Ovarian Germ Cell Tumours

Hypophosphatemia in Critically ill Patients

Drugs Prolonging QT interval

Hypocalcemia: A marker of Severe Dengue
AMRITA
GLOBALLY RANKED NO.1 PRIVATE UNIVERSITY IN INDIA

Global Rankings

No.1 RANKED Private University in India
No.1 RANKED International Outlook in India
No.1 RANKED International Faculty in India

www.amrita.edu
Editorial
02 Commercialisation of Medicine
H. Kumar

Spiritual Message
03 Work is Worship

Review Article
04 Ovarian Germ Cell Tumours: An update on the Newer Treatment Paradigms
Arun Philip, Anupama R, Vijaykumar DK, Pavithran K

"JUST DO IT!"
Correction of Hypophosphatemia in Critically ill Patients
Ajith V, Krupanidhi Karunanithi, Elson Kuriakose, Sreekrishnan TP, Gireesh Kumar KP

Original Article
20 The Laymans’ Perspective On The Limits Of Facial Asymmetry
Silpa A, Athish J, NK Sapna

25 Hypocalcemia: A Marker of Severe Dengue
Mithun Rathen Murugan, M Gopalakrishna Pillai

30 Usefulness of Chedoke McMaster scale in assessing Stroke recovery
Krishnan R, Mohan Das Kurup VK, Surendran K, George Joseph N

34 Working-Day Effects on The Acoustic Voice Parameters of Dubbing Artists: A Preliminary Study
Maya Varma R, Usha Devadas

Case Report
37 Anti-N-methyl-D-aspartate receptor encephalitis A diagnostic dilemma in Emergency Room
Ajith V, Ajith Kumar, Akta Trivedi, Bharath Prasad, Naveen Mohan, Arun Kumar, Krupanidhi Karunanithi, Sreekrishnan TP, Gireesh Kumar KP

41 Combined Central Retinal Artery & Central Retinal Vein Occlusion In Secondary Antiphospholipid syndrome (APS)
Harish Prabhu, Vishnu S Chandran, Jesmy Chacko, K K Velayudan, Gopal S Pillai, R N Sharma
Commercialisation of Medicine

H. Kumar

There was a time when it was considered unethical to advertise any aspect of the medical profession. But times appear to be changing fast. Today as you drive along the road there are any number of giant bill boards advertising surgical procedures and other specialised services in particular institutions. When you go to watch a movie and you see blatant advertisements of pleasantly uniformed smiling staff welcoming you to have a cup of coffee while you are being examined and recommended various medical treatments. Similar advertisements on television have become the norm. Often these advertisements give misinformation or sometimes even false information. One can see various dubious medical products being advertised in newspapers and magazines, often endorsed by some official medical organization or professional association.

Patients generally feel that we are too trigger happy with the use of investigative tools. Too many blood tests and scans tend to be ordered and this often creates suspicion about whether there is a commercial motive behind this tendency to over investigate. The threshold to perform invasive procedures and surgeries is sometimes very low. There is a widespread public perception that elective caesarean sections for example, are being done more often than necessary. Many exorbitantly costly surgical procedures are sometimes undertaken without any clear indications or outcomes.

The pharmaceutical industry is of course quite blatantly profit oriented. Unfortunately health care facilities too are increasingly perceived as being profit oriented rather than service oriented. It is a sad commentary on the changing times and fast changing values of our profession. Unless we change track and return to our core basic values of patient care and a service oriented practice of Medicine, we run the risk of seeing the erosion of patient’s trust in doctors and the medical profession at large in the coming years. At the end of the day it is our patients and our professional integrity which makes us what we are, not the income we have generated from the practice of medicine. Let us not compromise our professional integrity and values for commercial gains either overtly or covertly.
The main cause of stress for a large number of people is their work. Many people are not happy with the work they are doing. They feel that the work they are doing is not the type of work they want to do, or they complain that if they were given better opportunities then they could have exhibited their talents much better, or that they are bored with the work they have been doing for many years. A lot of people complain about lack of job satisfaction, lack of motivation and of course almost everyone is unhappy and dissatisfied with their salary. I have heard many complaining that “the job is not challenging enough” or “there is too much work and I can’t cope” or “I feel very pressurised by the targets I am set or the expectation of my superiors”. So in a variety of ways one’s work can become a major source of stress.

It is actually a question of having the right attitude towards one’s work and duties. To illustrate this point Amma once narrated the following parable. Once in an Ashram a Guru lived with his many disciples. Each of the disciples was given specific tasks and duties to perform. One day one of the disciples confessed to the Guru that he had committed an offence. The Guru called a meeting of all the disciples and asked them to decide an appropriate punishment for the disciple who confessed his offence.

“Let him cut vegetables and wash all the dishes for one year” suggested the disciple who was in charge of the kitchen. “No, a harsher punishment would be for him to give the cattle fodder and clean the dung in the cowsheds for a year”, suggested the disciple who was in charge of looking after the cows and cowsheds. “I have a better idea- let him clear the weeds in the garden and put manure for all the plants in the garden for a whole year”, said the disciple who was responsible for the maintenance of the garden. The Guru then said, “Each of you have suggested your own duties as a punishment. This means that you view your own work and responsibilities as a burden and a punishment. This is not the right attitude.” He addressed the gardener and said, “Instead of complaining about the nature of your work and considering it demeaning, you should work in the garden with love and sincerity. You should carefully plant and lovingly nurture each plant in the garden. You should spend time talking to the plants. In this way the plants will flower and blossom and the garden will become a beautiful expression of your loving attitude towards your work. Regardless of whatever work you do, if you have the right attitude whether it is cooking or gardening or tending the cows, it will be fulfilling for you and society. But if you view your work as a punishment then you are wasting your time and energy and the output from your work will not be of benefit to any body.”

This thought provoking parable reminds one of the old saying – “Work is Worship”. It is not what you do, but the attitude with which you do that is important.
Ovarian Germ Cell Tumours: An update on the Newer Treatment Paradigms

Arun Philip*, Anupama R**, Vijaykumar D K**, Pavithran K*

ABSTRACT
Germ cell tumours of the ovary are a group of tumours which are considered highly curable even in the advanced stages. Till a few decades back, these tumours were uniformly fatal in the advanced stages. Chemotherapy has dramatically improved survival, so much so, that the cure rates even in the advanced stages reach 75%. With such high cure rates, the focus of treatment now is on preservation of fertility without compromising survival. The current review focuses on the emerging treatment paradigms in malignant ovarian germ cell tumours.

INTRODUCTION
Ovarian Germ Cell Tumours (OGCT) are a heterogeneous group of tumours of the ovary, originating in the primordial germ cells, reflecting the capacity of multiple lines of differentiation of the main stem cell system. These neoplasms comprise approximately 20 to 25 percent of ovarian tumours overall, but account for only about 5 percent of all malignant ovarian neoplasms. OGCTs arise primarily in young women between 10 and 30 years of age and represent 70 percent of ovarian neoplasms in this age group. Though less common than their epithelial counterparts, they are in contrast, rapidly growing, highly curable malignancies. They differ in their clinical presentation, histology and biology.

Embryology
Primordial germ cells which originate in the yolk sac endoderm around the 4th week of gestation, migrate around the hindgut to the genital ridge on the posterior abdominal wall. Migration is thought to be mediated by the c-kit receptor and its ligand, Stem cell factor (expressed with an increasing gradient from yolk sac to gonadal ridge). Any abnormality in these primordial cells would result in neoplastic transformation along the route of migration or more commonly in the ovary.

Epidemiology
The incidence of OGCT increases from the age of 8-9 years, and peaks at 18 years. The mean age of presentation of GCT is around 19 years. The proportion of malignant ovarian germ cell tumours (MOGCT) among ovarian neoplasms ranges from 1% to 6% as reported in the west and from 8% to 19% as reported in Asia. Pathogenesis and Genetic features
The presence of Isochromosome short arm 12 (i12p) in both male and female GCTs and the similarities in other secondary chromosomal imbalances (+7, +8, +12, +21, -13) indicate that these tumors evolve through some of the same pathogenic mechanisms in both sexes. Immature teratomas develop through a different pathway than that of other MOGCTs; these tumors are typically diploid and do not have i12p or other imbalances of chromosome 12.

Histopathological classification
MOGCTs are broadly divided into Dysgerminoma & Non-dysgerminomatous tumours. The Non dysgerminomas may belong to one of the following subtypes: Yolk sac tumor, Embryonal carcinoma, Polyembryoma, Choriocarcinoma (Non gestational), Gonadoblastoma,Immature teratoma. The most common histologies encountered are Dysgerminoma, Immature teratoma and mixed germ cell tumours.

Clinical Presentation
They usually present with features of a rapidly growing tumor. The average duration of symptoms is 2 -12 weeks. Common symptoms and signs are abdominal pain, distension and a palpable abdominal mass. Menstrual irregularities are encountered in 10 -20% of girls. Median tumor diameter at presentation is around 16-20 cm. Though quite large, approximately 60% are confined to the ovary. Dysgerminomas have a propensity for bilaterality and come bilaterally in 10-15% of cases. Precocious puberty and hyperemesis, seen in a small proportion of patients, is related to the hCG production by the tumor (Choriocarcinomas & embryonal carcinomas).

Investigations
Serum tumour markers: bHCG & AFP are diagnostic except in dysgerminomas where the markers are usually normal. These are used in assessing response to chemotherapy after each cycle and also in monitoring for relapse during follow up. AFP has a half life of 5-7 days whereas the half life of bHCG is 24-36 hours.

Tumour markers in the different histological subtypes

<table>
<thead>
<tr>
<th>HISTOLOGY</th>
<th>AFP</th>
<th>bHCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgerminoma</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>Yolk Sac tumour</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Embryonal carcino</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Choriocarcinoma</td>
<td>-</td>
<td>++</td>
</tr>
</tbody>
</table>
Stage I - limited to one or both ovaries
- IA - involves one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings.
- IB - involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings.
- IC - tumor limited to ovaries with any of the following: capsule ruptured, tumor on ovarian surface, positive washings.

Stage II - pelvic extension or implants
- IIA - extension or implants onto uterus or fallopian tube; negative washings.
- IIB - extension or implants onto other pelvic structures; negative washings.
- IIC - pelvic extension or implants with positive peritoneal washings.

Stage III - microscopic peritoneal implants outside of the pelvis; or limited to the pelvis with extension to the small bowel or omentum
- IIIA - microscopic peritoneal metastases beyond pelvis.
- IIIB - macroscopic peritoneal metastases beyond pelvis < 2 cm in size, nodes negative.
- IIIC - peritoneal metastases beyond pelvis > 2 cm or lymph node metastases.

Stage IV - distant metastases (excluding peritoneal metastasis) to the liver or outside the peritoneal cavity. Pleural effusion must have a positive cytology.

The Childrens Oncology group in 1993 refined the FIGO schema by FIGO - AJCC 7th edn (Changes expected in AJCC 8th edition)
adopted approach is maximal debulking at presentation followed by chemotherapy.

A secondary cytoreductive surgery may be advocated in case of post chemotherapy residual tumors that initially contained teratoma elements (Incomplete staged), or those with sluggish tumor marker response after two cycles of chemotherapy. A residue of less than 3cm with normal markers post surgery may be followed up. Although literature is scarce in this regard, we have some data to suggest that survival of patients with immature teratoma who underwent secondary cytoreductive surgery is superior compared to those with other histologies12.

In the war on GCT, Chemotherapy is one weapon that dramatically improved survival. The chemotherapy regimens have mainly evolved based on data from testicular GCT. The commonly used chemotherapy regimes include BEP (Bleomycin, Etoposide, cisplatin), PVB (Cisplatin, Vinblastine, Bleomycin), VAC (Vincristine, Actinomycin, cyclophosphamide). The combination of BEP is currently the most favoured and is generally accepted as the standard of care in patients with MOGCT11. Experience to date indicates that the cure rates for patients with early stage MOGCT approaches 100% and even in advanced stages, cure rates are at least 75%.

