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ASSAM JOURNAL OF INTERNAL MEDICINE

Official Journal of Association of Physicians of India, Assam Chapter

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Editorial

Organophosphorous Poisoning

S. M. Baruah*

Introduction :

Organophosphorous poisoning has become one of the major health problems globally over the past few decades. These compounds have been easily accessible and widely used as pesticides since the Green revolution in 1960s. Organophosphorus (OP) pesticide self-poisoning or attempted suicide is the most important global form of acute poisoning, affecting over one million people each year and killing around 100,000[1]. These are irreversible cholinesterase inhibitors . Some of these have also been used in the medical treatment of myasthenia gravis, e.g. diisopropylphosphorofluoridate (DFP), tetraethyl pyrophosphate (TEPP), and octomethyl pyrophosphotetramide (OMPA). Some OP esters are still used to treat glaucoma (Ecothiopate). In addition to these beneficial agricultural and medical uses, some highly potent OP anticholinesterase compounds, including tabun, sarin, soman, and VX have been used as "nerve gases" in chemical warfare. They are also been used as plasticizers, stabilizers in lubricating and hydraulic oils, flame retardants, and gasoline additives.[2]

Epidemiology :

Organophosphorous poisoning accounts for about 80% of pesticide related hospitalizations.[3] The first global estimates of the extent of pesticide poisoning were published in 1990 by the World Health Organisation[4]. 3 million cases of pesticide poisonings were reported worldwide annually with 2,20,000 deaths. The potential adverse impact on human health from exposure to pesticides is likely to be higher in countries like India due to easy availability of highly hazardous products, and low risk awareness, especially among children and women. The effective number of cases of pesticide poisoning occurring in India annually has been estimated by G. Ravi et al in 2007 to be up to 76,000, much higher than the figure of NCRB. Furthermore, Gunell et al, 2007 calculated that the number of intentional cases alone reaches some 126,000 cases annually.[5]

Pathophysiology and Toxicology :

The first organophosphorus (OP) compound tetraethyl pyrophosphate (TEPP) was synthesized by de Clermont in France. Later, von Hofmann synthesized methyl-phosphoryl dichloride (Fest & Schmidt, 1982). Organophosphate compounds avidly bind to cholinesterase molecules and share a similar chemical structure. Cholinesterase is responsible for rapid hydrolysis of acetylcholine (Ach) after completion of neurochemical transmission. The major toxicity of organophosphate compounds is the covalent binding of phosphate radicals to the active sites of the cholinesterases, transforming them into enzymatically inert proteins.[3,6] Thus it inactivates the enzyme irreversibly. The inhibition of cholinesterase activity leads to the accumulation of acetylcholine at synapses, causing overstimulation and subsequent disruption of transmission in both the central and peripheral nervous systems.

They can be broadly classified into:

1.NERVE AGENTS :

A) G AGENTS – sarin , tabun , soman

B) V AGENTS – VX, VE

2.INSECTICIDES :

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A) DIMETHYL COMPOUNDS- dichlorvos , fenthion, malathion

B) DIETHYL COMPOUNDS- diazinon , parathion, chlorpyrifos

Kinetics : The degree of absorption depends on the contact time with the skin, the lipophilicity of the agent involved and the presence of solvents, for example xylene, and emulsifiers in the formulation which can facilitate absorption. For powders, the finer the powder the more rapid and complete is skin absorption.[2] These compounds accumulate rapidly in fat, liver, kidneys and salivary glands. The phosphorothioates (P=S), for example diazonin, parathion, and bromophos, are more lipophilic than phosphates (P=O), for example dichlorvos, and are therefore stored extensively in fat which may account for the prolonged intoxication and clinical relapse. These lipophilic compounds can cross the blood brain barrier. Elimination of metabolites occurs mostly in urine with lesser amounts in faeces and expired air.

Clinical Manifestations :

Organophosphates stimulate both the sympathetic and parasympathetic nervous systems. A typical clinical scenario will involve symptoms of overstimulation of the parasympathetic system. An exception is in children, as they typically have a predominance of symptoms mediated by nicotinic receptors.[7]

The common mnemonic that captures the muscarinic effects of organophosphate poisoning is DUMBELS:

D = Defecation/diaphoresis
U = Urination
M = Miosis
B = Bronchospasm/bronchorrhea
E = Emesis
L = Lacrimation
S = Salivation.

The nicotinic effects are :

Muscle Fasciculations
Paralysis
Pallor
Muscle weakness
Hypertension
Tachycardia
Mydriasis (rare)

Other clinical features include anxiety, confusion, drowsiness, emotional lability, seizures, hallucinations, headaches, insomnia, memory loss and circulatory or respiratory depression. The most common cause of death is respiratory failure which can be due to bronchoconstriction, bronchorrhea, central respiratory depression or weakness/paralysis of the respiratory muscles. The patient may develop long term complications if he/she survives the acute poisoning.

Table 1 : Clinical Features of OP Poisoning Based on time of Manifestations[8]

Time of manifestation	Mechanism	Manifestation
Acute (minutes to 24-h)	Nicotinic receptor action	Weakness, fasciculations, cramps, paralysis
	Muscarinic receptor action	Salivation, lacrimation, urination, defecation, gastric cramps, emesis, bradycardia, hypotension, miosis, bronchospasm
	Central receptors	Anxiety, restlessness, convulsions, respiratory depression
Delayed (24-h to 2-week)	Nicotinic receptor action	Intermediate syndrome
	Muscarinic receptor action	Cholinergic symptoms-bradycardia, miosis, salivation
	Central receptors	Coma, extra-pyramidal manifestations
Late (beyond 2-week)	Peripheral-neuropathy target esterase	Peripheral neuropathic process

Intermediate neurologic symptoms typically occur 24 to 96 hours after exposure. Symptoms include neck flexions, weakness, decreased deep tendon reflexes, cranial nerve abnormalities, proximal muscle weakness, and respiratory insufficiency. With supportive care, these patients can have a complete return to normal neurologic function within 2 to 3 weeks.

Evaluation :

Diagnosis of OP poisoning is strictly clinical. Most of the times, no history of exposure or ingestion of organophosphates is obtained. Therefore, clinical manifestations and a characteristic garlic or petroleum odour should point towards OP poisoning. A trial of atropine may be employed. If symptoms resolve after atropine injection , this increases the likelihood of an acetylcholinesterase inhibitor poisoning.

Laboratory Findings :

Routine investigations are usually unremarkable. However in some cases , few derangements have been noted. Non-ketotic hyperglycaemia , glycosuria and hypokalemia have been observed in numerous case reports.. Leukocytosis, both with and without a left shift, was a common finding in Hayes's study[9]. Elevated serum amylase secondary to pancreatic injury because of parasympathetic overstimulation and hypersecretion has been noted in human beings. The ECG may display a variety of abnormalities in acute organophosphate poisoning like, sinus bradycardia, atrioventricular block, and ST&T wave abnormalities and prolongation of the Q-T interval also has been commonly observed.[2] Red blood cell acetylcholinesterase activity helps in diagnosis, however it is not easily available.

Management :

Severe OP poisoning is a medical emergency. The first step is to put on personal protective equipment. These patients may still have the compound on them, and we must protect ourself from exposure.

1. Patient should be decontaminated. All clothings should be changed. The patient's skin needs to be flushed with water. Dry agents such as flour, sand, or bentonite also can be used to decontaminate the skin.

2. Airway , breathing , circulation should be secured. The patient should be placed in the left lateral position, with the neck extended. Treatment must ensure that the patient has a patent airway and adequate breathing and circulation. Ideally, oxygen should be provided at the first priority.

3. Lavage should be considered only if the patient arrives within 1 hour of ingesting poison. Gastric decontamination should only be done after the patient has been stabilized and treated with oxygen, atropine and an oxime. Activated charcoal can be given if the patient presents within 1 hour of ingestion, but studies have not shown any benefit.

4. The definitive treatment for organophosphate poisoning is atropine, which competes with acetylcholine at the muscarinic receptors. The initial dose for adults is 2 to 5 mg IV or 0.05 mg/kg IV for children until reaching the adult dose. If the patient does not respond to the treatment, double the dose every 3 to 5 minutes until respiratory secretions have cleared and there is no bronchoconstriction. In patients with severe poisoning, it may take hundreds of milligrams of atropine given in bolus or continuous infusion over several days before the patient improves.[7]

5. Oximes reactivate acetylcholinesterase inhibited by organophosphorus compounds. WHO recommends oxime in all symptomatic patients who need atropine.[10] A bolus of at least 30 mg/kg in adults or 20 to 50 mg/kg for children should be given over 30 minutes. Rapid administration can cause cardiac arrest. After the bolus, a continuous infusion of at least 8 mg/kg/hr for adults and 10 to 20 mg/kg/hr for children should be started and may be needed for several days.[11,12]

Other oximes used are :

Obidoxime should be administered in adults at dose of 250mg given by slow intravenous injection followed by continuous infusion of 750 mg/24 h (0.4 mg/kg/h) to reach plasma concentrations of 10–20 μmol/L.[2]

Asoxime (HI-6): Clinical studies showed that HI-6 dosed at either 250mg or 500mg by intramuscular route reached plasma concentrations >4 mg/L in 4–6 min.[2]

6. Acutely agitated patients can be given benzodiazepines. Diazepam is the benzodiazepine of choice.

7. Other therapies:

- Magnesium sulphate blocks ligand-gated calcium channels, resulting in reduced acetylcholine release from pre-synaptic terminals, thus improving function at neuromuscular junctions, and reduced CNS over-stimulation mediated via NMDA receptor activation.
- The alpha2-adrenergic receptor agonist clonidine also reduces acetylcholine synthesis and release from presynaptic terminals. Animal studies show benefit of clonidine treatment, especially in combination with atropine, but effects in human beings are unknown.
- Removing OP from the blood could allow optimum action of other therapies. The roles of haemodialysis and haemofiltration are not yet clear; however, a recent non-randomized controlled study in China suggested a benefit of haemofiltration after poisoning with dichlorvos, which has poor solubility in fat and therefore should have a relatively small volume of distribution.

Newer Therapies :

- Butyrylcholinesterase scavenges OP in plasma, reducing the amount available to inhibit acetylcholinesterase in synapses. It has been cloned and military research now aims to inject soldiers with the enzyme before exposure to OP nerve gases. Such a prophylactic approach is not practical for self-poisoning with OP because we cannot predict when a person is going to ingest the pesticide.
- Recombinant bacterial phosphotriesterases, or hydrolases breakdown OP pesticides enzymatically and protect from poisoning. Future clinical development of such enzymes could reduce blood concentrations of OP, allowing optimum activity of other treatments.[13]
- HUPERZINE A : HupA has been proven to be a powerful, highly specific, and reversible inhibitor of acetylcholinesterase. It was developed in China for treatment of Alzheimer's disease. HupA has better penetration through the blood–brain barrier, higher oral bioavailability, and longer duration of AChE inhibitory action.
- ZT-1 : ZT-1 has similar properties to HupA regarding the ability to cross the blood–brain barrier, its oral bioavailability, and its longevity of action.
- **Butane - 2, 3-dionethiosemicarbazone** is an oxime with antioxidant properties. It has been demonstrated that butane-2,3-dionethiosemicarbazone has an antioxidant activity in scavenging different forms of reactive species.
- ANTI – OXIDANTS : The toxicity of OP compounds is mediated by generation of nitric oxide and other free radicals. These toxic molecules can be counteracted by antioxidants such as vitamins C and E, spin traps, melatonin and low molecular weight thiols.

Challenges Ahead :

Debilitating and deadly diseases that can be caused or spread by pests such as insects, rodents,and microbes pose a serious risk to public health. Due to the toxicity of pesticides and the risk involved in treatments, there is general agreement that emphasis should be on preventing pesticide illness rather than relying on treatment. Easy availability of these compounds in the market and inadequate knowledge of utilizing these pose a challenge.

Conclusion :

Organophosphorus compounds have become increasingly popular for agricultural, industrial and home use and represent a significant potential health risk. Prompt recognition and aggressive treatment of acute intoxication are essential in order to minimize the morbidity and mortality from these potentially lethal compounds. Hence , proper training should be given to the farmers who use these compounds. Proper use of gloves and washing of hands after use should be taught. Prevention is always better than cure.

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Original Article

Correlation of cholinesterase levels in diagnosis, severity and prognosis in organophosporous compound poisoning

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Abstract

Objectives: We evaluated diagnostic & prognostic reliability of cholinesterase levels and correlated with severity of poisoning (SOP) in organophosphorous compound poisoning (OPCP)

Methods: We assessed cholinesterase levels (Serum and red blood cell (RBC)) in healthy volunteers (reference) and patients with OPCP (test) at admission, days 3, 7, 14, and week 16. SOP was classified as mild, moderate, severe.

