent fatigue in 67%[7] cases. It has been classified electrophysiologically into demyelinating and axonal forms. The acute inflammatory demyelinating polyneuropathy (AIDP) subtype is the most commonly identified form. It is generally preceded by a bacterial or viral infection. Nearly 40% of patients with AIDP are seropositive for *C. jejuni*. Symptoms generally resolve with remyelination.

AMAN is a distinct subgroup in GBS, commonly seen in paediatric and young age group. Patients typically have high titres of antibodies to gangliosides (i.e., GM1, GD1a, GD1b). Particularly in the Indian context, the clinical features of the axonal variant (acute motor axonal neuropathy-AMAN) are not well characterised. It is generally characterised by rapidly progressive symmetrical weakness and ensuing respiratory failure. It shows certain distinguishing features, the most notable being predominant weakness of finger extensors and paucity of cranial nerve involvement. This paucity of cranial nerve involvement is specific for AMAN. Viser *et al*[8] in their study on pure motor forms of GBS also observed the same. One-third of patients with AMAN may actually be hyperreflexic.

George *et al*[9] in their small series found that AMAN patients had a characteristic pattern of severe distal upper limb weakness with varying degrees of proximal weakness. This pattern consisted of severe finger extensor weakness (i.e., at the metacarpophalangeal and interphalangeal joints) in the presence of relatively normal power in finger flexion, wrist flexion and wrist extension-the "finger drop sign" .This finger extensor weakness was bilateral in all the AMAN patients. Predominant weakness of finger extensors seems to be relatively specific for the AMAN variant of GBS.

Tsivgoulis *et al*[10] described bilateral claw hand to be caused by weakness of intrinsic hands muscles due to affection of median and ulnar nerve in GBS. Complete recovery was documented four weeks later following treatment with intravenous immunoglobulin.

Paliwal *et al*[11] revealed demonstrable conduction blocks, delayed distal latencies, slowed conduction velocities and normal sensory conductions in another 2 cases of "finger drop sign".

In a retrospective cohort study of 464 consecutive patients with GBS, Moris *et al*[12] found that 33 (7%) of the patients had hand-onset GBS. Weakness was limited to the upper limbs in four patients (12%), while it spread to the legs in all the other 460 (88%).

Prognosis is often quite favourable in AMAN and recovery for many is rapid. Patients with AMAN were considered to have greater long-term disability[13] whereas patients with AIDP were generally at high risk for rapid deterioration and need of mechanical ventilation[14].

Similarly, our case also presented with predominant weakness of bilateral finger extensors along with ascending weakness of all four limbs and did not show any demyelinating features electrophysiologically. There was complete recovery four weeks following treatment with IVIg.

Conclusion

Early recognition of atypical manifestations of GBS variants has a strong clinical impact, as it helps in overcoming the differential diagnostic hindrances and leads to the specific treatment as early as possible.

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PICTORIAL CME

JIACM 2018; 19(1): 74-75

Fundoscopy Unravels Mystery of PUO

M Mahesh, N Jeswanth Reddy***

A 25-year-old male presented with history of moderate grade fever of one-and half-months duration. He had history of cough with mucoid expectoration but denied history of breathlessness, headache, joint pains, or weight loss. He was a chronic smoker and alcoholic.

On examination, he was moderately built and nourished. Mild pallor was present. There was no icterus or lymphadenopathy. Pulse Rate was 90 bpm regular BP: 120/70 mmHg, temperature: 101° F. Respiratory system examination revealed a few crackles in infrascapular and infraaxillary areas. Other systems were unremarkable. Fundoscopy done at the bedside by the physician was suggestive of choroid tubercle (Fig. 1). Fundus findings were confirmed by the ophthalmologist. Chest X-ray showed miliary mottling (Fig. 2). HIV was negative.

The above findings of choroid tubercle and chest X-ray features clinched the diagnosis of disseminated tuberculosis.