Adjuvant chemotherapy is recommended in all cases of surgically staged malignant GCTs except in case of Dysgerminoma Stage Ia & Immature teratoma St Ia, grade 1. The preferred adjuvant therapy is BEP x 3-4 cycles11. We now have some data to suggest that any residual disease more than 1cm would qualify for 4 cycles of adjuvant therapy and in cases where the residue is less than 1cm, BEP x 3 cycles may suffice. The preferred chemotherapy regime in case of advanced disease, planned for upfront chemotherapy is again BEP for 4 cycles. In contrast to testicular GCTs, carboplatin may represent an acceptable therapeutic alternative to cisplatin for the treatment of OGCTs [GOG study on adjuvant Etoposide/Carboplatin in Dysgerminomas St Ib-III]. However, in the absence of randomized trial data, it would be preferable to treat these patients with cisplatin-based therapy, especially given that the administration of chemotherapy in these patients is with curative intent13,14.

Follow Up strategy & Relapses

Routine follow up is very important in picking up early relapses, as salvage options are satisfactory and cure rates decent. Nevertheless, over the years, the follow up recommendations have become more conservative. Clinical examination is advocated every three months during the first two years and yearly thereafter. Tumor marker studies are advised once in 3 months only for the first 2 years, thereafter may be done only if relapse is suspected. Routine imaging is not recommended on follow up unless the tumour markers were normal at initial presentation15. After the first two years, follow up is only with a yearly clinical examination.

About 15-20% of cases relapse after achieving remission. Most relapses occur within the first two years and commonly in the abdominal cavity. Salvage is primarily with chemotherapy. The regimes commonly used are TIP (Paclitaxel, Ifosfamide, Cisplatin), VIP (Etoposide, Ifosfamide, Cisplatin), Velp (Vinblastine, Ifosfamide, Cisplatin). Patients relapsing within 6 months are usually chemorefractory and may be candidates for autologous stem cell transplant. The average cure rates in the relapse setting is 30-40%.

Conclusions

Chemotherapy has dramatically improved survival in MOGCTs over the past 3 decades. In the very early stages, adjuvant therapy may be avoided, especially in Dysgerminomas and Immature teratomas. Unlike in Epithelial ovarian tumours, fertility preservation can be attempted even in late stages and emerging data suggests that conservative surgery has not affected survival in this setting. In the advanced stages of MOGCTs, upfront chemotherapy, followed by conservative surgery aimed at fertility preservation, is considered the current standard of care.

References


"JUST DO IT!"
Correction of Hypophosphatemia in Critically ill Patients
Ajith V, Krupanidhi Karunanithi, Elson Kuriakose, Sreekrishnan TP, Gireesh Kumar KP

ABSTRACT
Hypophosphatemia is frequently encountered in emergency and intensive care units. Redistribution of phosphate from the extracellular fluid into cells, decreased intestinal absorption of phosphate and increased urinary phosphate excretion are possibly the three major mechanisms which results in hypophosphatemia. Hypophosphatemia can produce various problems like neurological defects, cardiac problems and weaning failure in mechanically ventilated patients. It is advisable to correct hypophosphatemia as soon as possible.

Calcium, phosphate and urinary phosphate level are few of the common investigations which will help to differentiate the type of hypophosphatemia. Patient with hypophosphatemia should be managed effectively. Safe and efficacious intravenous phosphate repletion regimens should be practised.

INTRODUCTION
Hypophosphatemia is frequently encountered in emergency and intensive care units. Critically ill patients are at increased risk for developing hypophosphatemia due to the presence of multiple risk factors. Currently, no major guideline exists for the approach towards critically ill patients with hypophosphatemia and it is uncertain when and how to correct hypophosphatemia, and whether correction affects outcome in such patients. Hypophosphatemia can produce various problems like neurological defects, cardiac problems and weaning failure in mechanically ventilated patients. It is advisable to correct hypophosphatemia as soon as possible. Many practitioners are unaware about these issues and hence, do not concentrate on correction of this serious defect.

Normal range
The normal range for phosphorous is 2.5-4.5 mg/dL. The kidneys excrete (get rid of) phosphate from our bodies.

Hypophosphatemia
Mild Hypophosphatemia : 2-2.5 mg/dL, or 0.65-0.81 mmol/L.
Moderate Hypophosphatemia : 1-2 mg/dL, or 0.32-0.65 mmol/L.
Severe Hypophosphatemia : < 1 mg/dL, or 0.32 mmol/L.

How it Occurs
1. Redistribution hypophosphatemia-
   Stimulation of glycolysis increases the production of phosphorylated carbohydrate compounds in the liver and skeletal muscle. The source of this phosphate is the inorganic phosphate in the ECF; as a result, serum phosphate levels (and urinary phosphate excretion) lowers rapidly. This can occur in following situations.
   - Increased insulin secretion, particularly during refeeding.
   - Acuterespiratory alkalosis (mainly due to hyperventilation).
   - Hungry bone syndrome Parathyroidectomy or rarely thyroidectomy in preexisting osteopenic patient can result in very high deposition of calcium and phosphate in bone in the immediate postoperative period and lead to hypophosphatemia and hypocalcaemia.

2. Decreased intestinal absorption
   Inadequate intake, antacids containing aluminum or magnesium such as sucralfate syrup, steatorrhea and chronic diarrhea.

3. Increased urinary excretion
   a) Primary and secondary hyperparathyroidism.
   b) Vitamin D deficiency or resistance - Vitamin D deficiency can cause hypophosphatemia both by decreasing gastrointestinal phosphate absorption and by causing hypocalcaemia and secondary hyperparathyroidism, resulting in increased urinary phosphate excretion.
   - Primary renal phosphate wasting (rare)
   - Fanconi syndrome - It refers to a generalized impairment in proximal tubular function leading to urinary wasting of multiple compounds.
   - Other causes Osmotic diuresis (glucosuria), proximally acting diuretics (acetazolamide and metolazone), acute volume expansion (which diminishes proximal sodium reabsorption), and IV iron administration.

Note: Spurious hypophosphatemia can be caused by interference of para-proteins with the phosphate assay.

Incidence of hypophosphatemia
Although rare in the general population, the incidence of hypophosphatemia is high in patients with various comorbid conditions:
1. Sepsis (65 to 80%)
2. Major trauma (75%)
3. Patients admitted to intensive care units (28.85 to 33.9%)
4. Chronic obstructive pulmonary disease (21.5%)
5. Hospitalized patients (2.2 to 3.1%)

Clinical features (all are due to ATP depletion)
Clinical features occur mainly when plasma phosphate falls < 1 mg/dL(0.32 mmol/L)³,⁴.
CNS Manifestations
Nervous system involvement is very common in patients with severe hypophosphatemia. Irritability and paresthesias, which can progress to confusion, seizures, delirium, and coma. This can lead to metabolic encephalopathy due to ATP depletion.

Cardiopulmonary system manifestation
Myocardial contractility may be impaired with ATP depletion (leads to cardiac failure).

Hypophosphatemia can result in arrhythmias in patient with acute myocardial infarction.

Respiratory failure (due to diaphragmatic weakness) can also occur.

Diminished respiratory rate and tidal volume in mechanically ventilated patients.

Skeletal and smooth muscle problems
Muscle weakness is the most common physical finding of hypophosphatemia.

Proximal myopathy (limb weakness like hypokalemia), dysphagia and paralytic ileus (affecting smooth muscle). Acute hypophosphatemia upon preexisting severe phosphate depletion can lead to rhabdomyolysis

Blood Hemolysis, defective clot retraction and thrombocytopenia are also very common.

Investigation and interpretations
1. Serum phosphate, calcium, magnesium, potassium, PTH
2. Urinary phosphate or 24-hour urine phosphate level – daily urine phosphate excretion should be <100 mg and the fractional excretion of phosphate (FEPO4) should be well below 5 percent (normal value is 5 to 20 percent) if the kidney is responding normally and renal phosphate wasting is not the cause of the hypophosphatemia. The formula for this is:

   \[ \text{FE PO4} = \frac{\text{U. PO4} \times P \times \text{Cr} \times 100}{\text{U. Cr} \times \text{P. PO4}} \]

   where U and P refer to the urine and plasma concentrations and Cr for creatinine. Urinary phosphate excretion >100 mg/day or a FEPO4 >5 % is indicative of renal phosphate wasting in patients with hypophosphatemia.

   • The triad of hypercalcemia, hypophosphatemia, and urinary phosphate wasting is usually present in primary hyperparathyroidism.

   • Hypocalcaemia, hypophosphatemia, and urinary phosphate wasting is usually present in secondary hyperparathyroidism.

   • Hypophosphatemia and urinary phosphate wasting without hypercalcemia think about vitamin D deficiency.

Treatment
In asymptomatic patients with a serum phosphate less than 2.0 mg/dL (0.64 mmol/L), are to be given oral phosphate, 30 to 80 mmol of phosphate/day in 3 divided doses. They can alternatively be given skim milk, which contains nearly 15 mmol of phosphate / 480 mL(or approximately 1gm/L). Often, oral phosphate correction is not desirable in critically ill patients mainly due to malabsorption. Traditionally, IV phosphate treatment is recommended if serum phosphate level is <1.0mg/dL (0.32 mmol/L), or symptomatic. Given the potential physiologic benefits of phosphate repletion in these patients, considerable interest has been given to developing safe and efficacious intravenous phosphate repletion regimens.

Traditional Management
If the serum phosphate is >1.3 mg/dL (0.40 mmol/L), give 0.08 to 0.24 mmol/kg over six hours (up to a maximum total dose of 30 mmol).

If the serum phosphate concentration is <1.3 mg/dL (0.40 mmol/L), give 0.25 to 0.50 mmol/kg over 8 hours (up to a maximum total dose of 80 mmol). The lack of efficacy of traditional protocols, along with concerns of compromising intravenous lines during prolonged phosphate infusions, has led to a move toward more aggressive intravenous phosphate repletion regimens.

Aggressive Management
Correction according to body weight and phosphate level in aggressive correction method in critically ill patients in ICUs. If the serum phosphate is 2.2 to 2.5 mg/dL (0.73 to 0.96 mmol/L), 0.32 mmol/kg should be given over 4 hours. If the serum phosphate is 1.6 to 2.2 mg/dL (0.51 to 0.72 mmol/L), 0.64 mmol/kg should be given over 4 hours. If the serum phosphate is less than 1.6 mg/dL (0.50 mmol/L), 1.0 mmol/kg should be given over 4 hours.

IV administrations should be diluted in 5% dextrose or 0.9% normal saline.

Desperate Management
- Administration of 15 mmol of intravenous sodium phosphate over 2 h (repeated up to three times over 24 h) is also a well tolerated regimen for patients with moderate hypophosphatemia (0.32 to 0.64 mmol/L), normal renal function, and normocalcemia.

- Administration of 0.8 mmol/kg intravenous phosphate over 30 min to patients with severe hypophosphatemia (less than 0.32 mmol/L), is also well tolerated.

- Existing evidence suggests the overall advantage of faster, more aggressive and tailored intravenous phosphate repletion regimens.

- Urinary phosphate wasting can be treated with Tab. Dipyridamole (75 mg four times daily)

CONCLUSION
Hypophosphatemia is a common but missed electrolyte abnormality that we come across in intensive care practice. Hypophosphatemia per se can aggravate critical illness. Patient with hypophosphatemia should be managed effectively. We recommend a safe and efficacious intravenous phosphate repletion regimens as stated below:

- If the serum phosphate is 2.2 to 2.5 mg/dL (0.73 to 0.96 mmol/L), 0.32 mmol/kg should be given over 4 hours.

- If the serum phosphate is 1.6 to 2.2 mg/dL (0.51 to 0.72 mmol/L), 0.64 mmol/kg should be given over 4 hours.

- If the serum phosphate is less than 1.6 mg/dL...
In regards to hypophosphatemia, there are practitioners who are confused about how to correct the imbalance. In a modern day setting, hesitation of correction of hypophosphatemia is not warranted and as we recommend, practitioners should—“Just do it!”

**REFERENCE**


(0.50 mmol/L), 1.0 mmol/kg should be given over 4 hours.
INTRODUCTION

QT interval reading on the electrocardiogram (ECG) is gaining clinical importance mainly due to its interval prolongation predisposing to a potentially fatal ventricular arrhythmia named as torsades de pointes (TdP). TdP is type of polymorphic ventricular tachycardia with rapid asynchronous complexes which is life-threatening expressed as a distended baseline on electrocardiogram. In the last decades, many drugs are being withdrawn due to the undesirable effects of TdP, leading to detailed assessment of drug QT interval. Multiple factors are involved in the occurrence of QT prolongation and TdP. Among these, the usage of QT interval prolonging medications draws special attention. Bringing awareness about QT prolongation and the risks associated with TdP can help the treating clinicians, pharmacists and health care providers to improve the treatment and management of patients in arrhythmias. The purpose of this article is to caution and guide the health care providers by reviewing the classified drugs commonly used in and around Amrita School of Medicine and its hospital as well as the prevention modalities to consider while prescribing and dispensing QT interval prolonging medications. This will help reduce the occurrence of this potentially fatal condition and promote overall improvement of patient care.