Results: Thirty patients, mean±SD age of 26.8±9.56 years were included. Nausea and vomiting (87%) excessive sweating and/or salivation (57%), abdominal pain (37%) were common. Tachycardia (09) was common ECG findign; Bradycardia (03), short PR interval, ST–T changes were in same patients.Mean±SD RBC and Serum cholineesterase levels were 0.996±0.562 U/mL and 1525.867±944.663 U/mL, respectively. There was statistically significant decrease in cholinesterase in test group, in RBCs ($P<0.001$) and serum ($P<0.001$). There was no significant age and gender specific difference. 50.0% had severe (50.0%) degree SOP. Youngerpatients had milder degree poisoning and higher enzyme levels. SOP and enzyme activity were inversely related.

Death (n=04) within 2-4 hours of admission, pulmonary oedema (n=06) requiring respiratory support, aspiration pneumonia (n=05) and comvulsions (n=05) were reported.

Conclusion : Cholinesterase levels reduced in OPCP. Estimation of serum cholineesterase levels can be used as a diagnostic and prognostic tool in OPCP.

Key words: *Acetylcholinesterase, diagnsotic reliability, healthy volunteer, Organophosphorous compound poisoning.*

Introduction :

Agricultural revolution with the use of fertilizers and Organophosphorous compounds (OPCs) is a two edged sword which, on one hand increased agricultural yield, on the other hand not only has hazardous effect on the human health but also resulted in increased use of these chemicals for suicidal purpose[1,2]. In very rare occasions accidental poisoning has been reported. India being an agricultural country, poisoning due to OPC is a frequent clinical encounter in emergency medicine. Varied prevalence rates have been reported from different parts of India and is associated with significant mortality; Jesslin J et al reported the mortality due to insecticides as 40%[2] Mortality rate has been reported to be a low as 20% and as high as 70%[3,4].

Acetylcholinesterase (AchE) an enzyme that catalyses the breakdown of the neurotransmitter acetyl choline (Ach) is increased in the presence of certain AchE inhibitors (AchEIs). OPCs react with the enzyme & form phosphorylated enzyme complex which prevents enzyme's degradation resulting in increased concentration of Ach at the central and peripheral nerve synapses. Thus, OPCs are AchEIs and estimating the AchE would serve a useful diagnostic biomarker in poisoning due to these compounds. AchE present in redblood cells is known as true esterase while that in serum is called pesudocholineserase; though both enzymes have been implicated in the diagnosis of OPC poisoning (OPCP), there is debate over the better indicator among these two. Serum cholinesterase levels were found to be reliable, sensitive biomarker[5,6].

Serum cholinesterase (ChE) assays are useful in the diagnosis of OPC poisoning and also in monitoring the clinical course. Cholinesterase recovery >10% of normal is correlated with good prognosis. Even with the more

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accurate RBC cholinesterase, the point at which various authors have suggested that toxicity begins to appear ranges from 40%-75% of normal values[7,8]. There is inconclusive conclusions on the role of serum and blood cholinesterase in the diagnosis accuracy of OPCP. While few support the determination of AchE activity in whole blood as the most appropriate tool for diagnosis of OP intoxication while others recommend RBC or serum levels.However, there is still no convincing evidence to support the diagnostic role of these enzymes in OPC poisoning.

In the absence of a definite history, establishing a diagnosis and assessing the prognosis is a major hurdle faced by physicians in treatment administration. Hence, we analysed the cholinesterase levels in acute OPCP, evaluated its diagnostic role and accuracy in assessing clinical prognosis.

Materials & Methods :

This clinical prospective study was conducted on inpatients of a tertiary care, teaching hospital after the clearance of institutional ethics committee. Prospective participants were screened after obtaining written informed consent from volunteers, patients and/parents.

This study was conducted to determine the diagnostic and prognostic reliabiltiy of true and pseudocholinesterase activity in OPCP. We also attempted to correlate the levels of these enzymes with the severity of the poisoning (SOP). In addition, we attempted to derive management strategies with reference to cholinesterase levels.

Prospective patients were identified from the acute medical care unit. Patients aged >16 years, admitted with history of ingestion of insecticidal OPCs were included. Poisoning due to other causes was excluded from the study. Detailed history including demography, quantity of ingestion of OPC, time of interval between ingestion and hospital admission were collected. True cholinesterase and pseudo cholinesterase enzymatic estimations were done calorimetrically (kinetic method), at admission, on days 3, 7, 14, and at week 16.Similarly, other laboratory tests including haemoglobin, renal function and Liver Function Tests were performed at admission and days 3, 7, 14 and at week16. Severity of poisoning was classified as mild, moderate and severe based on clinical and laboratory test results. Clinically patients were evaluated daily till the patients were discharged from the hospital.

We conducted this study in two phases. We assessed the cholinesterase levels (Serum and RBC) in healthy volunteers to obtain a reference level among our population and in patients with OPC poisoning. After establishing a reference range of normal blood cholinesterase levels, the levels of enzyme in latter were compared with the reference. Estimation of enzyme activity was mesured as per standard laboratory tests.

Estimation of cholinesterase level in RBC (kinetic method)

2 ml of blood was drawn from the patient in a EDTA bottle and centrifuged at 2000 rpm. Separated Plasma was preserved in the refrigerator; remaining RBC was washed in saline,re-centrifuged and saline was removed. Distilled water was added to RBC to make it upto 10gm% (for calculations), and preserved for estimation of cholinesterase levels in RBC. In the same manner normal samples were collected and estimated.

Principle

The rate of hydrolysis of acetylcholine by a red cell suspension at pH 7.2 was measured at 412nm by the reaction of thiocholine with DTNB to give the yellow 5-thio-2-nitrobenzoateanoin (molar absorptivity, 13.6×10 6 L/mol/cm). The activity is expressed per litre of packed red cells.

Reagents

- Phosphate buffer, 50mmol/L in 9g/L sodium chloride, Ph 7.2
- Substitute solution, acetylthiocholine iodide, and 31mmol/L. The stock reagent is available (Boehringer Coorparation) at a concentration of 156mmol/L, Diluted with water 1 in 5 for use.
- Colour reagent, DTNR 250micromol/L, in phosphate buffer, 50mmol-L, pH7.2. (Broehinger Coorparation).
- Sodium chloride, 9g/L.

Technique

The fractional packed cell volume (PCV) of the anticoagulated blood sample was determined. 100µL blood in a glass tube of 100×12mm was taken, and washed thrice with saline, centrifuging between washes. The last supernant was removed as completely as possible and resuspended the cells in 10ml buffer, mixing well. To 1mL suspension, 4mL buffer and remix was added. Into two

silica cuvettes (1 cm optical path) pipette 2ml(for test) or 2.1ml (for blank) of the colour reagent and 1ml cell suspension to each was added, having ensured that it is homogenous. The cuvvetes were placed in the thermostated (30°C) cuvette holder of a spectrophotometer set to 412nm. 100microL substrate was added to the test, after 3 min. The contents of both cuvettes were mixed and the absorbance of the test against the blank was determined. The readings were repeated every minute for at least 6min, remixing the cuvette contents before each reading. The mean change of absorbance per min (ΔA412/min) was calculated using the following formula -

$$= \frac{\Delta A_{412}/\text{min} \times 500 \times 10^3 \times 10^3 \times 3 - 1}{\text{PCV} \times 13.6 \times 103 \times 1}$$

$$= \frac{\Delta A_{412}/\text{min}}{\text{PCV}} \times 114$$

Reference Value 3 - 8 U/ml

a. Estimation of serum cholinesterase **(Kinetic test)**

Principle:

Butyrylthiocholine is hydrolyzed by cholinesterase to produce thiocholine in the presence of potassium hexocyanoferrate(III), the absorbance decrease is proportional to the cholinesterase activity of the sample.

Reagents:

Reagent I: Buffer Reagent

Reagent II: Butarylthiocholine iodide Reagent

Sample: Serum

Reagent Preparation:

Mix 4 parts of reagent I and 1part of reagent II.

Procedure:

Pipette into Test Tube with 15µL and reagent 1000µL. Mix well and wait for 1 minute. Measure absorbance decrease after 30, 60 and 90 seconds at 405 nm. Determine the change in absorbance per minute.

Calculation and Linearity:

ΔA/ minute X 62000 U/L

This method is linear upto 12000U/L

Reference Values: Serum Cholinesterase levels at 37°C 4850 – 12000U/L

Statistical Analysis

Data was collected on Microsoft Excel worksheets. Analysed data was expressed as descriptive analysis in terms of frequency, mean±SD, percentage and descriptive analysis.

Table 1. Age distribution among the study population

Age group (years)	Female (n%)	Male (n%)	Total (n%)
< 20	7 (23.3%)	2(6.7%)	9 (30.0%)
20-25	6 (20%)	4 (13.3%)	10 (33.3%)
26-30	2 (6.7%)	3 (10%)	5 (16.7%)
31-35	1 (3.3%)	0 (0.0%)	1 (3.3%)
36-40	0 (0.0%)	2(6.7%)	2(6.7%)
> 40	1 (3.3%)	2(6.7%)	3 (10%)

Results :

Phase I – Estimation of cholinesterase levels of volunteers : 10 healthy volunteers with a mean±SD age of 29.8±4.87 yrs. were included. Minimum age of volunteers was 24 yrs. while maximum was 40 yrs. and median of 29 years. Males (N=07, 70%) outnumbered females (n=03, 30%).

The reference range obtained for cholinesterase levels in RBC was 3.1-3.9 u/ml and that for serum was 3988-9890 u/mL from the initial kinetic study.

Table 2. Clinical presentation of Organophosphorous compound poisoning among study population

Symptom	N	Percentage
Nausea and Vomitting	26	87%
Miosis	24	80%
Sweating or Salivation	17	57%
Fasciculation	16	53%
Pulmonary Edima	12	40%
Abdominal Pain	11	37%
Techycardia	9	30%
Hypotonia	7	23%
Coma	7	23%
Hypotension	5	17%
Diarrehoea	3	10%
Bradycardia	3	10%

Table 2 describes the levels of RBC and serum choline sterase levels among healthy volunteers compares with study population.

Phase II : Estimation of cholinesterase in patients with OPC poisoning : 30 patients with history of OPC poisoning were included. Mean±SD age of these patients was 26.8±9.56 years (range 16 - 50 years), median age was 25 years. Patients aged< 25 years were predominant comprising 63.30% of the study population.

There was female (n=17, 56.66%) preponderance over male (N=13, 43.33%) population. Table 1 tabulates gender distribution among different age groups.

Table 3. Spectrum of cholinesterase level among study population

Characteristics	RBC (U/mL)		Serum (U/mL)	
	Reference	Test	Reference	Test
Levels (Mean ± SD)	3.54±0.31	0.996±0.562	688.2±2326.235	1525.867±944.663
95% Confidence Interval	3.316422, 3.753578	0.7863149, 1.205685	5184.112, 8512.288	5184.112, 8512.288
Minimum	3.1	0.2	3968	436
Maximum	3.9	1.9	9890	3900
Median	3.55	0.85	6226	999.5
Clinical significance	Normal	Decreased	Normal	Decreased

All our patients reached the hospital within 4 hours (90%), while only 10% reached between 4-6 hours.

Of the symptoms complained of, nausea and vomiting (n==26, 87%) was the most common presenting symptom; other symptoms included excessive sweating and/or salivation (n=17,57%), abdominal pain (n=11, 37%).Miosis (n-24, 80%) was the frequent sign followed by fasciculation (n=16, 53%), pulmonary oedema (n=1240%).Their clinical presentation is shown in table 2. There was no significant difference in the symptoms among different age groups and between male & female population. Bradycardia documented on ECG was seen in three patients while others had tachycardia (n=09, 30.0%). Bradycardia, short PR interval, ST–T changes were seen in the same patients and one patient had multiple ventricular premature contractions.

Our patients had a Mean ± SD RBC and Serum cholinesterase levels of 0.996±0.562 U/mL and 1525.867±944.663 U/mL, respectively (Table 3). There was a statistically significant decrease in the levels of Acetylcholine sterase in both RBCs ($p<0.001$) and serum ($p<0.001$) compared to the reference. The degree of reduction in both RBCs and serum were in correlation with the each other. There was no significant difference in the reduction of enzyme (serum as well as RBC) level age and gender specific (Table 4).