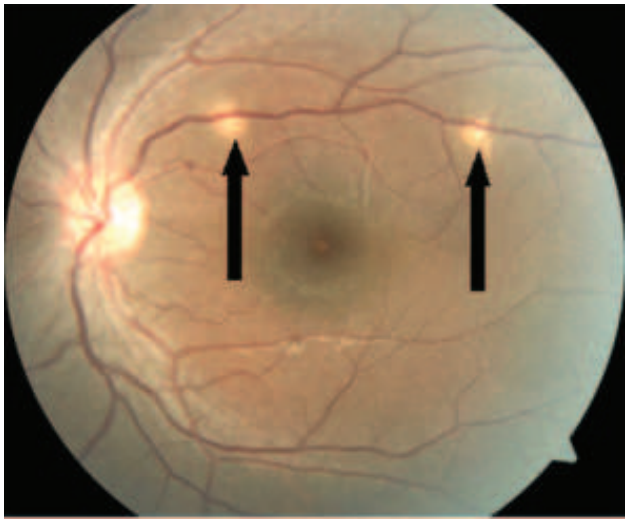

Fig. 1: *Pale, yellowish lesions located near the optic nerve.*

Discussion

Fundoscopy is nowadays a neglected art as far as physicians are concerned. Most physicians lack proper technique of fundoscopic examination, and therefore refer the patient to an ophthalmologist. In this case, fundoscopy was done by the physician and yielded rich dividends. A bedside procedure revealed the final diagnosis even before imaging studies, chest X-ray, haematological and serological investigations.

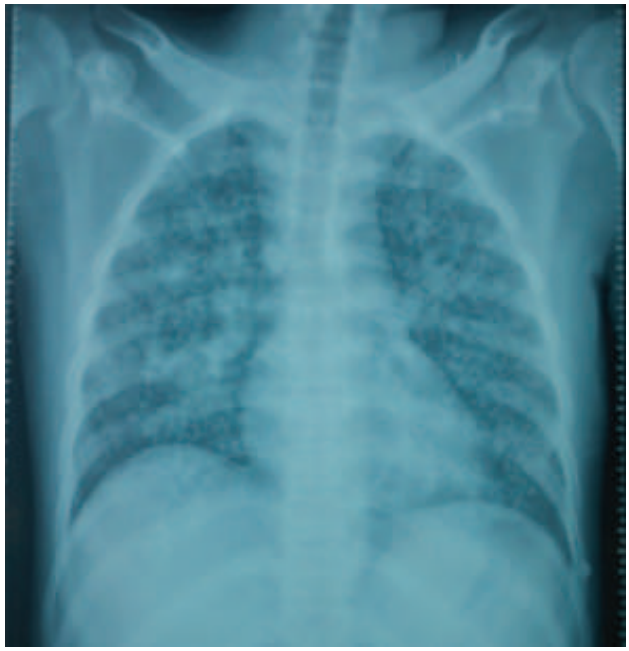

Fig. 2: *Miliary opacities in both lung fields.*

Choroidal tubercles are an important and highly specific manifestation in patients with pulmonary and systemic tuberculosis[1]. Haematogenous spread of *Mycobacterium tuberculosis* leads to formation of choroidal tubecles[2]. They are of two types; solitary tubercle or granuloma (seen in chronic tuberculosis) and choroidal miliary tubercles (seen in acute miliary tuberculosis)[3]. The tubercles are located deep in the choroid, are usually unilateral, may be solitary or multiple lesions, yellowish, with indefinite borders and located in the posterior pole. They vary in their presentation with features such as associated haemorrhage, striae, or exudative retinal detachment[4]. Macular involvement may cause visual loss, and delay in appropriate treatment results

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in irreversible visual loss. Peripherally situated tubercles are asymptomatic. Untreated tubercles can grow into a large tumour-like mass called tuberculoma. Delay in treatment, or misdiagnosis, may lead to irreversible visual loss[5]. Differential diagnosis for choroid tubercles are Roth's spot, and cotton wool spot. Roth's spots are retinal haemorrhages with a pale centre and are associated with bacterial endocarditis. Cotton wool spots appear as fluffy white patches on the retina and are associated with diabetes. The importance of diligent fundoscopic evaluation by the physician is, again, emphasised by the above case.

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