BACKGROUND

Prolonged QT interval is an important risk factor known for the occurrence of ventricular arrhythmia and sudden cardiac death. QT prolongation is one of the most common reasons for drugs withdrawal from the market, despite the benefit quotient of these drugs for certain patient population. In drug safety studies, QT interval prolongation is often combined with TdP which is a rare ventricular arrhythmia known to have association with QT prolongation and drugs contribute to relatively 5% frequency of TdP. Approximately 1 in 1200 patients are reported to have a prolonged QT interval without any subjective symptoms and the time window of drug induced TdP is considered to be from several hours to months post consumption of these drugs. The first clinical descriptions of congenital long QT syndromes of drug induced arrhythmias, and distinctive arrhythmia TdP were dated back to 1950s and 1960s.

In the earlier days, preclinical modelling of in vitro and in vivo data was established to assess the safety boundary for clinical use and to provide some assurance of human safety. In phase III clinical trials, the studies similarly included ECG assessment mainly for signal detection and general patient safety instead of an absolute definition of QT effect. However recently the pattern for new molecular entities has shifted which means the QT assessment has moved to the forefront of safety assessment in drug development. Role of genetic variants associated with large adverse drug effects might be an important key in understanding the risk stratifications which can give more insight into the genes and proteins relevant for drug induced QT interval prolongation and arrhythmias. It can result in personalized prescription if effect is fully dependent on a genotype. As ethnic differences ultimately reflect genetic variation, it is useful to be aware about the susceptibility to drug induced QT interval prolongation. Studies prove that Caucasians seem to be more sensitive to drug induced QT interval prolongation than other ethnicities. Thus, ethnicity is considered as an important factor when determining the risk of ventricular arrhythmias.

QT interval prolongation is one of the leading causes of drug relabeling or withdrawal of drugs from the market. Prolongation of QT interval is analyzed as a biomarker for assessing the development of cardiac arrhythmias, including TdP arrhythmias. Women comprise 70% of a meta-analysis of 332 reported cases of cardiovascular drug related TdP in a study. They are prone to have longer QT intervals and higher risk of TdP than men largely because of effects of sex hormones on myocardial tissue.

ABSTRACT

Drug induced prolongation of QT interval is a unique clinical entity evolving from an electrophysiological parameter that has become the focus of health concern to health care professionals and regulatory bodies today. This entity triggers a serious adverse event that disturbs the benefit risk balance, which reflects on the drug prescription of the specific drug by a clinician as well as dispensing clinical Pharmacists. This review outlines the commonly used drugs within and around Amrita Institute of Medical Sciences (AIMS) that has the potential to prolong QT interval to create awareness amongst the health care providers for improved patient safety.

Medicines Known To Prolong The Q-T Interval: Calls For Attention Of Clinicians, Clinical Pharmacists And Health Care Providers

Divya M George, P G Nayar

INTRODUCTION

Potential to prolong QT interval to create awareness amongst the health care providers for improved patient safety.

Dept. of Pharmacology, AIMS, Kochi.
Human Ether-à-go-go Related Gene (hERG) is a gene that encrypts the alpha subunit of voltage gated potassium channel (pore-forming) in the heart/nervous tissue. The hERG potassium channels conduct the delayed rectifier potassium current that is important for the repolarization of action potential. Hence a reduced HERG current due to adverse drug effect is expressed as prolonged QT interval or an increased TdP risk and sudden death leading to the occurrence of hereditary or acquired long QT syndromes. A normal corrected QT (QTc) interval ranges from 370 milliseconds to 440 milliseconds for men and up to 460ms in women. A QTc greater than or equal to 500ms or an increase in the QTc interval by 60ms from baseline increases the risk of drug induced TdP. Drugs with potential to cause TdP are associated with QT prolongation. The common feature of drugs associated with acquired long QT syndrome and TdP is their ability to produce pharmacological inhibition of activity of hERG potassium ion channel and its native cardiac equivalent, the rapid delayed rectifier K+ current. Obstruction of IKr current manifests clinically as prolonged QT interval and emergence of other T or U wave abnormalities on the surface ECG. During cardiac depolarization, positive ions such as sodium or calcium flow into the cardiac cells followed by efflux of potassium which exceeds the influx of sodium and calcium resulting in ventricular repolarization. Disruption of this process leads to excess of positive ions intercellularly causing further ventricular repolarization and prolongation of QT interval.

A normal corrected QT (QTc) interval ranges from 370 milliseconds to 440 milliseconds for men and up to 460ms in women. A QTc greater than or equal to 500ms or an increase in the QTc interval by 60ms from baseline increases the risk of drug induced TdP. A prolonged heart rate corrected QT interval is usually defined as above 450ms in men and above 470ms in women thereby increasing the risk of TdP. Drugs with potential to cause TdP frequently inhibit the rapid component of IKr which causes a reduction in the net repolarizing current and results in prolongation of ventricular action potential duration and a prolonged QT interval on the ECG (Fig.1). Drug induced QT prolongation acts as a marker for risk of progression to TdP. However, drug induced QT interval prolongation always does not lead to TdP. Multiple risk factors are known to facilitate TdP with QT prolonging drugs amongst which the most common risk factor is female gender. Women post puberty have a prolonged baseline QT interval and show adverse response to IKr blocking drugs when compared to males.

**CLINICAL PRESENTATION**

The clinical symptoms related to TdP are similar to other arrhythmias which include tachycardia, hypotension, dizziness, chest pain, shortness of breath, syncope and seizure. TdP can be self-limiting but can rapidly progress into ventricular fibrillation causing sudden cardiac death due to lack of circulation. Any clinical feature which indicates ventricular tachycardia such as dizziness, lightheadedness, syncope or palpitation/outbreak of polymorphic ventricular tachycardia can be seen on continuous electrocardiographic monitoring which demands immediate measurement of QT and QTc on electrocardiographic tracing.

**QT INTERVAL-PROLONGING DRUGS**

Many drugs are associated with QT prolongation. The common feature of drugs associated with acquired long QT syndrome and TdP is their ability to produce pharmacological inhibition of activity of hERG potassium ion channel and its native cardiac equivalent, the rapid delayed rectifier K+ current.

The most commonly reported drugs prescribed in and around Amrita hospital known to cause QT interval prolongation and/or TdP are summarized based on the organ classification.
# MOST COMMONLY REPORTED QT PROLONGING MEDICATIONS AND/OR IN ASSOCIATION WITH TORSADES DE POINTES

<table>
<thead>
<tr>
<th>Class of Drugs</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholinesterase inhibitor</td>
<td>galantamine</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>diphenhydramine, hydroxyzine, terfenadine</td>
</tr>
<tr>
<td>Histamine H2 receptor antagonist</td>
<td>famotidine</td>
</tr>
<tr>
<td>Cortisol receptor blocker</td>
<td>mifepristone</td>
</tr>
<tr>
<td>Hormone</td>
<td>oxytocin</td>
</tr>
<tr>
<td>Phosphodiesterase Type 5 Inhibitor</td>
<td>vardenafil</td>
</tr>
<tr>
<td>Skeletal muscle relaxant</td>
<td>tizanidine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>citalopram, desipramine, doxepin, imipramine, nortryptiline, lithium, venlafaxine, sertraline</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>clozapine, haloperidol, risperidone, quetiapine</td>
</tr>
<tr>
<td>Opioid</td>
<td>methadone</td>
</tr>
<tr>
<td>Anaesthetic agent</td>
<td>propofol</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>disopyramide, flecainide, ibutilide, sotalol, procainamide, quinidine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class of Drugs</th>
<th>Generic Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>hydrochlorothiazide, indapamide, torsemide</td>
</tr>
<tr>
<td>Gastroprokinetic</td>
<td>cisapride</td>
</tr>
<tr>
<td>Antiemetic</td>
<td>domperidone, metoclopramide, granisetron, ondansetron</td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>pantoprazole</td>
</tr>
<tr>
<td>Antimicrobial</td>
<td>metronidazole, norfloxacin, azithromycin, clarithromycin, erythromycin, gemifloxacin</td>
</tr>
<tr>
<td>Antifungal</td>
<td>ketoconazole, voriconazole</td>
</tr>
<tr>
<td>Antiviral</td>
<td>saquinavir</td>
</tr>
<tr>
<td>Fluoroquinolone antibiotics</td>
<td>ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin, ofloxacin, sparflxacin</td>
</tr>
<tr>
<td>Antimalarial</td>
<td>halofantrine, hydroxychloroquine, chloroquine</td>
</tr>
<tr>
<td>Macrolide antibiotic</td>
<td>roxithromycin</td>
</tr>
<tr>
<td>Anticancer</td>
<td>tamoxifen</td>
</tr>
<tr>
<td>Kinase inhibitor</td>
<td>sorafenib</td>
</tr>
<tr>
<td>Anti Hyperlipidemic Imunosuppressant</td>
<td>probucoc, tacrolimus</td>
</tr>
</tbody>
</table>
I. DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

Galantamine, a reversible inhibitor of acetyl cholinesterase is prescribed for the treatment of Alzheimer’s disease. The drug being a weak blocker of HERG channel further results in mild prolongation of QT interval. Hence, patients are prone to cardiac arrhythmia on over dosage or with drug interactions involving cytochrome 2D6 drug metabolizing enzyme.

II. AUTACOIDS AND RELATED DRUGS

The second generation non sedating antihistamines have been reported to cause QT prolongation and in some cases TdP. These drugs are mostly metabolized via hepatic cytochrome P450 CYP3A4 system. Overdoses, consumption at normal doses with concurrent use of drugs that inhibit hepatic cytochrome P450 enzymes, impaired liver function, or in patients with congenital long QT syndrome contribute to incidence of prolonged QT interval. In addition, co administration of non sedating antihistamines with other drugs causing QT prolongation like antiarrhythmic, antipsychotics, tricyclic depressants increase their adverse effect on cardiac repolarization. However, the overall review of literature indicated that potential to cause TdP is not a class effect of non-sedating antihistamines except drugs like terfenadine having potent pro arrhythmic risk whereas loratadine, cetrizine are probably not associated with QT prolongation.

The most commonly used QT prolonging antihistamines today are diphenhydramine, famotidine, hydroxyzine and terfenadine.

Diphenhydramine is a freely available over the counter H-1 antihistamine with anticholinergic and local anesthetic properties prescribed for allergies, cough and sleep. At higher concentrations, diphenhydramine is reported to inhibit potassium channels resulting in QT interval prolongation and abnormal ventricular repolarization. The literature reports a case of a 44 year old woman who consumed more than 3g of diphenhydramine along with alcohol as a suicidal attempt. The woman presented with palpitations and chest pain to the emergency room. She was examined and noted to have shown QTc interval prolongation at 786ms on ECG with non-sustained polymorphic ventricular tachycardia. The changes reverted to normal by day 5 with normal QT interval with supportive treatment. The report suggested that an overdose of diphenhydramine with concomitant alcohol use could induce TdP in an otherwise normal heart.

Famotidine, an H2 receptor inhibitor used for the treatment of peptic ulcer has shown QT prolongation administration. In a study, it has been proved that famotidine use especially in subjects with electrolytes imbalance increases the proarrrhythmic potential. An analysis of QT/QTc intervals from a database of ECG recordings observed that famotidine administration induced a prolonged QTc interval that was potentiated in patients with risk factors for cardiovascular irregularities. Hydroxyzine, first generation antihistamine with anticholinergic properties is approved for the treatment of chronic urticaria, mild anxiety and as second line therapy for insomnia in children up to 6 years and as premedication prior to general anesthesia. Literature reports a case of a 72 year old man where hydroxyzine was identified to induce QTc interval prolongation in the patient’s active medication. Before hydroxyzine treatment QTc was determined at 450ms. On day 1, hydroxyzine was introduced and on day 4, the patient presented several syncopal events concomitant with QTc prolongation measured as 590 and 582 ms respectively at day 6 and 10 along with acute renal and liver failures, sinus bradycardia and hypokalemia. On discontinuation of hydroxyzine, QTc returned progressively to normal value without recurrence of syncope.

The association of hydroxyzine especially at high posology, TdP risk factors such as hypokalemia and bradycardia could induce QT prolongation and life threatening TdP. It is marketed as a drug with conditional risk of TdP and is contraindicated for patients with congenital long QT syndrome.