We categorised patient into mild (n=05, 16.66%) moderate (n=10, 33.3%) and severe (n=15, 50.0%). Younger patients had milder degree of poisoning associated with higher levels of enzymes, while severe forms were seen in higher age group where enzyme levels were significantly reduced. (Table 5)

Table 5. Comparison of severity of symptoms to age and cholinesterase levels

Severity of poisoning (%)	Age (in years)		RBC Cholineesterase (U/mL)		Serum Cholineesterase (U/mL)	
	Mean ±SD	*Range (years)*	*Mean± SD*	*Range (Median)*	*Mean ±SD*	*Range (Median)*
Mild (16.67%) Male – 02 Female - 03	22±4.38	16-28	1.243± 0.55	0.35-1.8 (1.5)	2196.546 ± 961.632	683–3900 (1960)
Moderate (33.33%) Male – 03 Female - 07	27.3±10.1	17-40	1.0643± 0.563	0.2-1.9 (01)	1572.4 ±834.96	696–3014 (1359)
Severe (50%) Male = 08 Female = 07	28.07±9.69	16-50	0.996 ±0.56	0.2-1.9 (0.85)	1179.467 ±840.92	436–3289 (787)

Levels of acetylcholine in red blood cells and serum were compared between healthy volunteers and those who consumed OPC and there was statistically significant ($p<0.05$) difference between these groups. Among the latter group, statistically significant ($p<0.05$) difference in the enzyme levels (both in red blood cells and serum) was noted which varied with severity of poisoning. Enzyme levels were inversely proportional to the severity of poisoning with greater reduction seen in those who had severe degree of poisoning. RBC esterase levels rose at a faster rate compared to serum esterase which was statistically significant ($p<0.05$), but both took longer time to return to normal levels (Mean 7-14 days).

Table 4. Enzyme levels in male and female patients belonging to different age groups.

Acetylcholinesterase	Male			Female		
	16-25 y n=06	26-35y n=03	>35 Y n=04	0-25 Y n=13	26-35 Y n=03	>35y n=01
RBC	0.916	0.76	1.0375	1.074	1.063	0.8
Serum	1876	1752.67	907	1567.46	1552.33	600

All patients, recovered completely except the four who died. The time interval between the ingestion of poison and the treatment is directly proportional to the severity. All patients who recovered showed rising levels of both erythrocyte and serum cholinesterase, though the rise of

plasma was much slower and lower than erythrocyte cholinesterase levels.

Figures 1 & 2 depict the changes in the cholinesterase levels during the course of the treatment.

There were twenty severe adverse events in our study; death (n=04) within 2-4 hours of admission, pulmonary oedema (n=06) requiring respiratory support in terms of assisted ventilation, aspiration pneumonia (n=05) and convulsions (n=05). Four patients who died, had low levels of both RBC and serum choline sterase levels. However, we could not correlate enzyme levels in these patients.

Discussion :

Deliberate self-harm by suicidal poisoning is common all over the world. Organophosphorous compound poisoning is the common poisoning reported by various studies. Workers in agriculture and in organic chemical industries are subjects to poisoning by inhalation of these materials or by contact with them. Jesslin et al reported 71% of all poisoning cases were due to OPC poisoning[2]. Younger patients (<30 yeasr) were more likely to consume OPCs[9]. In our Hospital, OP poisoning constituted for more than 92% during the study period. Increase in stress because of unemployment, poverty and conflicting relationships in young couples.

Diagnosis is based on the clinical features; however, certain laboratory investigations aid in arriving at an appropriate diagnosis, and in assessing the prognosis. Levels of AchE is one such laboratory assessment useful to assess the severity of poisoning and prognosis. RBC cholinesterases are better correlators of CNS toxicity and are considered to be useful markers a good indicator of OP poisoning. Serum cholinesterase levels are influenced by many factors such as potency of the OP compound, production in the liver, temperature variations etc, and on repeated testing, variation in the level has been shown upto 50%.Cholinesterase levels in serum are useful as an indicator of possible insecticide poisoning, for the detection of patients with atypical forms of the enzyme or as a test of liver function.

The levels indicate normal muscle functioning and thus indirectly the requirement of atropine; those with at least 30% enzyme activity generally do not require atropine.

If enough material is absorbed to inactivate all the actylcholinesterase of nervous tissue, results in death. A 40% drop in serum enzyme activity occurs before the first symptoms are felt, and a drop of 80% is required before neuromuscular effects become apparent. Near zero levels of enzyme activity require emergency treatment of the patient with such enzyme reactivators as pyridine-2-aldoxime because of the increased mortality [10]. A 50% reduction in the RBC cholinesterase levels indicates organophosphorous toxicity, and these levels are more reliable than serum values in diagnosing the poisoning [11]. Aygun D et al did not find significant difference in the serum AchE levels in their patients and did not correlate with symptom severity and development of neurological symptoms. They did not find any significant difference in the enzyme levels in those who died during the study period; however, there was significant difference in the serum enzyme levels on day 1 and on last day in those who survived. Thus, it was concluded that low levels can support the clinical diagnosis in acute poisoning but does not correlate with symptom severity[12].

Indian study has reported that poisoing was more common in younger age group (mean 25.5 years, range 21-30 years) and males (65.7%). Peripheral symptoms were mainly ophthalmic findings i.e., congested conjunctiva (87%), pin point pupil (83%), lacrimation (80%), and non-reactive pupil (75%); vomiting (78%), respiratory distress (60%) and abdominal pain (37%) were other symptoms. Mean (SD) PChE was 3672.4 (4200.1) IU/L. At presentation >75% reduction in enzyme activity was associated with cyanosis, muscle weakness, convulsion, respiratory distress and fasciculation that indicated severity of poisoning and poor prognosis, while, ophthalmic symptoms (constricted and non-reactive pupil, lacrimation and congested conjunctivae) correspondened to 50-75% reduction. Enzyme activity <50% corresponded to less severe symptoms and abdominal pain, dryness of conjunctiva, vomiting and diarrhea. Respiratory distress resulted in death in the patients who died in this study and these patients had the lowest mean PChE level at baseline (1270.2). This study proved relationship between plasma ChE levels, clinical presentation and prognosis in Indian population[13]. Venkateshwarulu et al, reported that patients aged 31-40 years were the most affected. Greater percentage (63.30%) of our study population were <25 years. Clinical presentation was similar to the previous studies[14].

Clinical correlation of changes in the cholinesterase levels in RBC and serum poses difficult as there have been reports of variation in normal range among individuals; it is interesting to note that the levels vary within the individual during different phases. Variation from laboratory to laboratory is also reported[15]. Hence, interpretation of the results is crucial in clinical practice and requires accurate clinical judging as severe toxicity may be seen in few with upper level of the normal range and even with effective treatment, levels may come down to the levels which may be on the lower limit of the normal range. Hence, we decided to establish the normal range of RBC (3.54±0.31U/mL) and serum cholinesterases (688.2±2326.235 U/mL) in volunteers as one part of our study.

Inhibition of the both erythrocyte and plasma cholinesterase activity in OP poisoning is well proved and we too observed the reduction in levels of both enzymes in all cases. Assessing the levels of these enzymes can help the physician in diagnosis when the history is less reliable. In our study, decreasing enzyme was seen till the first week of treatment, which gradually increased over a period of time;however, clinical improvement was observed much earlier to this, in few cases as early as first week. This observation is in similar lines with that of Bobba R et al[16], Y amanaka S et al[17], Brahmi N et al[18].

We noted a reductin of enzyme levels upto 70% nearly in all patients supporting the fact that it can serve as a diagnostic tool and determinant of therapeutic outcome. Previous studies have suggested the diagnostic reliability of estimation of cholinesterase in OP poisoning[14,19]. Estimation of serum cholinesterase level has proved an easy method not requiring technical expertise and any special equipments, less time consuming. In addition, these kits are readily available[14].

Our study proves the diagnostic and prognostic reliablity of estimating the serum cholinesterase levels in patients with OPCP, supporting the observations of Chaudhary et al[6] and Hiremath P et al[20].

Small sample size was the limitation suggesting the need of studies in larger population. We did not correlate the time lapse between time of OPC consumption and initiation of treatment. We did not assess the technical ease in estimating both enzyme levels. Though we observed the effects of pralidoxime clinically, we did not substatiate and correlate with enzyme levels. Despite these limitation, our study supports the diagnostic utility of serum cholinesterase levels in OP poisoning.

Proper handling of the sample, maintainance of correct temperature are required for enzyme assessmnet to obtain reliable result. Understanding and interpretation of the assay is utmost important particularly among the primary health care providers for better treatment plan.

Conclusion :

OP poisoning is still the most opted chemical for self poisoning. Cholinesterase levels are reduced in OP poisoning. Clinical symptom severity depends on the percentage reduction below the normal range. RBC cholinesterase levels rise earlier than serum cholinesterase levels. Estimation of serum cholinesterase levels can be used as a diagnostic and prognostic tool in the management of OP poisoning.

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Article Submission

ASSAM JOURNAL OF INTERNAL MEDICINE

Manuscript Submission : Check list for Contributors

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Original Article

A Study of the Clinico-Etiological Profile of UTI in Patients of Type 2 Diabetes Mellitus in A Tertiary Care Hospital of Upper Assam

P Dihingia[*], D Choudhury[**], S M Baruah[***], T K Das[***], C Dutta[****]

Abstract

Introduction: Patients with type 2 diabetes mellitus are more prone to infections, most commonly of the urinary tract. Numerous explanations exist like hyperglycemia induced autonomic neuropathy, urine with high glucose load acting as a culture medium and immune compromise in diabetes. **Aims and objectives:** To find the prevalence of UTI in patients of type 2 diabetes mellitus and to study the clinical profile. **Materials and Methods:** This is single centre, prospective, observational study carried out in all patients of type 2 diabetes mellitus aged 30 years and above admitted in Medicine Unit-5 of Assam Medical College and Hospital, Dibrugarh in the period from March 2016 to February 2018. Pregnant and oncology cases were excluded. Data were collected in a proforma which included particulars of the patient, duration of diabetes and the clinical features at presentation. **Results:** Out of 301 taken up for study, 12 were asymptomatic and had no evidence of UTI in routine urine examination. Of the remaining 289, 181(62.6%) were males and 108(37.3%) were females. 94(32.5%) had evidence of UTI as defined by the above criteria. Of these 94 with UTI, 58(61.7%) were females and the rest 36(38.3%) were males. *E. coli* was the most common organism, followed by *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. However, majority of the samples turned out to have no growth after 48 hours of incubation. Fever as a presenting complaint with no other source of infection was present in only 5 cases(5.3%) but was present in 21 cases(22.3%) of the study group if all infective causes were combined. Dysuria was present in 13 cases(13.8%) and lower abdominal pain in 10 cases(10.6%). 49 cases(52.1%) were asymptomatic and were incidentally found to have evidence of UTI. **Conclusion :** Diabetic patients have an increased risk of UTI. If not detected early, it can cause significant morbidity and mortality. It is a potential source of sepsis. Hence, all diabetic patients should be routinely screened for UTI.

Keywords: *Diabetes mellitus, UTI, clinical features, etiologic agent.*

Introduction :

Type 2 diabetes mellitus is a heterogeneous group of disorders which share the common feature of hyperglycemia. Patients with type 2 diabetes mellitus are more prone to infections, with the urinary tract being the most frequent infection site[1-4]. Potential explanation of the increased risk of urinary tract infection (UTI) in diabetic patients might be the hyperglycemia induced autonomic neuropathy that results in dysfunctional voiding. This in turn leads to a persistent residual urine volume and reduced physical clearance of bacteria with micturition[5,6]. Another explanation may be high glucose levels in urine improve the growth of the bacteria in the urine[7]. Moreover, diabetes mellitus is an immune-compromised state. There is decrease in certain cytokines such as IL-6 and IL-8 in the urine of diabetic patients[8] which may increase the risk of developing infection.

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Aims and objectives :

1. To find the prevalence of UTI in patients of type 2 diabetes mellitus.

2. To study the clinical profile of UTI in the same group of patients.

Materials and Methods :

This is single centre, prospective, observational study carried out in all patients of type 2 diabetes mellitus admitted in Medicine Unit-5 of Assam Medical College and Hospital, Dibrugarh in the period from March 2016 to February 2018. Data were collected in a proforma which included particulars of the patient, duration of diabetes and the clinical features at presentation.

Inclusion criteria : 1. Type 2 diabetes mellitus patients above the age of 30 years admitted in Medicine

Unit-5 of Assam Medical College and Hospital, Dibrugarh.
2. Informed and written consent.

Exclusion criteria:

1. Type 1 diabetics.
2. Pregnant women.
3. Known malignancy.
4. Refusal to give consent.

A total of 301 patients were taken up for study after fulfilling the above criteria. All patients had routine examination of their urine. 289 patients having either of or a combination of dysuria, lower abdominal pain, fever, urinary catheterization>5 days, presence of more than 2 pus cells and/or bacteria in urine were subjected for urine culture and sensitivity testing. Blood samples were collected for the estimation of total leukocyte count, fasting, 2-hr post-prandial plasma glucose levels and HbA_1c levels.

Urine Collection and Processing :

Clean voided midstream morning urine samples were collected in sterile urine collection containers. All urine samples were inoculated using a calibrated inoculation needle with 10µL of urine and each sample was inoculated on two types of media: blood agar and MacConkey agar plates. All plates were incubated at 37°C for 24–48 hours for visible growth.

Identification of Isolated Micro-organisms:

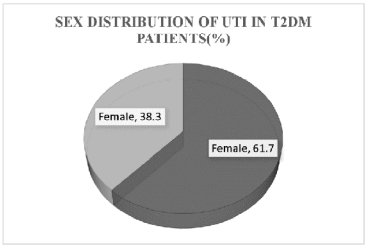
Urine samples that were considered to be positive for UTI were:

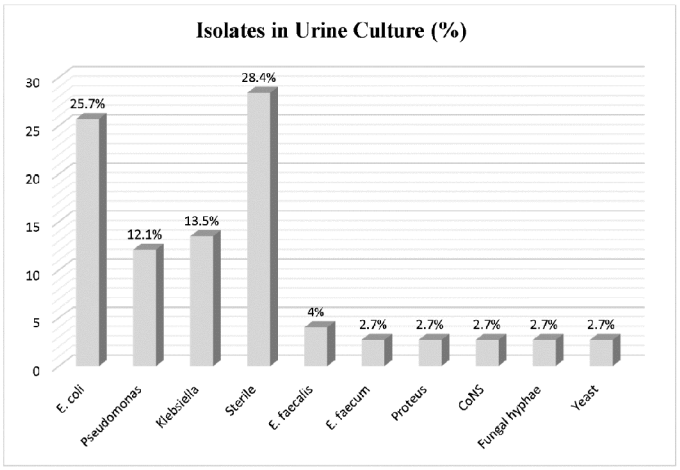
1. $\geq 10^4$ cfu/mL of urine in males.
2. $\geq 10^5$ cfu/mL of urine in females.
3. $\geq 10^3$ cfu/mL from a new catheter urine specimen in those with prolonged catheterization (>5 days).

UTI isolates were identified based on colony characteristics, lactose fermentation, and biochemical tests.

Results :

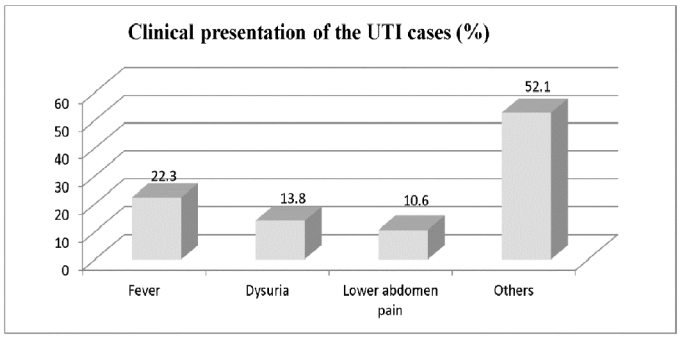
Out of 301 taken up for study, 12 were asymptomatic and had no evidence of UTI in routine urine examination. Of the remaining 289, 181(62.6%) were males and 108(37.4%) were females. 94(32.5%) had culture positive UTI as defined by the above criteria. Of these 94 with UTI, 58(61.7%) were females and the rest 36(38.3%) were males.





E. coli seemed to be the most commonly isolated organism, followed by *Klebsiella pneumonia* and *Pseudomonas aeruginosa*. However, majority of the samples turned out to have no growth after 48 hours of incubation.

Among the clinical features, it was found that most of the patients presented with symptoms not attributable to UTI. Fever as a presenting complaint with no other source of infection was present in only 5 cases(5.3%) but was present in 21 cases (22.3%) of the study group if all infective causes were combined. Dysuria was present in 13 cases(13.8%) and lower abdominal pain in 10 cases(10.6%). 49 cases(52.1%) were asymptomatic and were incidentally found to have evidence of UTI.



22 cases had evidence of sepsis. The average duration of diabetes was 2.5 years and the mean HbA_1c was 8.21%. 28.3% of the 112 with good control of plasma glucose($HbA_{1c} < 7\%$) had UTI while 44.1% of the remaining 177 with poor control had UTI.

Discussion :

Pontin et al[9] found also found that E.coli followed by Klebsiella were the most commonly isolated organisms. Similar results were obtained by Manjunath et al[10] and Sewify et al[11].

Moreover, those with poor glycemic control had greater risk of UTI as shown in the studies of Sewify et al[11] and Nigussie et al[12].

Conclusion :

Diabetic patients have an increased risk of UTI. Most of the patients seek medical care due to some other pathology and UTI is an incidental finding i.e. asymptomatic bacteruria is the most common presentation. These patients also have poor blood glucose control as reflected by the high HbA_1c levels. Thus, all diabetic patients should be screened regularly for the presence of UTI.

Limitations :

1. Small sample size.
2. Only hospitalized cases were taken up for study.
3. Most of the patients were already started on antibiotics, either before reaching our hospital or before urine samples were obtained. This might account for the majority cases turning out to be sterile on culture.

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Original Article

Evaluation of risk factors with special reference to carotid artery stenosis among ischemic stroke subjects admitted in a tertiary care hospital of Tripura

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Abstract

Tripura is a land-locked hilly state in the north-eastern corner of the country, inhabited by tribal and non tribal population of various religions with diverse food habits. CVA both ischemic and non-ischemic is common in both the population. Till date various studies have been done to correlate the development of stroke and its risk factors around the globe. The present study is the first scientific approach done at our state done to evaluate the risk factors responsible for ischemic strokes. Hypertension & hyperlipidemia are important risk factors associated. CIMT was also determined in all cases and positive co-relation was found with hyperlipidemia. Atherosclerotic carotid arteries were found to cause non-lacunar infarction more and it was statistically significant.

Key words : *Cerebro-vascular accident (CVA), hyperlipidemia, atherosclerosis, artery stenosis, CIMT (carotid artery intimal media thickness).*

Introduction :

Cerebro –vascular accident is an important issue. The Global burden of Diseases, Injuries and Risk factors ranked CVA as the second most common cause of death and the third leading cause of disability.

It occurs at an early age in our country as there is poor control of risk factors in comparison to our western counterparts. Simultaneously there is paucity of data about CVA regarding both mortality and morbidity from this part of our nation and more so from our state of Tripura.

We are already aware that there are host of risk-factors for ischemic strokes and unhealthy life style and food habits further contributes to hypertension, hyperlipidemia, diabetes mellitus & obesity which are known established risk factors along with smoking and ethanol abuse as major contributory factors.

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Carotid artery stenosis due to deposition of atheromatous plaque is one of the major issues for CVA occurrence.

Young age stroke in our state is a burning problem and it's attributed to uncontrolled risk factors & hence evaluation of risk factors is essential along with early detection for prevention of ischemic strokes.

This study done at our institute is the first of its kind carried out in our state of Tripura which deals with the demography and risk factors of ischemic stroke with special reference to carotid artery stenosis & it's subsequent with co-relation with hyperlipidemia.

Objective :

1. To evaluate the risk factors of ischemic strokes patients of Tripura
2. To study the demographic pattern of the patients with ischemic strokes.

Materials and Methods:

This descriptive cross-sectional study was done at AGMC & GBP Hospital Agartala. All patients both male and female with clinical presentation suggestive of CVA & radiological evidence showing 'Ischemic Stroke' are

included in our study, subjected to our inclusion and exclusion criteria.

Exclusion criteria includes patient with ICH ,TIA, recurrent CVA, death within one day of admission, refused for consent & patients on anti-coagulant therapy.

This study had approval from the Ethics Committee of our institution and all participants provided consent in written. Total numbers of patients included are 124.

All patients were first analysed for clinico-demographic profile which included parameters like age, gender, religion, ethnicity, socio-economic status, educational background, urban or rural residence and occupation.

Glasgow Coma Scale was calculated and Modified Rankin Scale was applied in each patient to judge the clinical status at admission & discharge both and to assess the mortality prognosis for each patient respectively. Patients were then analysed and investigated for all possible risk factors, namely hypertension, diabetes, hyperlipidemia & obesity by means of clinical history, clinical examination and subsequent blood bio-chemical investigations. Investigations that all patients are subjected with are Neuroimaging of brain (CT-Scan & MRI), ECG, Echo-cardiography, Carotid artery Doppler(intimal media thickness or CIMT measured with B-MODE ultrasound using linear probe at frequency of 9-11 MHz) and blood biochemistry which included Blood Sugar, KFT, LFT, Lipid Profile and Serum Electrolytes. All relevant data so collected were analysed with SPSS 15.0 Version & Chi-Square test was employed to find statistical difference in risk factors between various stroke subtypes. The p value < 0.05 was considered as statistically significant for all tests.

Results and Analysis :

Among 124 patients maximum patients were above 60yrs (61.3%) were below 40 age group affected is 10.5% .The proportions of male candidates were more (70.25%) than the females. Hindus were more than other religions, as the area was Hindu dominated 65.3% are non-tribal population belonging to Bengali community and Tribal population was 34.7%. Rural populations were more than urban (75%). And coming to educational status it was significantly seen that 41.9% of the study population are of primary educational status which dominated the study group and above higher secondary it was 6.5%. Most of them at the time of study were unemployed (79.8%).Most of the study population were of low-socioeconomic status

Parameter	**Male** N = 87	**Female** N = 37
Tribal	33	10
Non tribal	54	27
Rural	60	27
Urban	27	10
Primary edu- status	61	30
Higher Sec. Edu-status	26	07
Low socio-economic class	67	30
Upper middle class	20	07

(76.6%) and 23.4% were from upper socioeconomic status.

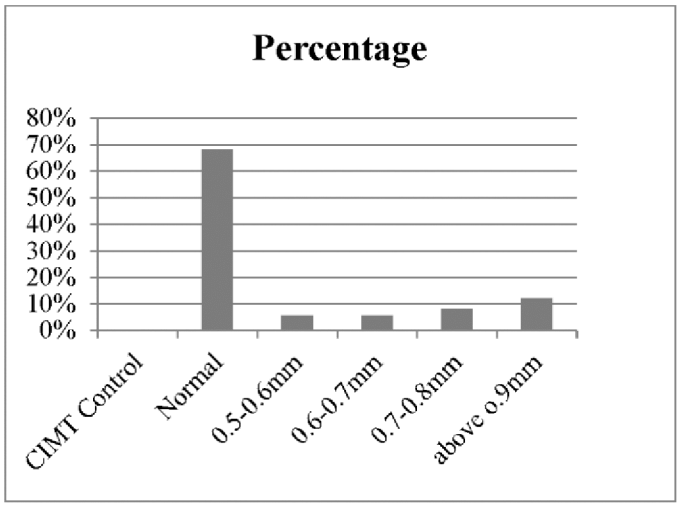
In analysis of risk factors hypertension was found in 68.5% of cases and 31.5% was non hypertensive. The frequency of Diabetes Mellitus was 36.3% & 73.4% of the study group was found to be hyperlipidemic. Among these dyslipidemic subjects 15.3% had hypercholesterolemia, 13.7% had high LDL & 7.3% had hypertriglyceidemia, mixed hyperlipidemia was seen in 27.4%. However only 10.5% was found to be obese.54.8% of the patients were smokers and ethanol abuse was found in 21.0%. 10.5% of patients had previous history of CAD & atrial fibrillation was seen in 11.3% .Most of the patients had normal echo-cardio graphic findings (83.9%) and LVH was seen in 10.5% and motion wall abnormalities in 5.6% of cases.

PARAMETRS	RISK FACTORS
Hypertension	68.5%
Diabetes	36.3%
Hyperlipidemia	73.4%
Obesity	10.5%
No physical activity	93.5%
Smoking	54.8%
Ethanol abuse	21%

Those who were found to be non-hypertensive (31.5%), amongst them diabetes was seen in 45% cases and 91% of non-hypertensive were found to be dyslipidemic. And 68% of them were smokers.

CIMT	PERCENTAGE
NORMAL	68.5%
0.5-0.6mm	5.6%
0.6-0.7mm	5.6%
0.7-0.9mm	8.1%
More than 0.9mm	12.1%

Carotid Doppler was studied in all cases and artery involvement was seen in 31.45% of



cases and 68.55% cases had normal carotid arteries. Of the carotid artery involvement we had the following finding-

Neuro-imaging study (both CT-Scan & MRI was done as per clinical requirement) showed lacunar infarction in 21% cases and non lacunar infarction in 79% cases. During this study we had a death frequency of 12.1% cases.

Discussion :

In our observational study it was found that non-lacunar infarction (79%) were more. Maximum numbers of patients were elderly though percentage of young patient below 40yrs was also significant and was 10.5%. All of these young patients are of low socio-economic status with poor educational background and all of them had four risk factors namely poorly controlled hypertension & diabetes and had hyperlipidemia. All of them are smokers and had ethanol abuse and are male patients. We found a male dominance in the study population which is similar with most of the demographic profile of CVA studies done earlier. There is however no significant relationship between gender variation and ischemic stroke subtypes. In our study most of the subjects are from rural background with poor socio-economic status and had poor control of hypertension and diabetes. Though it's a Govt.hospital and it is expected that poor people will come and avail hospital facilities but this is entirely not true as this is the one of the two tertiary care hospital of the state and people of higher socioeconomic status also avails hospital facilities from this hospital and in this study it was 23.37%.