Terfenadine, is an anti-allergic drug with antihistaminic properties are reported to be associated with fatal cases where ventricular arrhythmia accompanied QT prolongation. The mechanism of QT prolongation by terfenadine involves prolongation of myocardial repolarization time via delayed outward K+ current inhibition. The FDA recommended to remove terfenadine from the market in 1997 due to its proarrhythmic risk for long QT related TdP and known effects on hERG.

III. HORMONES AND RELATED DRUGS

Mifepristone, an oral progesterone antagonist for termination of pregnancy along with its metabolites block IKr. It prolongs the QTc interval in a dose related manner. The prescribing information leaflet describes little or no experience with high exposure; avoid concomitant dosing with other QT-prolonging drugs or potassium channel variants resulting in a long QT interval. To minimize risk, lowest effective dose should be prescribed.

Oxytocin is a nine amino acid peptide having a physiological function in parturition and parenteral administration of the synthetic peptide used to induce labor and control post partum hemorrhage. Cases of intravenous oxytocin prolonged QTc intervals and triggered ventricular arrhythmia during cesarean section under spinal anesthesia has been reported by Guillon et al.; Liou et al. A large and transient QTc interval prolongation has been observed after oxytocin administration during first trimester induced abortion curettage under general anaesthetics.

Vardenafil, a potent and selective phosphodiesterase type 5 inhibitor (PDE5) indicated for treatment of erectile dysfunction is warned by the FDA as per post marketing studies for its risk of additive effect on QT interval prolongation with concomitant use of other drugs known to exert this effect.

IV. DRUGS ACTING ON PERIPHERAL NERVOUS SYSTEM

Tizanidine, centrally acting imidazoline muscle relaxant
prolongs the QT interval by blocking IKr. Patients are at risk of cardiac proarhythmia during impaired drug elimination such as in case of CYP1A2 inhibition during drug interactions24.

V. DRUGS ACTING ON CENTRAL NERVOUS SYSTEM

a. Antidepressant

Tricyclic antidepressants (TCA) are used for the treatment of multiple psychiatric and non psychiatric disorders have been reported to cause QT interval prolongation. TCAs prolong the Qtc predominantly by blocking the sodium channel which is more pronounced if a potassium channel blocking agent is co-administered10. Amitriptyline, desipramine, doxepin, nortriptyline and desipramine which are known QT prolonging medications are contraindicated for concomitant use with 2 or more QT/QTc interval prolonging drugs26.

b. Antipsychotic

Antipsychotic drugs are broadly used for treatment of schizophrenia, mood disorders and certain somatic symptoms. The first generation antipsychotics namely chlorpromazine, haloperidol were classified as torsadogenic drugs and carried a black box warning of sudden death27. Drug induced ventricular arrhythmia and sudden cardiac death (SCD) are reported as severe adverse events because medication that delay ventricular repolarization can provoke TdP progress to VA consequently resulting in SCD27. Antipsychotic drugs increase the risk of serious VA, through blockade of potassium channels and prolongation of cardiac repolarization29. These drugs prolong the QT interval in a dose dependent manner and are well known to cause TdP.

Thioridazine one of the most frequently prescribed antipsychotic drugs now carry a black box warning of an increased risk of cardiac arrhythmias and sudden death28. Other antipsychotic medications with an increased risk of VA/SCD included haloperidol, quetiapine and risperidone.

Clozapine, second generation antipsychotic blocked the hERG channel which is strongly associated with drug induced QT interval prolongation. The patients who are new antipsychotic users are prone to have the highest risk. Hence antipsychotics should be prescribed cautiously during the initial treatment phase27.

Haloperidol is potent blocker of IKr channel and prolongs QT interval by 15-30ms; it received FDA alert suggesting ECG monitoring with its IV use. Phenothiazines such as chlorpromazine have an antipsychotic and antiemetic effect. Both chlorpromazine and thioridazine have been implicated with QT prolongation and TdP due to their potassium blocking effect10.

The mechanism of QT prolongation in antipsychotics and antidepressants are reported to involve a quinidine-like effect, while a range of factors are cited in literature such as electrolyte imbalance, myocardial membrane enzyme disorder myocardial tissue regeneration and effects on autonomic nervous system21.

c. Opioid analgesic

Methadone is a synthetic opioid used for treating heroin addiction and chronic pain syndrome in palliative care. The drug delays cardiac repolarization by blocking the rapid component of potassium ion current potassium channels, encoded by hERG gene making it independently associated with a prolonged corrected QT interval and progression to TdP. The literature reported a case of 65 year old man who was a previous intravenous heroin user complaining of feeling unwell, chest pain during exercise, nausea, vomiting for few days, recurrent episodes of apnea, palpitation and dizziness since the night before. The patient was prescribed methadone syrup 240mg daily. The ECG demonstrated sinus bradycardia and QTc of 550ms following which he was hospitalised for ECG monitoring and developed an episode of TdP and ventricular fibrillation. The QTc interval progressively returned to normal limits on adequate treatment along with discontinuation of methadone and substitution with buprenorphine. The recommended dose for methadone therapy is about 60-100 mg/day; high dose has been reported to cause prolonged QTc interval28.

Clinicians should carefully review the patient’s current medications to look for other drugs that can prolong the QT interval. The patients should be instructed to report any episodes of palpitations, syncope; conditions that can cause hypokalemia eg. gastroenteritis or addition of diuretics to patient’s regimen. Periodic ECG monitoring of QTc interval and discontinuation of offending medications in the setting of prolonged intervals is ideal28.

d. Hypnotic/ Anaesthetic agent

Widely used anesthetic drug reported to prolong QT interval is propofol which is used for induction and maintenance of general anesthesia. Several investigators have described unexpected life threatening ventricular tachyarrhythmia, sudden cardiac arrest and death during general anesthesia in patients suffering from undiagnosed long QT syndrome. One such case of a 71 year old woman with acute myocardial infarction was reported who experienced marked QT prolongation during anesthesia with propofol to allow mechanical ventilation. Drugs concomitantly used were heparin, nitroglycerin, dopamine and pipercillin. The QTc interval shortened after withdrawal of propofol which was rechallenged and further prolongation of QT interval was noted. Propofol was replaced with midazolam without prolongation of QT interval29.

VI. DRUGS ACTING ON CARDIOVASCULAR SYSTEM

a. Antiarhythmic drugs

These group of drugs are the leading cause of drug induced TdP. Class IA agents (quinidine, procainamide and
disopyramide) block both sodium and potassium channels, and TdP can occur either at therapeutic or sub-therapeutic doses. Quinidine prolongs QT interval by an average of 10-15% within a week of initiation of therapy and carries 1.5% risk of inducing TdP. Disopyramide is implicated in TdP and is contraindicated in patients with heart failure, liver or renal dysfunction. Class III agents are potent IKr blockers and prolong QT interval in a dose dependent manner. Ibutilide and sotalol carry the highest risk for TdP whereas amiodarone has the lowest risk. Sotalol causes TdP in 2-4% patients with a higher risk in women. Intravenous ibutilide carries TdP risk of 1-3% with higher incidence in patients with structural heart disease, heart failure and electrolyte disturbance. Sotalol according to WHO is the commonest cause of drug induced TdP. It blocks the rapid component of IKr channels within the myocardium which delays repolarization prolonging the QT interval and increases the risk of ventricular arrhythmias. Flecaïnide, first line antiarrhythmic sodium channel blocker can induce QT prolongation leading to TdP which was reported in 32 year old man with structurally normal heart and persistent atrial fibrillation. The patient was prescribed diltiazem and flecaïnide 50mg twice/day a year prior to presentation which was increased to 150mg twice/day. This was associated with a progressive lengthening of his corrected QT interval. Hence the clinicians should be cautious and consider periodic evaluations with ECG. Indapamide is reported as blockade of slow component of delayed rectifier current leading to prolongation of cardiac repolarization. A case of woman with systemic lupus erythematosus and hypertension receiving prednisolone and indapamide respectively was reported to have developed long QT and TdP ventricular tachycardia. The drug can cause potassium independent prolongation of QT interval resulting in arrhythmia induced syncope.

VII. DRUGS ACTING ON KIDNEY

Diuretics indirectly increase the risk of TdP by causing the excretion of potassium and magnesium. If untreated, these electrolyte disturbances can increase patient risks. Effects of other drugs that prolong the QT interval are exacerbated by hypokalemia and hypomagnesemia. A case of TdP has been reported to occur during orthotopic liver transplantation in a 4 year old boy caused by an acute extracellular hypokalemia with normal serum magnesium concentration and no previous anti-arrhythmic drug exposure. Furosemide 15mg intravenously was given to the child during the hepatic phase when the urine output was minimal. Prolonged corrected QT interval of 600ms was noted followed rapidly by TdP of 5.6 seconds duration resulting in severe systemic hypotension. The commonly used diuretics with possible risk of TdP are furosemide, hydrochlorothiazide, indapamide and torasemide. Routine monitoring of electrolytes especially potassium is recommended in those who are on diuretics and QT prolonging medications.

VIII. DRUGS ACTING ON GASTROINTESTINAL SYSTEM

Cisapride, gastrointestinal promotility agent used for gastroesophageal reflux disease and delayed gastric emptying time was related to the greatest number of TdP cases next to antiarrhythmic agents resulting in its withdrawal from US market. Its structurally similar to procainamide having both IKr and IKs blocking effect. The Medicines Control Agency suspended the product license of cisapride in UK and US as the risks vs benefits balance was no longer considered favourable. The drug was reported to have caused QT prolongation in diabetic patients. A case describing QT prolongation resulting from concomitant use of cisapride and agents known to inhibit its metabolism was reported. Clarithromycin inhibits CYP3A4, isoenzyme responsible for the metabolism of cisapride. Concomitant administration of cisapride with agents inhibiting CYP3A4 like azole antifungals, erythromycin, clarithromycin have resulted in elevated cisapride concentrations which in turn is associated with QT prolongation, syncopal episodes and cardiac dysrhythmias. Case reports of arrhythmias have been reported in cisapride coadministration with metoclopramide.

Administration of 5-hydroxytryptamine 3-receptor antagonists such as granisetron, ondansetron as antiemetic agents is associated with prolongation in QT intervals on ECG. Intravenous granisetron but not ondansetron causes clinically asymptomatic and transient changes on ECG measurements in children receiving high dose methotrexate therapy. Ondansetron is used to prevent nausea and vomiting associated with cancer treatment and post operative procedures. A study of post operative nausea and vomiting found that post anesthesia patients possessed longer QTc intervals which raised a warning message for the drug to be used with caution post surgery owing to the risk of TdP.

IX. ANTI MICROBIAL DRUGS

Antimicrobials (erythromycin, clarithromycin, fluoroquinolones, antifungals and and antimalarials) are reported to cause TdP as a result of QT prolongation. Similar to class III antiarrhythmics and antihistamines, macrolides prolong the QT interval and cause dispersion of repolarization across the ventricular wall, resulting in the induction of TdP. Amongst the fluoroquinolones,sparfloxacin exerted a pure class III electro physiological effect whereas levofloxacin and ofloxacin do not. Apart from grepafloxacin and possibly sparfloxacin, the fluoroquinolones that are currently on the market or soon to be launched are safe from the point of view of QT prolongation and TdP. The frequency of this adverse event generally occurs at a rate of about one per million prescriptions. A case report of patient who developed TdP while taking levofloxacin was reported. Prolongation of QT interval is a class effect of fluoroquinolones including levofloxacin. The clinicians/clinical pharmacists should be careful when this agent is used with type IA and type III anti-arrhythmic agents and in situations such as hypokalemia and hypomagnesaemia that increase the risk of pro-arrhythmic events. Sparfloxacin with improved activity against gram positive cocci, including beta lactamase resistant pneumococci increases the duration of QT interval. Moxifloxacin and sparfloxacin are new quinolones reported to have developed TdP from QT prolongation, both drugs mechanism involves K+ channel inhibition. Antimalarials namely
chloroquine, halofantrine, hydroxychloroquine, quinidine are capable of prolonging the QT interval. Halofantrine induces a dose related prolongation of the QT interval and should not be given with other drugs that prolong QT interval or to patients with any form of cardiac condition associated with QT prolongation. Cardiotoxicity of antimalarials is increased in patients with acute renal failure especially after 3 days of treatment. Metronidazole is a widely used antimicrobial medication and a potent inhibitor of CYP3A4 and CYP2C9 isoenzymes. Thus it can cause QT prolongation by inhibiting the metabolism of other drugs having the potential to cause QT prolongation like omeprazole having the similar mechanism. As a result, metronidazole with concomitant use of omeprazole can cause indirectly QT prolongation and TdP through its interaction with other QT prolonging agents. Intravenous metronidazole can prolong QT interval in susceptible patients and should be used with close monitoring of ECG.