Various studies were done to support the risk factors for stroke and in our study 68.5% was found to be hypertensive establishing hypertension as the major risk factor. This finding is consistent with other studies conducted by Memon AR et.al(61%) & Kaul et.al(62%).Of the hypertensive patients in our study a significant number 92.3% had lacunar infarction. Diabetes was seen in 36.3% and is consistent with study of Kaul et.al (38%).It was also found that among the diabetic patients 56.69% had lacunar infarction and they do have simultaneously non involvement of carotid arteries. Other study done by Jackson & Sudlow also suggested diabetes favours lacunar infarctions. In our study 73.4% cases had hyperlipidemia according to NCEP-ATP3 criteria. Those patients which were found to be non-hypertensive had hyperlipidemia (91%) and combination hyperlipidemia was found to be 27.4% and 13.7% had low HDL levels. So it can be inferred that in our state also uncontrolled hypertension and hyperlipidemia are the two major risk factors which are having a positive co-relation with ischemic CVA occurrence.

Out of the 124 patients 31.45% had carotid artery stenosis & it was further observed that 39.79% of patients with non-lacunar stroke had significant narrowing of carotid arteries and 3.84% of patients of lacunar stroke had carotid artery involvement. So it was inferred that carotid artery stenosis ($p<0.05$) was significantly higher in patients with non lacunar stroke .Of the subjects that had carotid artery stenosis positive correlation was found with hyperlipidemic patients. It was concluded that CIMT is an objective sign of accelerated atherosclerosis in patients with poorly controlled hypertension & hyperlipidemia and developing non-lacunar infarction as a consequent complication. Smoking was found to be an important contributing factor with 38.46% of lacunar stroke and 59.18% of non lacunar stroke are smokers and below 40age group all patients are smokers.

Many studies have been done outside on the relationship of CVA with its risk factors and CIMT. This is first study done at our state of Tripura where we tried to highlight the subtypes of ischemic strokes encountered and its positive correlation with known established risk factors. We want to focus this issue that poor socioeconomic

group patients because of their ignorance and reluctance for avoiding the known risk factors and their tendency to avoid and discontinue dietary restriction, smoking abandoning and proper medications are worst sufferers from ischemic strokes.

Conclusion :

To study the risk factors of ischemic strokes this study was undertaken at Agartala Govt. Medical College. 124 Patients were included in this observational study. We also measured CIMT in all patients and tried to find out its correlation with occurrence of stroke. It was seen that hypertension and hyperlipidemia are mainly associated with ischemic stroke occurrence.

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Original Article

Study of clinical profile of patients of sickle cell disease presenting with crisis

B C Kalita*, S Das*, G Kalita***, H Soni***

Abstract

Introduction : Sickle cell disease (SCD) is one of the most common monogenic disorders globally with an autosomal recessive inheritance. At least 5.2% of the world population carry a significant variant of normal haemoglobin. The primary pathophysiology of sickle cell disease is based on the polymerization of deoxy-HbS within the RBCs causing a distorted sickle shape which eventually leads to vaso-occlusion of sickle red cells. In this study, we aimed to describe the clinical characteristics, management and outcome of adult patients with SCD admitted to the Medicine department of a tertiary hospital. **Methodology :** This prospective observational study was carried out in Department of Medicine AMCH. Study was carried out on 20 sickle cell anaemia patients and its variants presented with crisis, whose age is 13yrs and above. Detailed history and careful clinical examination performed on each patient. A battery of investigations to detect crisis and organ failure was carried out during study period. **Results :** This study carried out on 20 sickle cell anaemia patients and its variants. Out of 20 patients, 12 [60%] belongs to Austro-asiatic ethnic group which includes the tea garden community. Out of 12, 7 had sickle cell disease, 4 had sickle cell beta thalassemia. Symptoms of acute chest syndrome are more common in sickle cell disease group. Pain abdomen is more common in sickle cell disease group. Most common sign was pallor [17 cases, 85%], followed by splenomegaly [16 cases, 80%]. Splenomegaly was present in all Sickle thalassemia patients. **Conclusion :** Among 20 patients, 12 are of sickle cell anaemia, 3 patients of sickle cell trait and 5 patients are of sickle thalassemia syndrome. Most common symptoms of presentation are Bone pain and Abdominal pain. Most common signs are Pallor, Fever and Splenomegaly. Splenomegaly was found more common in the adolescent age group, especially in Sickle thalassemia patients. Vaso-occlusive crisis is the most common crisis of presentation.

Introduction :

Sickle cell disease (SCD) is one of the most common monogenic disorders globally with an autosomal recessive inheritance.[1] It is particularly common among those whose ancestors came from sub-Saharan Africa, South America, the Caribbean, and Central America, Saudi Arabia, India and Mediterranean countries such as Turkey, Greece, and Italy. This distribution results from a selective advantage conferred by this disorder in protecting against Plasmodium falciparum malaria infection in heterozygotes.[2] At least 5.2% of the world population carry a significant variant of normal haemoglobin. Haemoglobin S accounts for 40% of carriers and causes over 80% of disorders due to abnormal haemoglobin.[3]

James Herrick, a physician first described the characteristic sickle shaped red cells in a medical student from Grenada in 1910. Linus Pauling and his colleagues showed that sickle haemoglobin (HbS) had an altered electrophoretic mobility and they were the first to define it as a molecular disease in 1949. A few years later in 1957, Vernon Ingram discovered that sickle haemoglobin resulted from a single amino acid substitution in the haemoglobin molecule.[4]

The primary pathophysiology of sickle cell disease is based on the polymerization of deoxy-HbS with formation of long fibres within the RBCs causing a distorted sickle shape which eventually leads to increased haemolysis and vaso-occlusion of sickle red cells. However, the clinical presentation of SCD patients is extremely variable. Recent work has shown the importance of red cell dehydration, abnormal adhesion of RBCs to the vascular endothelium, inflammatory events, and activation of all the cells in the vessel and abnormalities of nitric oxide metabolism in the pathophysiology of this multi-organ disease.[5]

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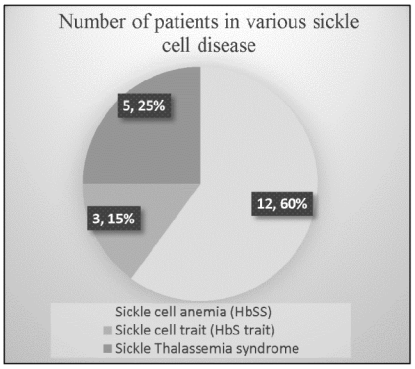
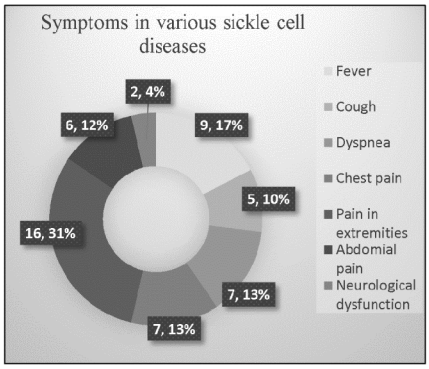
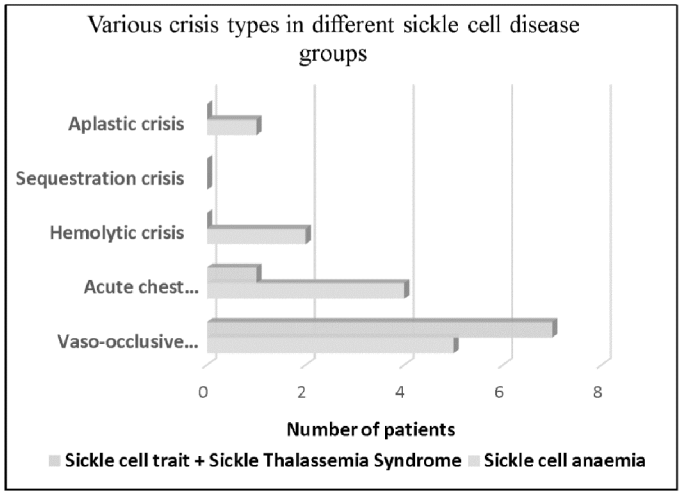
Despite the frequent occurrence, the aetiology and clinical presentation of sickle cell crisis has not been rigorously studied. In this study, we aimed to describe the clinical characteristics, management and outcome of adult patients with SCD admitted to the MEDICINE department of a tertiary hospital.

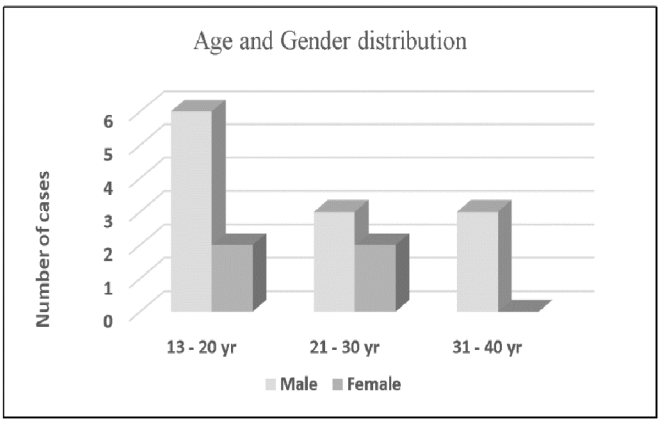




Materials and Methods :

This prospective observational study was carried out in Department of Medicine, Assam Medical College and Hospital, Dibrugarh during the period from September 2016 to August 2017. Study was carried out on 20 sickle cell anaemia patients and its variants presented with crisis attending the Medicine OPD and IPD, whose age is 13yrs and above willing to participate in study. Detailed history and careful clinical examination performed on each patient. A battery of investigations (given below) to detect crisis and organ failure was carried out during study period. The patients with SS pattern on electrophoresis were labelled as 'disease' and patient with AS pattern were labelled as 'trait'. The study was approved by hospital ethics committee and informed consent was obtained from each patient.





Laboratory Investigations Performed :

1. Complete Blood Count
2. Sodium metabisulphite test [sickling test]
3. High performance liquid chromatography (HPLC)
4. Renal Function Test & Liver Function Test
5. HBsAg, Anti-HCV antibody, ANA, Anti-HAV, Anti-HEV.
6. Ultrasonography of whole abdomen & Chest x ray[CXR] postero-anterior view.

Results :

This study carried out on 20 sickle cell anaemia patients and its variants.

Out of 20 patients, 12 [60%] belongs to Austro-asiatic ethnic group which includes the tea garden community. Out of 12, 7 had sickle cell disease, 4 had sickle cell beta thalassemia and 1 had sickle cell trait.

Symptoms of acute chest syndrome are more common in sickle cell disease group. Also pain abdomen is more common in sickle cell disease group. Most common sign was pallor [17 cases, 85%], followed by splenomegaly [16 cases, 80%]. Splenomegaly was present in 5 out of 5 Sickle thalassemia patients. 14 out of 16 patients with splenomegaly was found in the age group of 13-20 years, suggesting prevalence of splenomegaly in

adolescent sickle cell patients. Among blood parameters 14 out of 20 patients has haemoglobin level below 7g/dl. Four patients showed infiltrates in chest X ray which were later diagnosed as acute chest syndrome.

Discussion :

The sickle cell anemia is a very common genetic disorder, 50% of the world population affected by sickle cell anaemia reside in India. Prevalence SCD in India is 5.7% as per study by Kamble et al.[7] In present study, total 20 patients presenting to Assam medical college & Hospital were included. Of the 20 cases studied all the cases are within 40 years of age. Vasundhara M et al in which 86% of Sickle cell disease patients are <40 years of age.[8] The reason for recording few cases in this age group might be that most of the patients did not survive beyond this age. Out of 20 patients 12 [60%] belongs to Austro asiatic ethnic group which includes the tea garden community. It is supported by study done by Colah et al. which showed that the frequency of the sickle cell trait is as high as 35 per cent in some native communities in India.[4]

Age of onset of first symptom is found to be earlier in sickle cell anemia group though statistically not significant. Painful crisis of the extremities was the most common presenting symptom. This was seen in 80 percent of the patients, followed by fever, chest pain and breathlessness. This is similar to the varied symptomatic presentation in study by Vasundhara et al.[8] The risk of painful crisis and acute chest syndrome begins in the first year of life and increases steadily.

Most common signs were pallor [17 cases], followed by splenomegaly [16 cases,80%]. Its in accordance with Swarnkar et al in which splenomegaly (44.27%) was the most common sign.[9] Sickle cell disease patients in the study presented with different crisis, most common was vaso-occlusive crisis with 12 out of 20 patients had this feature followed by Acute chest syndrome (5 out of 20), Haemolytic crisis (2 cases) and 1 case of Aplastic crisis. The findings of present study is in correlation with Swarnkar et al.[9]

Complications other than vaso-occlusive crisis were found to be more common in sickle cell anaemia group as compared to the sickle thalassemia syndrome + sickle cell trait group, which is statistically significant. It implies more severe complications are more common in the sickle cell anaemia group. Sickle cell disease patients with HbF levels >10% had less recurrence of symptoms then HbF < 10%. Platt OS et all concluded improved survival with raised HbF levels.[6]

Conclusion :

Among 20 patients, 12 are of sickle cell anaemia, 3 patients of sickle cell trait and 5 patients are of sickle thalassemia syndrome. Most of the patients are present in age group of 13-20 years and belong to the tea garden community. Most common symptoms of presentation are Bone pain and Abdominal pain. Most common signs are Pallor, Fever and Splenomegaly. Splenomegaly was found more common in the adolescent age group, especially in Sickle thalassemia patients. Vaso-occlusive crisis is the most common crisis of presentation.

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Review Article

IgG4-Related Disease

P K Sarma*

Introduction :

IgG4-related (IgG4-RD) disease is an immune mediated multisystem disease. There is lack of understanding and awareness about this disease as it has only been recently described in the medical literature. In many patients it present with mass lesions and is often mistaken for pancreatic cancer, renal cancers, and variety of lymphomas or Sjögren's syndrome.

Many conditions previously regarded as isolated diseases involving solitary organ are now unified as IgG4 -RD: Autoimmune pancreatitis , Eosinophilic angiocentric fibrosis, Fibrosing mediastinitis, Hypertrophic pachymeningitis, Idiopathic hypocomplementaemic tubulointerstitial nephritis with extensive tubulointerstitial deposits, Inflammatory pseudotumour (affecting the orbits, lungs, kidneys, and other organs), Küttner's tumour, Mikulicz's disease, Multifocal fibrosclerosis (commonly affecting the orbits, thyroid gland, retroperitoneum, mediastinum, and other organs), Periaortitis & periarteritis, Inflammatory aortic aneurysm, Retroperitoneal fibrosis, Riedel's thyroiditis, and Sclerosing mesenteritis.[1]

It is a great mimicker of many malignant, infectious, and inflammatory disorders. Many patients have been reported undergoing Whipple's procedure for pancreatic cancer that actually had IgG4-RD. Therefore awareness of IgG4-RD is very important as it is treatable.

Epidemiology :

There is not much data about its epidemiology as IgG-RD started appearing in medical publications only after 2003. It is estimated that 180,000 people are affected in the United States with IgG4 –RD. The prevalence of type 1 (IgG4-related) autoimmune pancreatitis in Japan was 2.2 cases per 100 000 population[2]; it is an underestimate as the pancreas is only one of the many diverse organs affected by IgG4-RD and this study was done early before a good awareness about IgG4-RD.

Middle-aged to elderly man are commonly affected. The mean age at diagnosis is 67 years and the male to female ratio is 3:7 for autoimmune pancreatitis. The male to female ratio is equal for organs of the head & neck like the orbits, salivary glands, and sinuses.

Pathology :

The diagnosis of IgG4 -RD can be made with certainty only with histopathology.[3]

Three cardinal pathological features are:

1. Lymphoplasmacytic infiltration
2. Obliterative phlebitis
3. Storiform fibrosis

The lymphocytes and plasma cells are polyclonal. Eosinophils are also commonly seen and in few cases it can be so high that it resembles eosinophilic organopathy. Neutrophilic infiltration is rare.

If necrosis, discrete granulomata, and xanthogranulomatous changes are present, another diagnosis should be suspected.

Some fibrosis is present in all cases, even in early cases. ***Storiform fibrosis*** is the unique pattern of the disease; it is characterised by radially arranged collagen fibres weaving through the tissue.

We should think about another diagnosis if acellular, keloidal fibrosis is present.

Obliterative phlebitis with partial or complete obliteration of medium-sized veins can be seen. Obliterated veins

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commonly appear as an inflammatory nodule next to a patent artery.

The histological appearance is similar for all organs. Some organ-specific chages can be seen. Both obliterative arteritis and focal neutrophilic infiltration (in alveolar spaces) can occur in the lungs which is rare in other organs; unlike vasculitis it doesn't have vascular-wall necrosis.

Other minor pathological differences between organs include :

- Absence of storiform fibrosis within lacrimal glands and lymph nodes.

- Lower frequency of obliterative phlebitis in salivary glands, lacrimal glands, lymph nodes, and kidneys.

Immunostaining :

The hallmark of the disease is high numbers of IgG4-positive plasma cells in organs involved even if serum IgG4 is normal.

The finding of IgG4-positive plasma cells is helpful in differentiating IgG4-related disease from other plasma-cell-rich disorders, e.g. primary sclerosing cholangitis & multicentric Castleman's disease.[4]

IgG4-positive plasma cells are generally present diffusely throughout the lesions and focal aggregations are atypical.

The absolute number of IgG4-positive plasma cells must be interpreted according to the specific tissue: for sialadenitis the cut off value should be at least 100 cells/HPF; but in the pancreas > 50 cells/HPF is compatible with a diagnosis.[3]

The ratio of IgG4 to IgG-positive plasma cells must be at least 40% (typically e" 70%). As plasma cells can be present in other conditions, IgG4-RD cannot be diagnosed on the basis of infiltration by IgG4-positive cells alone.

Histological features can become less specific in longstanding disease as fibrosis predominates. Some undiagnosed or untreated cases of IgG4-RD may be categorised as idiopathic end-stage diseases—e.g. Chronic pancreatitis, cryptogenic cirrhosis, or honeycomb lung. If earlier biopsy samples are available, that could document the progression of IgG4-related disease.

Anatomical Changes :

Some organs like pancreas and kidneys become diffusely enlarged. In ductal organs (bile duct, bronchus) diffuse wall-thickening occurs and they may appear like **pipe-stem.** Occasionally discrete small nodules within an otherwise unremarkable organ are seen.

Unlike classic autoimmune disorders e.g. autoimmune hepatitis and Graves' disease, inflammation is not seen and there is non-selective cell injury.

Pathophysiology :

The pathological processes can be explained by:

1. Induction of a polarised CD4-positive T-cells, not definitely characterised, which activates innate immune cells, including macrophages, myofibroblasts, and fibroblasts leading to fibrosis. Activated B-lineage cells entering the damaged tissue collaborate this process.

2. Negative regulatory process, which might involve the generation of IgG4-secreting plasmablasts, plasma cells, and IgG4 antibodies.

IgG4 antibodies undergo Fab-arm exchange within the endosomes of endothelial cells. The heavy-chain dimers of an IgG4 molecule dissociate and each hemi-molecule associates with another, different, hemi-IgG4 protein. Most secreted IgG4 are functionally monovalent and cannot crosslink antigens to form the lattice structure found in immune complexes. Therefore, IgG4 antibodies do not directly fix complement, bind poorly to activating Fc receptors, and are non-inflammatory.[1]

It is known that in allergic disorders, IgG4 concentrations increases after IgE concentrations comes down. One possible view of IgG4 is that it evolves as non-inflammatory antigens sink which mop up antigen to attenuate inflammatory processes.[1]

T cells are also implicated in the disease pathogenesis as many CD4-positive T cells are present at the sites of inflammation. There is conflicting reports of role of Th1 cells and Th2 cells in the disease pathophysiology.[5,6]

The molecular mechanisms that drive the IgG4 class switch remain unknown, but roles for interleukins 4 and 10 have been suggested.[7] Some polarised T cells, nature of which is still unknown, could drive the storiform fibrosis and obliterative phlebitis.

One model of pathogenesis may be that in a genetically susceptible individual, some environmental factor, possibly a specific microbe, triggers tissue damage

and a break in immunological tolerance. A self-antigen-driven, polarised CD4-positive T-helper response occurs which leads to fibrotic process. Within the organs, increased CD4-positive T cells activate innate immune cells that secrete other cytokines. Antigen-presenting B cells helps to sustain the memory CD4-positive T cells and therefore B-cell depletion leads to clinical improvement. (8,9) Either the same antigen or some event triggered by fibrosis could trigger a parallel T-follicular helper response that would induce the development of germinal centres within lymph nodes and the generation of IgG4-secreting plasmablasts and long-lived plasma cells.

Serology :

High serum IgG4 concentrations are neither sensitive nor specific. Serum IgG4 concentrations are useful for screening but cannot be used as a single diagnostic marker. About 20% of patients with Type 1 autoimmune pancreatitis have normal serum IgG4concentrations at presentation.[10,11] The proportion with normal IgG4 concentrations can be lower in patients with multiorgan disease.[12] High serum IgG4 concentrations can be seen in 4–10% of both healthy and disease controls, including patients with pancreatic cancer.[11,13,14] Diagnostic specificity can be increased if ratios of IgG4 to total IgG (>10%) or IgG1 (>24%) is used.[15] High numbers of plasmablasts by flow cytometry in blood is more sensitive than serum IgG4 concentrations.[16,17]

Gross underestimation of the serum IgG4 concentration can occur by nephelometry in presence of large antigen excess because of **prozone phenomenon.**[18] Appropriate dilution of the serum sample during the assay process prevents the prozone effect.

Clinical Presentation :

The symptoms are diverse depending on the organs or tissues involved. Mass lesion or organ enlargement is the common manifestation. The most commonly affected organs are salivary & lacrimal glands, pancreas & biliary tract, and the kidneys; but any organ can be involved and multiorgan disease can be also seen.[19]

The infiltration and fibrosis can result in tissue or organ dysfunction in addition to tumour like effects that can cause obstruction or compression.[20]

Among the clinical features observed are exophthalmos including orbital pseudotumor, salivary gland enlargement, pancreatic failure, lymph node enlargement, retroperitoneal fibrosis, kidney disease with proteinuria & subsequent renal failure, and aortitis-related aortic aneurysm.[21]

A number of cases can present as an incidental finding on imaging. Presentation is usually subacute, and some patients might have more than one organ affected at the same time or years after the initial diagnosis.

Many patients have an existing allergic condition. Peripheral eosinophilia is not uncommon while fever is rare.[22] Weight loss of 5–10 kg can occur over months. Fatigue commonly occurs, especially when the disease affects several organ systems. Arthralgias and enthesopathy (inflammation in the site at which a tendon inserts into a bone) can occur.

Diagnosis :

Tissue biopsy is the gold standard for diagnosis.

Imaging is an important part of the diagnostic approach in many organs. Under some circumstances, the imaging findings in autoimmune pancreatitis can be regarded as diagnostic if the clinical presentation is typical.

As imaging findings elsewhere in the body are not specific, tissue diagnosis is important for patients with no pancreatic involvement.

PET can help to define the extent of organ involvement and can also be helpful in monitoring disease activity after treatment.

Differentiation of IgG4-RD from malignant tumours is crucial.

Common mimics of multi-organ IgG4-related disease are Sjögren's syndrome, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss syndrome), sarcoidosis, & multicentric Castleman's disease.

Single-organ diseases such as primary sclerosing cholangitis mus be excluded.

Following can be a diagnostic algorithm :

Step 1: Thorough history and physical

Step 2: Serology

IgG4> 135 mg/dl

Eosinophilia

Elevated circulating plasmablasts

Low C3 & C4 in cases of renal IgG4-RD

Step 3: Imaging

CT, PET CT, MRI, EUS, ERCP/MRCP

Step 4: Biopsy

Core Biopsy

FNAC if core biopsy not possible

Pancreatic FNA in cases of suspected autoimmune pancreatitis

Biliary brushing and FNA for cytology

Step 4: Histological findings and immune staining

IgG4+/IgG+ plasma cells> 40% Or igG4+ plasma cells > 10/HPF

Storiform fibrosis

Obliterative Phlebitis

Biospy negative for malignancy or other specific diseases.

Treatment :

Some patients with asymptomatic IgG4-RD can be watched without treatment, e.g. asymptomatic lymphadenopathy or mild submandibular gland enlargement.[21]

However most patients will require initiation of therapy. Special attention should be made to active IgG4-RD in the pancreas, biliary tree, aorta, mediastinum, kidneys, retroperitoneum and mesentery as in those cases starting therapy in an urgent fashion must be considered.[21] Another manifestation requiring urgent treatment is Pachymeningitis.[21]

Glucocorticoid gives good and quick response. A Metaanalysis that included 62 different studies with total number of 3034 patients showed that glucocorticoids are the most common initial therapy. The reported response rate for glucocorticoids monotherapy was 97% but a complete response rate was only 65 %.[19] The actual rate for relapse is unknown but one study reported a relapse rate of 54 % after cessation of steroids therapy in autoimmune pancreatitis (AIP).[23]

Initial glucocorticoids dose should be maintained for 2-4 weeks and then tapered slowly over 3-6 months depending on response.[21] Adding a steroid-sparing agent is reasonable especially if prednisone can't be tapered because of persistently active disease. Options of steroid sparing agents include Methotrexate, Azathioprine, Mycophenolate, 6-Mercaptopurine and cyclophosphamide.[21] To date there is no randomized controlled studies that compared prednisone monotherapy to combination of steroids with any immunosuppressive agent in IgG4-RD.