Antifungal agents fluconazole, ketoconazole, voriconazole prolong QT interval by blocking the IKr channels. Similar to antibiotics, ketoconazole and itraconazole inhibited the hepatic cytochrome P450 CYP3A4 isoenzyme. Thus their coadministration with another QT prolonging drug metabolised by cytochrome P450 CYP3A4 isoenzyme, such as terfenadine will result in a notably prolonged QT interval and increase the risk of TdP. A case of 16 year old boy with a 3.5 year history of Crohn’s disease was hospitalised for the treatment of an acute flare of Crohn’s disease and a perirectal abscess. The patient was prescribed ciprofloxacin intravenously 400mg twice daily and metronidazole 500mg every six hours. Within 48 hours of administration of ciprofloxacin, the patient became bradycardic. The ECG findings showed a mild prolongation of QT interval and low heart rate. The antimicrobial therapy was changed to ampicillin and then to linezolid and patient’s Q-T interval was normalised within 7 days of ciprofloxacin discontinuation. Roxithromycin is a widely used macrolide antimicrobial for broad variety of infections such as upper respiratory tract infection and community acquired pneumonia. Prolongation of QT interval after 3 days of treatment with roxithromycin was reported in 72 year old patient with congestive heart failure caused by ischaemic heart disease.

Azithromycin, semisynthetic macrolide antibiotic and levofloxacin, fluoroquinolone antibiotic are the most commonly prescribed antibiotics today especially in U.S. Both drugs are used alone or in combination with other antibiotics to treat common bacterial infections including respiratory infections, sexually transmitted diseases, urinary tract infections and uncomplicated skin and soft tissue infections. There was azithromycin induced potential QT prolongation and fatal torsades de pointes reported by the FDA. The decision to start azithromycin or levofloxacin treatment should be based on a careful evaluation of preexisting comorbidities, risk factors of QT prolongation and concomitant medication use. In addition, ECG should be monitored periodically for patients with an especially high risk of arrhythmia. Drug to drug interactions is reported to cause prolonged QT interval. Azithromycin when consumed with other QT prolonging drugs, they inhibit CYP enzymes and reduce the metabolism of other drugs by forming an inactive CYP complex. Chloroquine in combination with azithromycin was associated with dose dependent QT prolongation. Evidence of azithromycin induced QT prolongation and TdP are observed in patients with hypokalemia, HIV, previous history of cardiac abnormalities and in those patients concomitantly taking other QT prolonging drugs such as trazodone and methadone. Erythromycin causes QT prolongation by inhibiting the delayed rectifier K+ current and when combined with terfenadine or cisapride, erythromycin enhances QT prolongation by blocking drug metabolising enzymes. Saquinavir, anti retroviral agent which is an HIV protease inhibitor causes dose dependent QT prolongation with rare cases of TdP reported during post marketing surveillance. Based on the updated drug warning by manufacturing company in November 2010, the drug is contraindicated in patients with congenital long QT syndrome, those with refractory hypokalemia or hypomagnesemia and in combination with drugs that increase both saquinavir plasma concentrations and prolong the QT interval.

X. CHEMOTHERAPY AND NEOPLASTIC DISEASES

Molecular targeted cancer drug sorafenib is a kinase inhibitor drug approved for treatment of advanced renal cell carcinoma, liver cancer and radioactive iodine resistant advanced thyroid carcinoma reported to cause QT prolongation. Tamoxifen an anti-oestrogen drug is used in the treatment of estrogen positive breast cancer. The drug induced QT interval prolongation was reported in a 56 year old female patient with hormone dependent carcinoma of right breast. The case highlighted the risk of tamoxifen causing depression of electrical impulse in sino-atrial node, leading to symptomatic sinus bradycardia with prolonged QT interval. Another case of tamoxifen/norfloxacin interaction was reported leading to QT prolongation in an 83 year old patient with extra cranial hemangioma treated with radiation and hormonal therapy.

XI. OTHER MISCELLANEOUS DRUGS

Antihyperlipidemic drug probucol (cholesterol lowering agent) induced QT prolongation affect cardiac repolarization and prolong the QT/QTc interval. Probucol is reported to be used safely in patients with hypercholesterolemia, but ECG monitoring is necessary in female patients as well as in those with hypoalbuminemia or with ischémic heart disease. A case of TdP ventricular tachycardia associated with exacerbated prolongation of QT interval due to probucol in a patient with Romano-Ward syndrome has been reported. Tacroliumus, immunosuppressant may prolong QT/ QTc interval and cause TdP, hence should be avoided in patients with congenital long QT prolongation syndrome. ECG and electrolyte monitoring during treatment should be done in patients with congestive heart failure, bradyarrhythmia, on other medications like antiarrhythmics and with electrolyte disturbances. Use of this drug with amiodarone has been reported to result in increased tacroliumus whole blood concentrations with or without concurrent QT prolongation.
PREVENTION AND MANAGEMENT OF DRUG INDUCED QT PROLONGATION

Patients at risk for QT interval prolongation are advised to visit the emergency room if they experience palpitations, lightheadedness, dizziness or syncope. The physician should be cautious while prescribing QT prolonging drugs considering appropriate but effective dosing mechanism. If serious adverse reactions as a result of drug induced QT prolongation persists, it would be advisable to discontinue the medication and monitor the serum potassium levels. Pharmacist intervention plays a key role in minimizing the occurrence of QT prolongation and TdP by focusing on patient medication charts which aids in identifying patients at risk for QT prolongation and progression to TdP. The pharmacist has to take utmost care while dispensing QT prolonging drugs keeping in mind its risk benefit profile. The patients taking one or more QT prolonging therapies are at increased risk and require regular monitoring for QT interval changes. Electrolyte monitoring and necessary supplementation alter controllable risk factors for progression to TdP. Hospitalized patients taking diuretics who are already at risk for electrolyte abnormalities or TdP are at a high-risk group could be monitored by pharmacists on a daily basis.47

When initiating a drug with QT prolonging potential, it is necessary to consider if that drug’s benefit outweigh the risk. It is advisable to perform a baseline ECG prior to starting a new medication having a risk of TdP at a stable state. Also ensure to monitor/rectify electrolyte abnormalities throughout the course of therapy48. An ECG should also be obtained when symptoms like tachycardia, hypotension, chest pain, syncope are reported, while being prescribed with 2 or more QT prolonging medications concomitantly or when any abnormalities in electrolyte or cardiovascular disease is noted. QTc interval screening has been reported as the current approach to safety assessment of medications in clinical practice, drug development, post marketing surveillance and regulatory interventions.49

CONCLUSIONS AND PERSPECTIVES

Long QT interval is a crucial finding that is often missed by electrocardiogram interpreters. The risk for drug induced long QT syndrome is one of the most common causes of withdrawal or restriction of drugs that have been marketed. Patients in the intensive care unit (ICU) are prone to develop drug induced long QT syndrome as they receive several different intravenous medications. Additionally they can have impaired drug elimination because of reduced kidney or liver function and drug –drug interactions. The risk of QT prolongation has been reviewed to be increased in females, patients with organic heart disease such as congenital long QT syndrome, myocardial infarction, congestive heart failure; patients with hypokalemia and hepatic impairment. Preclinical and clinical evaluation is reported as cornerstone for assessing the arrhythmogenic potential of any new drug before approval.

When a QT prolonging medication is prescribed, it would be a good practice to educate the patient about the risk factors, precautions and contraindications for co-prescriptions. In clinical practice, adverse effects from QT prolongation drugs can be prevented by not exceeding the recommended dose, by restricting the dose in patients with pre-existing heart disease or other risk factors. The potassium concentration in such patients should be checked regularly and potassium sparing diuretics should be preferred.50 Pharmacovigilance studies using electronic health record data and post marketing surveillance have been reported to be a significant method of identifying potential QT effects of pharmacotherapies. To complement pharmacovigilance, post marketing surveillance allows detection of unanticipated events such as TdP, though such surveillance depends on voluntary reporting by clinicians and their ability to infer association with particular treatment.51 This review article is limited to the most commonly prescribed drugs in the hospital though there are multiple medications being reported to cause QT interval prolongation and associated TdP. In conclusion, the occurrence of TdP episodes and sudden cardiac death as an outcome of prolonged QT interval is a significant problem of all times. All health care professionals especially the clinicians and pharmacists along with patient population who receive these drugs should be aware of this risk and be provided education appropriately.

REFERENCES

Wang CP, Guo GB. Indapamide induced syncope in a patient


Important Changes to the INVIRASE® (saquinavir mesylate): Precribing Information: QT and PR Interval Prolongation and Drug Interactions.


The Laymans’ Perspective On The Limits Of Facial Asymmetry
Silpa A, Athish J, N K Sapna

ABSTRACT

Aim: To quantify laymans’ perspective on the limits of facial asymmetry that is considered esthetic.

Material and methods: Photographs of young adults, one male and one female, were selected. Photoshop CS5 was used to create an absolute symmetrical face. Three midline points, viz. glabella, subnasale and soft tissue point pogonion, were used to create a reference plane. Using the reference plane and pogonion, the photos were edited to create a mandibular asymmetry using Photoshop CS5. The photo quality prints of the edited photographs were evaluated by 65 randomly selected individuals between the age group of 18 to 25. They were asked to arrange it in the descending order as: most attractive(1), attractive(2), not attractive(3) and least attractive (4). The data was then statistically analyzed using independent T test.

Result and conclusion: Laymen identified a 4 mm shift of soft tissue point pogonion from the midline; anything more was considered unaesthetic.

Keywords: Facial asymmetry, Aesthetic, Shift of pogonion.

INTRODUCTION

Asymmetry is defined as “a lack of equality of equivalence between parts or aspects of something”\(^1\). The size, shape and arrangement of facial features contribute to the overall appearance of the individual. An imbalance in any of these on either side of the mid-sagittal plane leads to facial asymmetry. Malocclusion is not a disease state but rather a deviation from normal, so is asymmetry. Mild asymmetry of the body occurs in all individuals. This is true even in case of the face. It has been suggested that gender, culture, and race may also influence the perception of normal limits of asymmetry. Bishara et al has classified dentofacial asymmetry as dental, skeletal, muscular and functional asymmetry\(^2\). Numerous factors such as cleft lip, hemifacial microsomia, and childhood fracture of the jaw have been reported as etiological factors for various types of facial asymmetry. These conditions often result in severe and pathologic asymmetry of the face. Few studies have reported on the laterality of chin deviation, a subject that remains controversial\(^3\). Haraguchi et al documented a left sided deviation of the menton from the midline in 60% to 80% of patients with skeletal Class III malocclusion who exhibited facial asymmetry\(^4\). In contrast, other studies have reported no such trait in patients with skeletal Class III malocclusion and long faces\(^5\).

A comprehensive assessment on laymans’ perspective on facial asymmetry is still not documented in literature, which helps the orthodontists and maxillofacial surgeons, to assess the patient’s perspective and expectations. So, the aim of this study is to determine the range of soft tissue point pogonion deviation from the midline, which is considered to be aesthetic as perceived by the layman.