Rituximab (RTX) is promising option. Rituximab was associated with significant reductions in both IgG4 levels and circulating plasmablasts.[23,24] A prospective study of Rituximab showed that 77% patients met the primary outcome of response with no relapses for six months.[23]

Maintenance therapy for IgG4-RD after remission induction is recommended for patients with higher risk of organ dysfunction or high risk of relapse. There is no consensus on the optimal regimen or duration for maintenance therapy, however. Maintenance with small dose of glucocorticoids is the most practised approach in Japan for AIP.[21] A steroid sparing agent or Rituximab for maintenance can also be used. Disease relapse or flares should be managed with glucocorticoids and if the patient is not already on another immunosuppressive then starting an agent should be strongly considered.[21]

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Case Report

Systemic lupus erythematosus with neuropsychiatric manifestations, autoimmune haemolytic anaemia and cutaneous vasculitis in a patient of beta thalassemia minor

C Baruah*, A Biswas**, T Maitra***

Abstract

Introduction : Systemic Lupus Erythematosus (SLE) is an autoimmune disease which involves multiple organs and present with a variety of clinical features including cutaneous, musculoskeletal, haematologic, neurologic, cardiopulmonary, renal, gastrointestinal and ocular manifestations. In addition, other comorbidities may further complicate the clinical picture of SLE. **Case Report :** Our patient, a 37 year old unmarried female, who was a known case of beta thalassemia minor hailing from North Guwahati, presented to the Medicine OPD with history of fatigue and fever for one and half month along with presence of nonpalpable purpuric macules over bilateral lower limbs. She had history of loss of consciousness at the age of 28 years. She was found to have ANA positive, and responded to Methyl Prednisolone pulse therapy. She was then diagnosed as a case of Neurolupus. Presently the reports show ANA, Anti ss-A and DCT to be positive. Hence the patient has been diagnosed as a case of SLE with neuropsychiatric manifestations, Autoimmune Haemolytic anemia and cutaneous vasculitis with beta thalassemia minor. **Conclusion :** The association of SLE with beta thalassemia, though rare, is significant as it is associated with increased severity and disease activity of SLE. As the prevalence of hemoglobinopathies in Eastern India and North West is more[5], hence there is a need for increasing awareness in the North East region to thoroughly evaluate any case of beta thalassemia presenting with severe anemia and seek for coexistence of SLE and beta thalassemia patients.

Introduction :

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterised by auntoantibodies to nuclear antigens, most commonly encountered in women of child bearing age. The sustained production of antibodies and formation of immune complexes result in activation of complement pathway leading to release of cytokines, chemokines, vasoactive peptides, oxidants and proteolytic enzymes which cause multi organ damage in SLE. Severity of SLE varies from mild and intermittent to severe and fulminant. Approximately 85% of patients have continuing active disease while others have one or more flares of active disease annually. SLE might present with a variety of clinical features including cutaneous, musculoskeletal, haematologic, neurologic, cardiopulmonary, renal, gastrointestinal and ocular manifestations. In addition, other comorbidities may further complicate the clinical picture of SLE.

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The coexistence of haemoglobinpathies with SLE is an occurrence that has been reported less frequently. A study conducted by *Castellino et al* in the Ferrara and Rovigo areas of Italy showed that patients with SLE have a lower prevalence of beta thalassemia than a control group[1]. However it was found that if the two conditions coexist, SLE seems to have a more severe course, necessitating aggressive immunosuppression. The incidence of SLE in India is 3.2 per 1,00,000 population and that of thalassemia minor varies from 1.48 to 3.64%. A study by *M.B. Agarwal et al* showed that the prevalence of hemoglobinopathies in Eastern India and North West is more[5]. Hence there is a need for increasing awareness in the North East region to seek for coexistence of SLE and Haemoglobinopathies since early and prompt treatment is necessary as severity of SLE is more if these two conditions coexist.

Case Report :

A 37 year unmarried female presented to the Medicine OPD, GMCH with complaint of severe fatigue and fever over last one and half month. There was no history of significant weight loss, anorexia, cough or breathing difficulty, burning micturition.

Clinical Examination revealed presence of mild icterus, moderate palor and sparse scalp hair. Nonpalpable purpuric macules were noted over both legs below knee with scaly and hyperpigmented areas. No malar rash was found. No rash over other part of the body was seen.

Systemic examination was within normal limits.

Investigations revealed : TC- 8100, Hb- 5.8, ESR- 110; CRP-16, LFT- TSB: 2.9, Direct- .8, Indirect- 2.1, Urine RE- trace; 24 hour urine protein- 480mg; Direct Coombs test: positive. ANA : positive (Primary dilution: 1:40, Intensity: 4+, Pattern: speckled, End point titre: 1:2560), DsDNA antibody: negative, Smith antibody: positive, U1 RNP: negative, SS-A : positive, SS-B : positive, C-ANCA : weakly positive, APLA : Neg., HRCT Thorax: normal, CECT w/a: Paraaortic lymphadenopathy.

Past History : Year 2008: At her age of 27 years the patient had history of generalised weakness and easy fatigability. Investigations showed: Hb-5.2, Hb Electrophoresis: HbA2 raised. She was diagnosed as a case of beta thalassemia trait. Treatment: 2 units of Packed RBC and was continued on Tab. Folic acid(5mg) once daily.

Year 2009: The patient developed sudden onset loss of consciousness. Prior to that she had history of on and off headache for last 3 months. There was no history of fever, seizure or weakness. Investigations revealed: TC: 7800, ESR- 120, ANA: pos, dsDNA-neg, CSF: WNL, EEG: WNL, NCCT brain: WNL. Patient was diagnosed as a case of Systemic Lupus Erythematosus with Neurological Manifestations. Patient received Methyl prednisolone pulse therapy 1g per day for 5 days. She regained consciousness after 4 days and was continued on Tab. Prednisolone 1mg/kg body weight . Dose was tapered gradually in subsequent visits and she was maintained on Tab. Prednisolone(10mg) per day for 1 year.

Year 2010: After 1 year patient was lost to follow up. However she noticed skin changes gradually over bilateral lower limbs mostly below the knee joint. According to her, skin lesions were circular, initially red, which gradually turned scaly and hyper pigmented and recovered within a period of 20 days. They were found to be recurrent and aggravated on prolonged standing particularly during summer months. However patient did not seek for medical help. Gradually she developed alopecia and lack of concentration and had history of intermittent low grade fever which recovered with over-the-counter medications.

Patient was diagnosed to be a case of SLE with neuropsychiatric manifestations, cutaneous vasculitis and Autoimmune Haemolytic anemia with beta thalassemia minor. She was treated with oral prednisolone(1mg/kg body weight) and was relieved of symptoms. Patient was discharged from hospital after 1 week. Presently the patient is under treatment with Tab. Hydroxychloroquine (200) once daily and Tab. Folic Acid(5mg) once daily, Tab. Prednisolone 10 mg od . Her Skin biopsy has been done(reports awaited) and Renal biopsy has been planned.

Discussion :

Anemia of varying degrees is a common finding in SLE but its association with hemoglobinopathies, beta thalassaemia in particular has been rarely studied[1].

Studies done by *Castellino et al*[1] during 1998- 2003 in Ferrara and Rovigo areas of Italy, where the prevalence of beta thalassemia was high, showed that the association of Beta thalassemia trait in patients with SLE was lower in comparison to patients with Rheumatoid Arthritis and Sjogrens Disease. A remarkable finding in patients with combined SLE and beta thalassemia trait was an increased association with SS-A antibodies and a greater prevalence of CNS lupus and also serositis[1]. *Castellino et al*[1], reported that beta thalassemia is less common in patients with SLE than in general population but the symptoms of SLE were more severe if they did coexist.

The probable mechanisms to explain such associations of beta thalassemia with severe SLE as given by *Meric A. Altinoz et al* include:

■ A Close proximity of locus of beta chain of hemoglobin at 11p15.5 to eight genes with profound role in immune regulation. Beta thalassemia trait accompaniment to autoimmune disease may be the result of haplotypal association between the close proximity genes.

■ Changed concentration of hemorphins which are endogenous opioid peptides derived via proteolytic cleavage of hemoglobins that have anti-inflammatory role. Their reduced expression in thalassemia minor may explain a proinflamatory state and autoimmune vulnerability.

Conclusion :

The association of SLE with beta thallasemia, though rare, is significant as it is associated with increased severity of SLE. Beta thallasemia minor usually does not produce any severe manifestations except mild anemia . So any patient with beta thalassemia minor requiring blood transfusion should be thoroughly evaluated to exclude the presence of other associated conditions. The presence of cutaneous vasculitis in SLE patients should prompt us to search for other manifestation of systemic vasculitis.

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Case Report

A Case Report of A 48 Years Female with SLE with Secondary Sjogren's Syndrom with ALL

R Marak*, P Kashyap, B N Mahanta***, J Das*, A Dutta******

Abstract

Systemic lupus erythematosus is a multisystemic disease .Sometimes other connective tissue disorders are associated with SLE like Sjogren's syndrome. Haematological abnormalities are a very common finding.Though it has a very rare association with ALL it is still possible and we discuss in the following paragraphs regarding such a case.

Introduction :

Systemic lupus erythematosus (SLE)is an autoimmune disorder affecting predominantly the musculoskeletal and haematological systems. Association of SLE and haematological malignancies is widely repoted in adults[1-4] Most of the data show that the malignancy is detected after the diagnosis and treatment of SLE[4].Usually, SLE precedes the onset of lymphoproliferative diseases,[5-8] but the neoplasia can occur earlier[9] or simultaneously.[9]

Sjogren's syndrome (SS) is a chronic autoimmune disorder where T-cells destroy the salivery and lacrimal glands producing dry eyes and dry mouth.SS may involve any organ system of the body. Many patients experience debilitating fatigue and joint pains. When SS appears along with another primary disease like rheumatoid arthritis,lupus or scleroderma,it is known as Secondary Sjogren's syndrome.

SLE with Lymphoid leukaemia is a rare phenomenon.Lugassy G ,et al described 3 cases of CLL with SLE.There are only five pediatric cases of SLE with acute lymhoblastic lymphoma(ALL) are reported in literature,two developed simultaneously and three developed SLE after successful treatment of ALL

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Case Report :

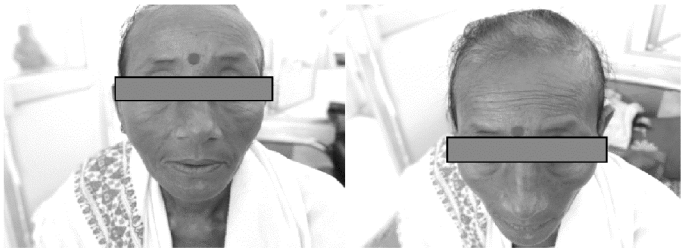
A 48 years old female from Jorhat was admitted in the department of medicine on 27/10/2018 with generalised weakness for 5 months, predominantly on bilateral lower limbs .She also had multiple neck swellings for 5 months prior to admission which was painless and resolved spontaneously. She also complained of hair loss for 3 months. Patient also recalls suffering from on and off low grade fever for the same duration. There was no history of joint pain, cough, chest pain, difficulty in breathing burning micturation ,skin changes or itching in any part of her body. Patient gave history of dryness of mouth for 2 weeks prior to admissions which persisted even after taking water or any liquid. She didn't have any oral ulceration.There is no history of mouth breathing, blood loss, nor any significant past history except for miscarriage 12 years back in the second trimester.

On examination- her B.P. was 110/80 mm of Hg,P.R.-96/mins. Temperature 99 F .Pallor-present.There is hepatosplenomegally and left axillary lymph node was palpable of about 2 cm large ,mobile and hard in consistency. Other group of lymph nodes were not palpable. On close observation we could find out the malar rash, which was less prominent due to her darker complexion. On further evaluation, the patient had bicytopenia with Hb-6.3 gm%,T.C.-13,900 N-70% L-40% M-1%,blast cells-88%,platelet count-36,000 and

ESR-108. Her PBS report showed subleukaemic leukaemia. Her PCV was 18%, MCV-87fl, MCH-30.pg, MCHC-34.8gm/dl.RDW-17.4%.Her renal function and liver function were within normal limit. She had hypokalemia initially which was corrected. Her coagulation profile was unaffected. Keeping all these in our mind, with strong clinical suspicion, we evaluated her for ANA blot and ANA-IFA.ANA came out to be postive with 1:80 titre,fine speckled. SS-A SS-B RO-52 were +ve. Diagnosis of ALL was confirmed by bone marrow study. Her FNAC of the lymph node showed only reactive lymphadenopathy. HBsAg ,antiHCV and HIV reports were negative. Her ultrasonography whole abdomen showed hepatomegally with right ovarian haemorrhagic cyst. Her Echocardiography study was normal.

After admission injectable Piperacillin-tazobactum 4.5 gm was started as the patient began to develop fever although it was of low grade. Tab prednisolone 10mg once daily was started.She received 3 units of fresh blood transfusion. General condition of the patient was improving although hair fall was persistant. Later, as the patient's condition stabilized, she was referred to a higher oncological centre for treatment of ALL.

PHOTOGRAPHS-



DISCUSSION-Based on clinical manifestations and serological abnormalities we have confirmed our diagnosis.our patient fullfilled the Systemic Lupus International Collaborating Clinic (SLICC) criterias for SLE.

There are only very few cases of SLE with ALL have been reported around the globe .The American college of Rheumatology has postulated various mechanisms to explain these two conditions-

The possibilities include a viral infection in a genetically susceptible host, facilitation of autoimmune process by the autoimmune disorder,and suppression of immune serveillance by cytotoxic therapy.Another possibility is oncogenic activation in the autoimmune disease could initiate neoplasia.For instance,lymphocyte from patients with SLE exhibit increase expression of proto-oncogenes c-myc and c-myb[10].

To conclude, at the time of presentation, if the patient has features of both autoimmune disease and ALL, then one should treat the ALL first, because, after treatment of ALL, the autoimmune symptoms more or less resolve plus ALL mandates aggressive and prompt treatment as the patient's life may be jeopardized .Hence, cases presenting with SLE or Sjogrens syndrome,a high degree of suspicion is warrented so as to channelize the treatment in the correct direction on the basis of what should be treated first and when.

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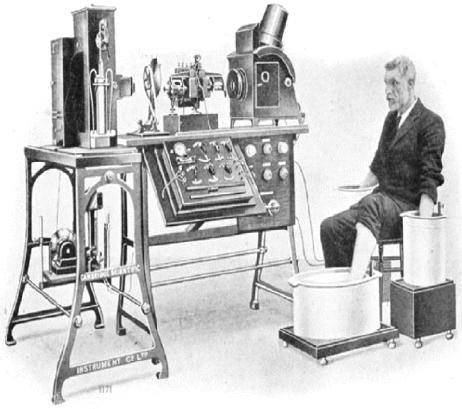
Medi-Quiz

Anupam Dutta*

1) Name the dog that lived for 70 days before dying of Diabetic keto-acedosis, with an injections of pancreatic extracts by Banting and Best and giving the world what we know today as INSULIN ?

2) Who was the first surgeon to ever receive a Nobel prize in Physiology or Medicine ?

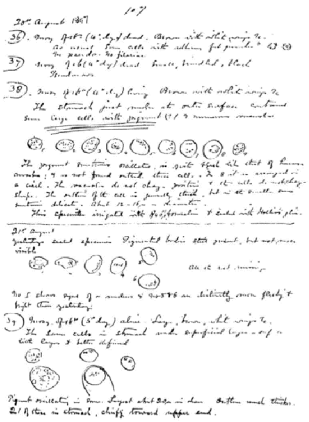
3) Name this machine that won its inventor the Nobel Prize winner in 1924 ?



4) Who was nominated 32 times for the Nobel Prize in Physiology or Medicine, but never awarded?

5) On December 31, 2005, at age 97, DeBakey suffered from a condition, in which he pioneered a surgery called "DeBakey procedure". He underwent the surgery named after himself and lived for another 2 years. Name the condition for which he underwent surgery ?

6) In July 1897, Sir Ronald Ross managed to culture 20 adult "brown" mosquitoes from collected larvae. He successfully infected the mosquitoes from a patient named Husein Khan for a price of 8 annas (one anna per blood-fed mosquito!). After blood-feeding, he dissected the mosquito and found an "almost perfectly circular" cell from the gut, which was certainly not of the mosquito. (This discovery was published in 18 December 1897 issue of *British Medical Journal.*) In September 1898, Sir Ronald Ross came to southern Assam, the Labac Tea Estate Hospital(His microscope and medicals tools are still preserved, and his sketches of mosquitoes are still on display at the hospital) to study an epidemic of which disease ?



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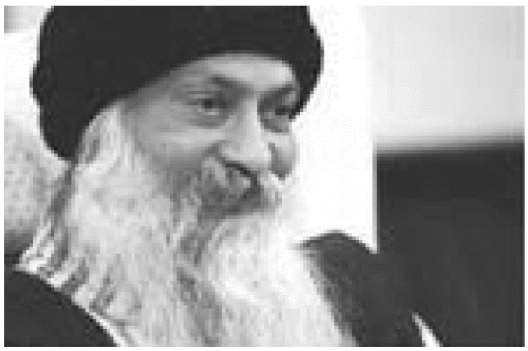
7) He completed his M.D. degree (an advanced degree in Scotland beyond the usual medical degrees) on the subject of *tabes dorsalis* in 1885. On 20 September 1879, he published his first academic article, "Gelsemium as a Poison" in the *British Medical Journal.* But he is famous in literature and every growing child's one of the favorite author. *Who is he ?*

8) Bellevue-Stratford Hotel in Philadelphia is famous for ?

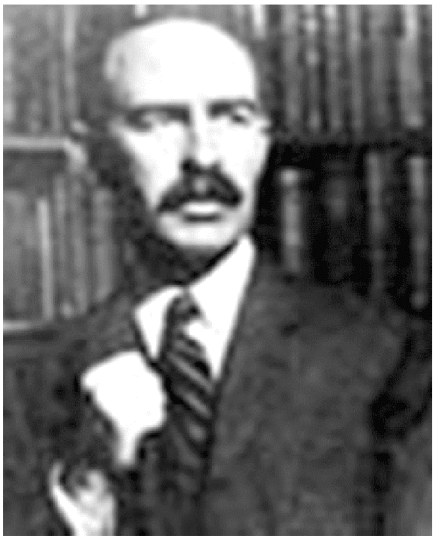
9) In Oregon in 1984, followers of the Bhagwan Shree Rajneesh attempted to control a local election by incapacitating the local population. This was done by infecting salad bars in 11 restaurants, produce in grocery stores, doorknobs, and other public domains with a bacteria in the city of The Dalles, Oregon. The attack infected 751 people with severe food poisoning. It was also the single largest bioterrorism attack on U.S. soil. Name the bacteria ?



10) 64 year old Chinese Dr Liu Jianlun is Known for ?

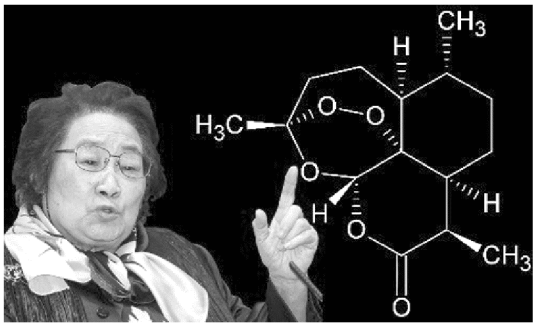
11) El Acróbata o Acróbata de Tlatilco is said to be the first documentation of what ?

12) George A. Soper, PhD (1870—June 17, 1948) was a sanitation engineer. What is he famous for?



13) Apart from Hemophilia, which other familial disease has been passed on to the royal families of Europe by the bloodline of Queen Victoria of Great Britain?

14) Tu Youyou, Chines Pharmacitical Chemist received Nobel Prize in Physiology or Medicine in 2015 for her work on which molecule and disease?



15) Name the medicine derived from the following plants –

a) Common Foxglove

b) Milk Thisle

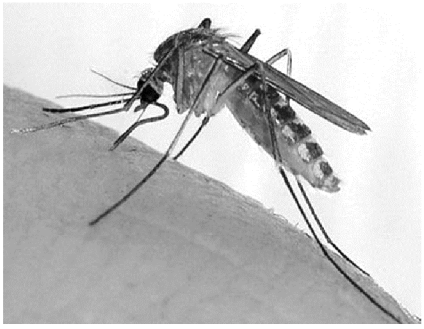
c) French Lilac or Goat's Rue or Professor Weed

d) Sweet Wormwood

Milk Thistle

16) Japanese Encephalitis (JE) virus of genus flavivirus is transmitted between vertebrate hosts principally by which mosquito?

17) Name five encephalitis caused by various members of genus flavivirus, family flaviviridae?



18) This French Detective was the inspiration for nomenclature of which medicine?

19) Who is the youngest Nobel Laureate in Physiology or Medicine?

20) Iron lung, colloquial for negative pressure ventilator, was originally developed for the treatment of victims of coal gas poisoning, but was most famously used in the mid-20th century of the treatment of respiratory failure caused by which disease?

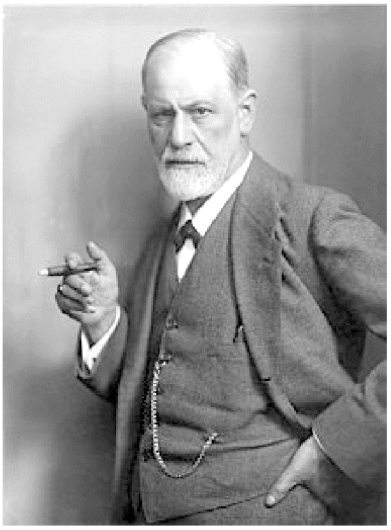
ANSWERS

1) Marjorie

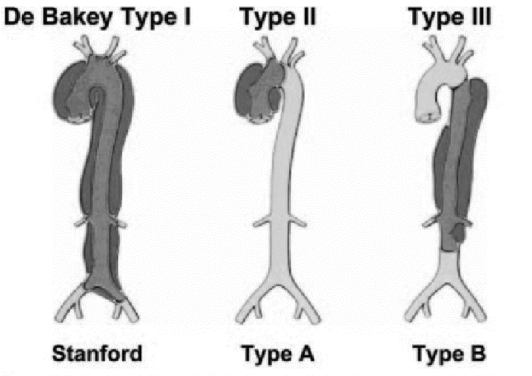
2) Emil Theodor Kocher

3) Electrocardiogram (ECG)

4) Sigmund Freud



5) Aortic Dissection



De Bakey

Type I	Originates in the ascending aorta, propagates at least to the aortic arch and often beyond it distally.
Type II	Originates in and as confined to the ascending aorta.
Type III	Originates in the descending aorta and extends distally down the aorta or, rarely retrograde into the aortic arch and ascending aorta.

Stanford

Type A	All dissections involving the ascending aorta, regardless of the site of origin.
Type B	All dissections not involving the ascending aorta.

6) Visceral Leishmaniasis (kala-azar)

7) Sir Arthur Ignatius Conan Doyle

8) *Legionella pneumophila (July 1976, when an outbreak of pneumonia occurred among people attending a convention of the American Legion at the Bellevue-Stratford Hotel in Philadelphia. Of the 182 reported cases, mostly men, 29 died. On January 18, 1977, the causative agent was identified as a previously unknown strain of bacteria, subsequently named Legionella, and the species that caused the outbreak was named Legionella pneumophila.*

9) *Salmonella typhimurium*

10) First reported case of SARS

11) Tetanus (Opisthotonas and *Risus sardonicus)*

12) He discovered Mary Mallon (Typhoid Marry)

13) Porphyria (Hence so many mad Kings)

14) Artemisin for malaria

15) a) Digoxin, b) Silymarin, c) Metformin, d) Artemisin

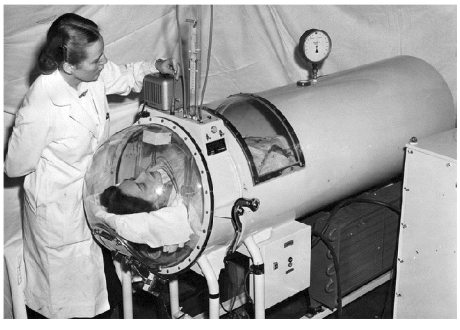
16) Culex tritaeniorhynchus

17) 1. Japanese Encephalitis, 2. West Nile Fever, 3. St. Louis Encephalitis, 4. Kunjin Virus Encephalitis, 5. Murray Valley Encephalitis

18) Rifampicin (Anti Tubercular drug)

19) Frederick Grant Banting (The youngest Nobel Laureate in Physiology or Medicine is Frederick G. Banting, who was 32 years old when he was awarded the Medicine Prize in 1923).

20) Polio



CONSENT FORM FOR CASE REPORTS

For a patient's consent to publication of information about them in a journal or thesis

Name of person described in article or shown in photograph :_____

Subject matter of photograph or article : _____

Title of article : _____

Medical practitioner or corresponding author : _____

I_____ [insert full name] give my consent for this information about MYSELF OR MY CHILD OR WARD/MY RELATIVE [insert full name]:_____, relating to the subject matter above ("the Information") to appear in a journal article, or to be used for the purpose of a thesis or presentation.

I understand the following :

1. The Information will be published without my name/child's name/relatives name attached and every attempt will be made to ensure anonymity. I understand, however, that complete anonymity cannot be guaranteed. It is possible that somebody somewhere - perhaps, for example, somebody who looked after me/my child/relative, if I was in hospital, or a relative - may identify me.
2. The Information may be published in a journal which is read worldwide or an online journal. Journals are aimed mainly at health care professionals but may be seen by many non-doctors, including journalists.
3. The Information may be placed on a website.
4. I can withdraw my consent at any time before publication, but once the Information has been committed to publication it will not be possible to withdraw the consent.

Signed:_____ Date: _____

Signature of requesting medical practitioner/health care worker:

_____Date:_____