REVIEW OF LITERATURE

Physical attractiveness affects human life in various ways and to a significant extent. It has been proven that the face is a slightly stronger indicator of overall attractiveness than the body\(^6\). Irregularities in the position of the teeth and jaws have a significant impact on the attractiveness and aesthetics of the smile and on quality of life. These irregularities can disrupt social interaction, interpersonal relationships, and mental wellbeing and may lead to a feeling of low esteem and inferiority\(^7\). The study done by Rotem Kownar in 1997 indicates that non pathological facial asymmetry does not play an important role in human interaction\(^8\). Yet another study by Rotem Kownar suggests that the low degree of facial asymmetry found in normal people does not affect attractiveness ratings probably because they are not tuned to perceive it\(^9\). Lusine Samsonyanova and Zdenek Broukal in 2013 published a review article which showed that dissatisfaction with one’s appearance, dentist recommendation, interests and worries of parents, and impact of peers who wear braces rank among the biggest motivation factors for seeking orthodontic treatment. Understanding these factors allows better planning of resources and better assessment of requirements and priorities of treatment\(^10\). Philipp Meyer-Marcotty et al, in 2011 shows in his study that rater’s profession did not influence the point at which they identified asymmetry. A left sided deviation of nose along the facial symmetry plane led to a more negative rating of facial appearance whereas a right sided deviation of chin was rated as less attractive\(^11\). Grainne McAvinchey et al has done a study in 2014 to investigate the perception of facial symmetry in young adults, to identify the amount of chin asymmetry that is considered as normal which may benefit from correction and concluded that the perception of facial asymmetry is affected by the amount of asymmetry and the observer group, with orthodontists being more critical\(^12\).
MATERIAL AND METHODS

Photographs of young adults, one male and one female, were randomly selected. Consent was taken from the selected adults, for using their photographs for the study. Photoshop CS5 was used to create an absolute symmetrical face, by cutting the original picture into two equal halves and stitching the left side on the right. The edited photographs were then divided into two halves at the soft tissue point subnasale. Following this, the pogonion point was shifted to the right by 2 mm for every picture [Fig 1 to Fig 8].
RESULTS

1. Any deviation of soft tissue point pogonion below 4.06 ± 1.96 mm was considered to be aesthetically acceptable for the male photograph by a layman, whereas any deviation above 5.94 ± 2.11 mm was considered to be a gross facial asymmetry.

2. Any deviation of soft tissue point pogonion below 4.20 ± 2.15 mm was considered to be aesthetically acceptable for the female photograph by a layman, whereas any deviation above 5.82 ± 2.03 mm was considered to be a gross facial asymmetry.

This shift was done with respect to a plane created by joining the midline points: glabella, subnasale and soft tissue pogonion. Four photographs were created in this manner with a mandibular deviation of 2 mm, 4 mm, 6 mm and 8 mm towards right side respectively. After editing the photographs, photo quality print of the edited photographs were taken on Kodak photo quality paper of size 5×7cm, using a Kodak Noritsu qss3701 printer, and given for evaluation to 65 randomly selected individuals, between the ages of 18 and 25. They were asked to arrange the photographs in descending order according to the attractiveness of the face. The filled observation sheets were collected in 5 minutes’ time, to ensure the standardization of evaluation.

Statistical Analysis

The descending order of attractiveness of the photos were grouped as most attractive (1), attractive (2), not attractive (3) and least attractive (4) [Graphs 1 and 2].

The data was again grouped into two, for the purpose of analysis. 1 and 2 were included in the ‘attractive group’; 3 and 4, in the ‘not attractive’ group. The mean of these two groups were taken separately for male and female photographs. Mean value for ‘attractive’ group was 4.2 and 4.06 for female and male photographs respectively, and the mean value for ‘not attractive’ group was 5.82 and 5.94 respectively (Tables 1 and 2). These values were further analysed using Independent T test in SPSS software, to compare the mean value of attractive and the non-attractive photos, for which P ≤ 0.00 was considered significant.

Table 1: Group Statistics for female photograph

<table>
<thead>
<tr>
<th>Image</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female Attractive</td>
<td>130</td>
<td>4.20</td>
<td>2.154</td>
<td>.189</td>
</tr>
<tr>
<td>Female not Attractive</td>
<td>130</td>
<td>5.82</td>
<td>2.030</td>
<td>.178</td>
</tr>
</tbody>
</table>

Table 2: Group statistics for male photograph

<table>
<thead>
<tr>
<th>Image</th>
<th>N</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>Std. Error Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Attractive</td>
<td>130</td>
<td>4.06</td>
<td>1.960</td>
<td>.172</td>
</tr>
<tr>
<td>Male not Attractive</td>
<td>130</td>
<td>5.94</td>
<td>2.112</td>
<td>.185</td>
</tr>
</tbody>
</table>
DISCUSSION
Facial asymmetry is the inequality of the facial structures on both sides of the face. The importance of symmetry of face and the influence of it in the social acceptance of an individual has long been studied and recorded in the literature. Edler et al and Meyer-Marcotte et al studied the subjective rating of facial asymmetry on the basis of frontal photographs. The more pronounced the asymmetry rating, the greater the need for treatment. There was a high correlation among clinical experts between the subjective rating of facial asymmetry and the need for orthodontic treatment. So, such a study sheds light on the need for quantification and correction of facial asymmetry. Taking this necessity into consideration, we conducted this study to define a limit on the facial asymmetry which could act as a guide in deciding if a major correction is needed or not.

Judgmental nature of human beings and the variation of this nature is reflected in the perception of facial asymmetry by individuals in various walks of life. Laymen’s perspective is more important than the perspective of a trained eye, as far as the patient is concerned. Variation in the perception between the orthodontist and a layman, and the variation among the various ethnic groups were studied by Grainne Mc Avinchey et al. The result showed that there were statistically significant differences in the amounts of asymmetry that the lay people and orthodontists consider to be normal (5.6 ± 2.7 mm and 3.6 ± 1.5 mm). As this showed that the influence of training can affect the judgment of facial asymmetry, we selected the layman of a particular community on a random basis for the study. These individuals had basic literacy level but neither belonged to the field of medicine nor had undergone any sort of treatment for facial asymmetry. This ensured that bias in the judgement is eliminated and the random nature of selection can result in a more generalized opinion on facial asymmetry.

No face is perfectly symmetrical. In fact, a perfect symmetrical face is not attractive. This was proved by Swaddle et al who showed a positive result towards facial asymmetry. Photographs of a male and a female were selected, and edited to create facial asymmetry. These photographs were then analysed by 65 randomly selected individuals. This data was then statistically analysed using Independent T test. The results show that any deviation of soft tissue point pogonion up to 4.06 ± 1.96 mm and 4.20 ± 2.15 mm for male and female photographs respectively is acceptable by a layman, and anything above this is considered to be gross facial asymmetry.

REFERENCES


Hypocalcemia: A Marker of Severe Dengue

Mithun Rathen Murugan, M.Gopalakrishna Pillai

ABSTRACT

Background and Objective: Dengue virus (DENV) infection is a mosquito-borne disease that has spread very fast in the last 50 years, and is endemic in all WHO regions, except Europe. Currently, there are means to diagnose DENV infection, but none for early prediction of severity of disease. Cases of non-severe dengue may later develop into severe dengue, without any warning signs. Hypocalcemia has been demonstrated, in certain cases of malaria, severe meningococcal infections and other severe acute illnesses, to be associated with poor prognosis. We evaluated association between serum corrected calcium level and severity of Dengue based on WHO 2009 classification.

Methodology: Observational Prospective Study. A probable case of dengue was diagnosed and classified according to World Health Organization criteria and confirmed by either IgM antibody or NS1 antigen detection. Patients were divided into Severe Dengue Fever and Dengue Fever as per WHO 2009 classification. The Mean Corrected Calcium was compared between the 2 groups. Socio-demographic details were collected using an interviewer-administered questionnaire.

Results: The sample size was 68. The mean age of patients was 32 years, 60% of which were males. 31 patients (46%) were diagnosed with severe dengue fever. The Mean Corrected Calcium was found to be significantly lower in Severe Dengue Fever patients (7.83 mg/dL) when compared to Dengue Fever patients (8.48 mg/dL) [p value <0.05].

Conclusion: Serum calcium levels correlated significantly with dengue severity, being lower in patients with Severe Dengue Fever. Further studies are required to determine whether hypocalcemia can be utilized as a prognostic indicator and to evaluate effectiveness of calcium therapy in prevention of dengue complications.

Keywords: Severe Dengue Fever, Hypocalcemia, Serum calcium, Severity in dengue fever, WHO 2009 Classification of severity in Dengue Fever.

INTRODUCTION

Dengue virus (DENV) infection is a mosquito-borne disease that has spread very fast in the last 50 years, and is endemic in all WHO regions, except European region. After 1960, the incidence of dengue has shown an exponential increase, with several recent outbreaks reported mainly from South Asian countries. It is estimated that 390 million become infected with dengue per year, of which 96 million manifest apparently. Currently there are means to diagnose DENV infection, but there is no accurate means to early predict the severity of disease, as cases of non-severe dengue without any warning signs may later develop into severe dengue. Therefore, search for other factors other than the consensus warning signs is very important to help in early prediction of the cases that might progress into severe dengue. Early prediction is very important to avoid unnecessary hospitalization, or to give more attention and hospitalization to those with non severe dengue that are predicted to progress into severe dengue. Due to its high prevalence and considerable mortality, there has been heightened interest in recent years to devise effective strategies to prevent complications in severe dengue. However, at present, the pathogenesis of complications of dengue fever are incompletely understood.

The dengue virus is a single-stranded RNA virus of the genus Flavivirus, comprising four distinct serotypes (DEN-1 to DEN-4). At present, the most accepted theory is that of an abnormal or amplified immunological response occurring in a secondary infection with a different serotype than in the primary infection. This results in an antibody-dependent enhancement of immunological reaction, resulting in endothelial injury, plasma leakage, reduced intravascular volume, and circulatory collapse. Although no specific pathway has been identified linking known immunopathogenic events with definitive effects on microvascular permeability, thromboregulatory mechanisms, or both, preliminary data suggest that transient disruption in the function of the endothelial glyocalyx layer occurs, which probably enhances leakage.

Serum calcium is known to be important in cardiac and circulatory function. The administration of intravenous calcium has been a routine practice in resuscitation protocols for traumatic, hemorrhagic and cardiogenic shock, a practice supported by the presence of hypocalcemia and the observed beneficial effects of calcium therapy in these conditions. Known cardiovascular manifestations of hypocalcemia include hypotension, reduced myocardial function, electrocardiogram (ECG) abnormalities, and heart failure. Alterations in calcium homeostasis, therefore, might play a role in the pathogenesis of shock in patients with dengue infection. Researchers have postulated that autonomic dysfunction might also contribute to hypotension in dengue shock syndrome (DSS). Calcium entry via neuronal calcium channels is essential for neurotransmission, hence calcium...
OBJECTIVE
To determine the association between Mean Corrected Calcium and the Severity of Dengue fever based on the WHO 2009 Classification.

Study Population and Sampling
A prospective observational study was conducted in AIMS from 2014 January to March 2015. Based on the mean & standard deviation of column in the dengue fever and severe dengue fever groups observed in existing literature (khwaja nazim Uddin et al.12) and with 99% confidence and 99% power, minimum sample size calculated came to 30 dengue fever cases and 30 severe dengue fever cases. We conducted the study on 68 inpatients aged 18-50 years. Ethical approval was obtained from the ethics review committee, Amrita Institute of Medical Sciences, Kochi. Written informed consent was not relevant as the study did not involve any intervention and was purely observational.

Inclusion Criteria
• Dengue IgM Positive (PAC-ELISA) or Dengue NS1 (Non Structural Protein 1) antigen positive
• Age 18-50 years

Exclusion Criteria
• Comorbidities: Type 2 Diabetes, Systemic Hypertension, Coronary Artery Disease, Chronic Kidney Disease, Chronic Liver Disease
• Drugs altering Calcium Homeostasis
• H/o Parathyroidectomy

Case Definitions
Dengue Fever was diagnosed as per WHO Classification 2009 (Fig1). Dengue IgM Positive or Dengue NS1 positive were the criteria for inclusion in the study. The included patients were further classified into Severe Dengue and Dengue fever based on the parameters provided in WHO Classification 2009. Patients were considered as Severe Dengue, in case of hypotension requiring IV Fluid bolus (20mL/Kg) for resuscitation or use of inotropic supports, desaturation requiring oxygen support, severe bleeding manifestations warranting pooled platelet transfusions, severe organ impairment [liver failure, renal failure], drowsy/stuporous/comatose state, myocarditis, bradycardia.

The WHO Classification(2009)
Symptomatic dengue infection

Dengue +/- warning signs
Probable dengue
live in/travel to dengue endemic area.
Fever and 2 of the following
-Nausea, vomiting
-Rash
-Aches
-Tourniquet test positive
-Any warning sign and suppotive serology; or
-Occurrence at the same location and time as other confirmed dengue cases

Warning signs**
-Abdominal pain and tenderness
-Presistent vomiting
-Clinical fluid accumulation
-Mucosal bleed
-Lethargy, restlessness
-Liver enlargement > 2cm
-Laboratory:increase in hematocrit concurrent with rapid decrease in platelet count

Severe dengue
Any of the following :
- Severe plasma leakage leading to shock or respiratory distress.
- Severe bleeding as evaluated by clinicians.
- Severe organ involvement
-liver (AST,ALT > = 1000)
-Heart and other organs

**requiring strict observation and medical intervention

Fig1
Data Collection and Analysis

Socio-demographic details were collected using an interviewer-administered structured questionnaire. The clinical parameters recorded were presence of suggestive symptoms (fever, headache, retro-orbital pain, arthralgia, myalgia, rash, and bleeding manifestations), evidence of fluid leakage (pleural effusion and ascites), pulse rate, and systolic and diastolic blood pressure, SpO2 saturation. In addition, the following investigations were performed: white cell count, platelet count, packed cell volume, serum free calcium level, ECG, liver and renal function tests. Blood samples for the estimation of serum calcium were drawn between days 5 and 10 of the fever. Hypocalcemia was defined as the presence of a serum corrected calcium < 8.5mg/dL. All data were double-entered and cross-checked for consistency. Data were analyzed using SPSS version 20 statistical software package. The significance of the differences between proportions (%) and means were tested using the z-test and student’s t-test.

RESULTS

The sample size was 68. Mean age of patients was 32 years (Range 18-50 years), 60% of which were males (n = 37). The Diagnosis was confirmed with Dengue NS1 or Dengue IgM ELISA. 46% of patients were classified as Severe Dengue (n = 31) and the rest was Dengue fever (n = 37, 54%) (Table 1). Of the Severe Dengue Patients, 67% had clinically significant bleeding requiring pooled platelet transfusion (n = 21), 32% had severe plasma leakage requiring IV Fluid bolus to maintain blood pressure (n = 10), 6% developed severe transaminitis (SGOT > 1000 IU/L) (n = 2), 3% died during the course (n = 1). The Mean Corrected Calcium in Severe Dengue Fever (7.83 +/- 0.4mg/dL) was significantly lower than Dengue fever (8.48 +/- 0.4mg/dL) [p value 0.001] (Table 2).

<table>
<thead>
<tr>
<th>Severity of Dengue</th>
<th>Corrected Calcium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue Fever</td>
<td>8.48</td>
</tr>
<tr>
<td>Severe Dengue</td>
<td>7.83</td>
</tr>
</tbody>
</table>

Table 1

Comparison of Mean Corrected Calcium Between Severe Dengue And Severe Fever
DISCUSSION

Dengue is the most prevalent mosquito-borne viral infection in the world. Each year, there are 50 million dengue infections and 500,000 individuals are hospitalized with Dengue, mainly in Southeast Asia, the Pacific, and the Americas. The average total economic burden faced by dengue epidemic in India in 2006 was estimated to be 27.4 million United States Dollar (USD). In the last decade, dengue has assumed pan-India proportions. Outbreaks and deaths have been reported from northern states of Haryana, Punjab and Uttar Pradesh; southern states of Andhra Pradesh, Tamil Nadu and Karnataka; western states of Gujarat and Rajasthan; and eastern state of West Bengal. In fact, the case fatality rate has been above 1% over the last 10 years.

To our knowledge, this is the first study evaluating the relation between Serum Corrected Calcium and severity of dengue fever based on WHO 2009 Classification. The WHO 2009 classification of Dengue Fever, includes clinically significant bleeding as well as organ failure into severe dengue which the earlier classification did not. Hence, our study has shown that hypocalcemia could be an early predictor of organ failure, clinically significant bleeding as well as severe plasma leakage which has been evidenced in previous studies. Serum calcium measurement is not a routine practice in patients with dengue infection. Further studies are required to determine whether the presence of hypocalcemia at the onset of the illness can be utilized as a prognostic indicator to predict disease severity. A pilot study conducted in Mexico on a limited number of patients with dengue infection demonstrated that oral CaCO3 plus vitamin D3 supplementation improved the overall clinical condition and reduced the duration of illness. In a similar study, oral CaCO3 supplementation significantly increased the number of platelets in patients with dengue infection when compared with a control group.

However, there are currently no randomized control trials evaluating the effectiveness of calcium therapy in the prevention of complications in dengue infection. Hence, oral or IV calcium therapy is not routinely included in published guidelines. Transient sympathetic blunting or failure could be a mechanism partially responsible for blood pressure changes in DHF. Further studies are needed to see whether serum calcium levels play a role in the above. Also, human and animal studies have to be done with special reference to elicit the role of calcium in sympathetic dysfunction. The exact mechanism for hypocalcemia in severe dengue infections also requires further study. Possible mechanisms include leak into the potential third spaces, disturbance in cellular transport, or changes in hormones involved in calcium metabolism. There are several limitations to our study. Dengue virus infection was confirmed by different serological tests (Dengue IgM ELISA, Dengue NS1 antigen). The blood tests were done on different days after onset of fever based on the patient’s presentation.

CONCLUSION

We demonstrated that serum calcium levels can be used as a marker of severity in dengue fever based on 2009 WHO Classification. Previous studies demonstrated hypocalcemia in severe plasma leakage, based on previous classification system. Our study proved the hypothesis that hypocalcemia can be used as marker of organ failure, as well as clinically significant bleeding episodes in Severe Dengue apart from plasma leakage alone. Larger trials are required to determine whether the presence of hypocalcemia can be used to prognosticate outcome in dengue fever.

REFERENCE


Usefulness of Chedoke McMaster scale in assessing Stroke recovery

Krishnan R*, Mohan Das Kurup V K**, Surendran K*, George Joseph N*

** ABSTRACT**

**Back ground & objectives:** Cerebrovascular accident is a leading cause of mortality and morbidity worldwide. The effectiveness of any rehabilitation program is decided by the functional independence achieved by the patient. The different assessment tools to determine the functional recovery includes the, commonly used FIM scale, modified Rankin assessment, Fugl Meyer scale etc. Chedoke McMaster stroke assessment scale is specifically designed for functional assessment in stroke patients.

**Methods:** 51 Patients were followed up for six months using Chedoke McMaster stroke assessment scale. All persons selected were oriented in place, time and person, and were able to comprehend instructions. Only first time stroke patients were selected for the study who were confirmed radiologically. They were evaluated at 10th day, then at six weeks and at six months post stroke.

**Results:** Thirty patients [58.82%] had cerebrovascular accident with right hemiparesis and 21 patients [41.18%] had left hemiplegia. Infarction was seen in 49 patients [96.08%] and 2 had [3.92%] hemorrhage. Chedoke Mc Master stroke assessment was done at 10th day, 6th week and 6 months to evaluate functional outcome. Statistically significant difference (P<0.001) were seen in the study among the values at 10th day, 6th week and 6 months in both impairment and activity inventory.

**Conclusion:** Chedoke McMaster Stroke Assessment could be used as a comprehensive tool to assess prognosis for locomotor recovery in patients with good comprehension after stroke. The assessment is accompanied by a clinical database and is suitable for judging the prognosis of individual patients while in rehabilitation.

**Key words:** Stroke recovery, Functional Assessment, Chedoke McMaster Stroke Assessment.

**INTRODUCTION**

Cerebrovascular accident is a leading cause of mortality and morbidity worldwide. The effectiveness of any rehabilitation program is decided by the functional independence achieved by the patient. There are different assessment tools to determine the functional recovery that includes, the commonly used FIM scale, modified Rankin assessment, Fugl Meyer scale etc. Chedoke McMaster stroke assessment scale is specifically designed for functional assessment in stroke patients. The Chedoke –McMaster Stroke Assessment is a stroke specific instrument that has demonstrated high levels of validity and reliability and though time consuming, is more useful in stroke rehabilitation. This article is based on a study conducted in Rajah Muthiah Medical College Hospital, Chidambaram, from October 2011 to May 2013.

**Stroke as a major healthcare issue**

It is estimated that around 20 million people suffer from stroke every year, and about 5 million among them die (Dalal et al 2007). 85% of deaths due to stroke occur in developing countries. Cerebrovascular accident is also a leading cause of functional impairment, with 20% of survivors requiring institutional care after 3 months and 15-30% being permanently disabled (AHA 2009). Stroke is a life changing event that affects not only the sufferers but also their families and care givers.

In one study, population-based annual stroke incidence in India was found to be 89/100,000 in 2005, which is projected to increase to 91/100,000 in 2015 and to 98/100,000 in 2030. (Ezzati et al 2004). The prevalence in India is 55.6 per 100,000 in all ages (Dalal 2007). The 28-30 day case fatality ranges from 18-41% (Dalal et al 2008, Das et al 2007). The Disability Adjusted Life Years (DALY) in India in 2009 was 6,398000, according to WHO.

**Chedoke–McMaster Stroke Assessment Scale**

The Chedoke McMaster stroke assessment includes two outcome domains: a physical impairment inventory and an activity inventory [previously called a disability inventory]. It is a direct performance examination. The time to complete the assessment is approximately one hour. The physical impairment inventory has six dimensions: shoulder pain, postural control, the arm, the hand, the leg and the foot. Each dimension is measured using a seven point ordinal scale corresponding to the stages of motor recovery. The activity inventory has two subscales: gross motor function and walking. There are 10 items in the gross motor sub scale which includes rolling, sitting, transferring, standing etc and 5 items in walking subscale including walking indoors, walking outdoors, stairs climbing etc. The activity inventory is suggested to be used with Uniform Data system for Medical Rehabilitation, which includes the FIM score. Scoring for each item is on a seven point Likert scale based on the assistance needed for that particular item, except for 2 minutes walk test which has 0 to 2 points. A higher score indicates more independence. The maximum score for the activity inventory is 100.

The Chedoke –McMaster stroke assessment was 1.92 times more responsive when compared with the FIM.
The two-inventory design can facilitate measuring treatment effects because it provides a way to classify stroke survivors into homogenous subgroups based on motor recovery. However, the scope of the activity inventory may be too narrow if administered alone because it only measures mobility function.

DETAILS OF THE STUDY

METHODOLOGY

Inclusion criteria

1. First time stroke patients
2. Duration less than 10 days
3. Medically stable patients with intact comprehension
4. Presence of radiological evidence for stroke (CT / MRI)

A pretested proforma was used to collect the data from the patients which had two parts. The first part includes personal data and second part consists of history of stroke, risk factors and co-morbidities. All the pre conditions for the clinical study were met as per stipulations. The Chedoke-McMaster Stroke Assessment (Chedoke Assessment) scale was used because it was specifically designed for functional assessment in stroke patients.

Assessment using this scale was initiated on 10th day of disease because

1. Chedoke McMaster scale is valid only after first week of stroke.
2. To ensure uniformity, as stroke patients generally report here after few days of treatment from local hospitals.

Patients were evaluated at 10th day, then at six weeks and at six months post-stroke. The Chedoke-McMaster Stroke Assessment (Chedoke Assessment) is a two-part measure made up of both a physical impairment inventory and a disability inventory. The impairment inventory can classify patients into homogeneous subgroups based on the stage of motor recovery, and the disability inventory measures change in disability (or inversely, physical function), not just impairment.

The purpose of the Chedoke Assessment’s impairment inventory is to determine the presence and severity of common physical impairments to classify or stratify patients when planning and selecting interventions and evaluating their effectiveness. Brunnstrom’s definitions of the stages were revised and test items for staging the arm and leg were modified. Four dimensions were added (shoulder pain, postural control, the hand, and the foot), and items for determining the stage of each were identified.

The purpose of the Chedoke Assessment’s disability inventory is to measure clinically important change in physical disability (apart from the arm). This inventory is designed to be used in conjunction with the Uniform Data System for Medical Rehabilitation (UDS), which includes the Functional Independence Measure (FIM). The disability inventory consists of a gross motor function index and a walking index. The measurement of these attributes is considered important for the evaluation of outcome and for the determination of effectiveness of therapeutic interventions.

The inventory has a maximum total score of 100 (70 from the gross motor function index, which has 10 items and 30 from the walking index, with five items). With the exception of item 15, each item is scored on the same 7-point scale as the FIM. To score item 15, the 2-minute walking test is used to assess the gait efficiency of ambulating patients. If the distance in meters, walked within 2 minutes is age and sex appropriate, a 2-point bonus is assigned.

Data were entered in SPSS Software and analysed using Wilcoxon signed rank test, ANOVA and paired t test.

ANALYSIS OF DATA

Age: The average age of study population was 57.8 years ± 11.8 years. The age ranged from 26-81 years. Majority (47.07%) of population was in the age group of 60-74 years. Age group of less than 40 years accounted for 7.84%; 75 and above, 5.88%.

Gender:

Males were 72.5%, females 27.5%

Stages of motor recovery

- At day 10, all 51 patients were at stage 1. At 6 weeks, 39.2% of patients were at stage 2 and the rest in stage 3. At 6 months, 19.6% were at stage 6 and 78.4% were at stage 5. Wilcoxon signed rank test was used for analysis. Difference between 10th day, 6th week and 6th month values was found statistically significant p<0.001.
- Median stage at 10th day was 1 which improved to stage 3 at 6 weeks. Similarly differences between 6 weeks median value of 3 and 6 months median value of 5 was also found significant p<0.001.
- Shoulder function between 10th day, 6th week and 6th month was also found statistically significant. Median value of 2 at 10 days improved to 4 at 6 weeks. ’p’ value<0.001. Similarly values between 6 weeks and 6 months were also found statistically significant ’p’ value<0.001.

Stage of shoulder pain

With respect to shoulder pain, 96.1% of subjects were in stage 1 at day 10. At 6 weeks 45.1% were at stage 4, and at 6 months 62.7% improved to stage 4 and 25.4% improved to stage 6. The differences between these median values were found to be statistically significant p<0.001.

Stage of postural control

Median stage of 1 at 10th day improved to stage 4 at 6 weeks and 5 at 6 months p<0.001.

Stage of Arm

Arm function improved from 1 at day 10 to 4 at 6 weeks and 6 at 6 months p<0.001.

Stage of Hand

The hand function improvement was also statistically significant from a median stage of 1 at 10th day to 3 at 6 weeks and 5 at 6 months p<0.001.

Stage of Leg

Recovery of lower extremity function also was significant with the Stage of Leg improving from 2 at 10 days to 4 at 6 weeks and 6 at 6 months, p<0.001.
15. *Age appropriate walking distance for 2 minutes (2 Point Bonus).*

At 10th day all patients had score 0 which improved to 2 in 96.1% at 6 weeks by 6 months 100% were in score 2.

The analysis of all values from 1 to 15 in activity inventory was statistically significant between 10th day and 6 weeks and 6 months. The total mean activity inventory score was 31.3 on 10th day which improved to 58.3 at 6 weeks and further improved to 82.1 at 6 months. Total mean activity score was analysed using ‘t’ test and ANOVA and was found to be statistically significant.

### Discussion

Fifty-one patients were followed up for six months using Chedoke McMaster stroke assessment scale. All persons selected were oriented in place, time and person, and were able to comprehend instructions. Only radiologically confirmed first time stroke patients were selected for the study.

Thirty (58.82%) patients had cerebrovascular accident with right hemiparesis and 21 (41.18%) had left hemiplegia. Infarction was seen in 49 (96.08%) patients and 2 (3.92%) had hemorrhage. There was no history of transient ischemic attack or seizures in any of the patients. 4 (7.84%) patients had ischemic heart disease prior to developing stroke. Giddiness was seen in 4 (7.84%) patients. 14 (27.45%) patients had urinary incontinence at 6 weeks.

Chedoke McMaster stroke assessment at 10th day, 6th week and 6 months was done to evaluate functional outcome. Statistically significant difference (P<0.001) was seen between the values at 10th day, 6th week and 6 months in both impairment and activity inventory.

Chedoke McMaster Stroke assessment measures changes in disability and not just impairment. The impairment inventory can be used to classify patients into homogenous subgroups based on the stages of recovery. For many years, Brunnstrom stage of motor recovery has been used in rehabilitation settings as a meaningful way to describe a patient’s improvement. The level of standardization of stages was missing; Chedoke McMaster Stroke Assessment provides a useful tool in these circumstances. Using Chedoke McMaster Stroke Assessment, one could establish the stages of recovery of various impairments and provide a significant prognostic indicator for outcome.

The outcomes considered were activities of daily living, recovery of arm, leg, postural control, gross motor function, gait and shoulder pain. Based on the assessment data, we could predict the recovery which would help the rehabilitation team in setting goals.

For disability inventory, FIM score was used for conceptualizing the degree of independence of the patient, or inversely the degree of burden on the caregivers. The disability inventory provides additional information needed to plan a therapeutic intervention that stresses functional activity. The study evaluates a measure of physical impairment and improvement to 3 in 49% at 6 weeks and to 5 in 70.6% at 6 months.
disability that can be used for classifying patients according to their stages of recovery for predicting probable rehabilitation outcomes and for evaluating the effectiveness of interventions aimed at improving the function of individuals with stroke. The various parameters like stages of motor recovery, shoulder, postural control, arm, hand, leg and foot and various activities in activity inventory(1–14) except 15 (the age-appropriate walking for two minutes at 6 weeks), were found to be statistically significant. In the impairment inventory and stages of motor recovery assessment, the maximum differences in mean between 10th day and six months value was 4.4 for stage of arm followed by 4.3 for stages of foot and postural control, 4.2 for stage of motor recovery, 3.9 for stage of leg, 3.8 for stage of hand and 2.6 for stage of shoulder pain. In activity inventory, maximum change in mean was 51.2 seen in total scores between 10th day and sixth months followed by 4.7 for waking outdoors, over rough grounds, ramps and curbs for 150 meters and least mean score was 2 for age-appropriate walking distance for 2 minutes. In present times, when healthcare cost is of major concern to healthcare providers and patients, the availability of valid outcome measure suitable for use in both clinical and research settings are greatly helpful.

Chedoke McMaster Stroke Assessment could be used as a comprehensive tool to assess prognosis for locomotor recovery in patients with good comprehension after stroke. The assessment is accompanied by a clinical database and is suitable for judging the prognosis of individual patients while in rehabilitation.

REFERENCE
Working-Day Effects on The Acoustic Voice Parameters of Dubbing Artists: A Preliminary Study

Maya Varma R*, Usha Devadas**

ABSTRACT

Introduction: Dubbing is the post-production of recording and replacing voices on a motion picture or television sound track subsequent to the original shooting schedule. Dubbing artists need to produce different modulations in the voice to different characters with good lip synchronization. They are a unique group of professional voice users, whose style of voice use to match with appropriate characters, can act as a basic risk factor for voice disorders.

Aim: To investigate the effect of vocal loading on the acoustic voice parameters in dubbing artists.

Method: Eight female professional dubbing artists who were members of FEFK (Film Employees Federation of Kerala) union for dubbing artists with mean age of 24 years (range; 18-40 years) participated in the study. The phonation of vowel /a/ was recorded for individual participant at the beginning and end of the dubbing session during one working day. The Multidimensional Voice Program (MDVP) was used to assess the possible pre-post vocal loading changes objectively.

Results: Out of 20 acoustic parameters, shimmer % and amplitude perturbation quotient (APQ) showed significant difference between pre and post dubbing sessions.

Conclusion: These findings demonstrate that voice use in dubbing can induce measurable changes in acoustic voice parameters. The underlying mechanisms for these changes remain unclear and warrant continued investigation using more refined methods.

Key words: Dubbing artists, vocal loading, acoustic voice measures.

INTRODUCTION

Professional voice users are those individuals who are directly dependent on vocal communication for their livelihood1. In the literature, singers, actors, teachers, ministers, attorneys, radio and TV personalities, telemarketers have all considered as professional voice users. Apart from these professionals, dubbing artists who use their voice for certain characters on a motion picture or television vision could also be considered as professional voice users as they use their voice for their profession. The main characteristics of a dubbing artist are good voice quality, appropriate lip synchronization, ability to produce different modulation in voice to different characters. The dubbing artists work in serials, films, advertisements, documentary etc. and it is an inevitable part of postproduction. Hence, a subtle change in the voice quality may preclude them from their daily dubbing session. Even though effects of environmental factors are minimal in dubbing artists’ voice, the amount and style of voice use itself can act as a basic risk factor for the voice disorders2. Dubbing artist’s voice or speech for different characters is recorded at a stretch for 2-3 hours with repeated trials. They need to alter their pitch, loudness, style of speaking (different emotions) to match it with appropriate characters. This can lead to vocal loading effects and vocal fatigue in these professionals. These are the unique group of professional voice users whose vocal symptoms and vocal demands are less addressed in the literature. Like any other group of professional voice users, dubbing artists also have a vocal demand and vulnerability of voice strain and this is seen as important risk factors for the development of voice problems3.

Hence, a preliminary attempt is made in the present study to understand the effect of vocal loading in this group of professional voice users using acoustic voice parameters.

METHOD

Participants

Eight female professional dubbing artists who were members of FEFK union for dubbing artists (Film Employees Federation of Kerala) with mean age of 24 years (range: 18-40 years) working in Thiruvananthapuram, Kerala participated in this study. All the dubbing artists had more than five years’ experience and dubbed for more than two hours per day. Those who had not participated in dubbing for the past twelve months and those with previous history of vocal fold lesions were excluded from the study.

Procedure

The voice samples were recorded at the beginning and at the end of the dubbing session during one working day to identify the effect of vocal loading in acoustic voice parameters. The voice samples (phonation of vowel /a/) were recorded at their workstation (sound treated rooms) using WaveSurfer software program loaded on to the Dell Inspiron laptop using multi-pattern USB condenser microphone (Samson CO3U studio condenser) maintaining constant mouth to microphone distance of 10 cm. Two to three trial sessions were given to each participant prior to actual recording.

The recorded voice samples were captured by the Multi-Dimensional Voice Program (MDVP; model 5105, Kay Elemetrics Corp.), using Computerized Speech Lab (CSL) hardware for analysis and interpretation. The initial
and final parts of the phonation of vowel /a/ were eliminated and a 3 sec signal (the central part of the phonation being the most regular, least affected by onset and offset of the vocal signal) was captured and analyzed for all the MDVP acoustic parameters.

Statistical Analysis
The effect of vocal loading on acoustic voice parameters was analysed using Non parametric 2-related sample test.

RESULTS
Twenty acoustic parameters (MDVP) including fundamental frequency related, frequency perturbation, amplitude perturbation and noise related parameters were analyzed from the voice samples recorded before and after dubbing sessions during one working day. Non parametric 2-related sample test (Wilcoxon signed rank test) did not reveal any significant difference in acoustic voice parameters between pre and post loading sessions except the parameter shimmer % and amplitude perturbation quotient. In the post loading session, the shimmer % and amplitude perturbation quotients were found to be significantly increased (Table 1) compared to preloading session.

DISCUSSION
The purpose of comparing the acoustic parameters between pre and post dubbing session was to determine whether they can indicate the effects of vocal loading in dubbing artists on the presumption that acoustic measures

| Table 1: Median values of acoustic voice parameters for the dubbing artists before and after dubbing session |
|---------------------------------------------------------------|-------------------|-------------------|-------------------|
| **Fundamental Frequency Information Measurements**             | Preloading (Median) | Post loading (Median) | P Value |
| Average fundamental frequency (Fo), Hz                         | 199               | 206.4             | 0.237             |
| Average pitch period (To), ms                                  | 5.017             | 6.0327            | 0.735             |
| Highest fundamental frequency (Fhi), Hz                        | 204.734           | 210.93            | 67.6              |
| Lowest fundamental frequency (Flo), Hz                         | 171.451           | 156.09            | 0.237             |
| Standard deviation of fundamental frequency (STD),Hz            | 1.7050            | 1.9337            | 0.735             |
| Phonatory fundamental frequency semitone (PFR)                  | 2.00              | 2.00              | 0.655             |
| **Frequency Perturbation Measurements**                        |                   |                   |                   |
| Absolute jitter (jitta), μs                                    | 51.368            | 36.54             | 1.00              |
| Jitter (jitt), %                                                | 0.544             | 0.6047            | 1.00              |
| Relative average perturbation (RAP), %                         | 0.4187            | 0.4787            | 0.735             |
| Pitch period perturbation quotient (PPQ), %                    | 0.3143            | 0.3647            | 0.612             |
| Smooth pitch period perturbation quotient (sPPQ), %            | 0.6207            | 0.5673            | 0.499             |
| Fundamental frequency variation (vFo)                          | 0.9080            | 0.879             | 0.499             |
| **Amplitude Perturbation Measurements**                        |                   |                   |                   |
| Shimer (ShdB)                                                  | 0.2070            | 0.1971            | 0.866             |
| Shimmer (Shim), %                                              | 2.366             | 2.6043            | 0.028             |
| Amplitude perturbation quotient (APQ), %                       | 1.7113            | 1.91              | 0.018             |
| Smooth amplitude perturbation quotient (sPPQ), %               | 3.4977            | 3.617             | 0.237             |
| Coefficient of amplitude variation (vAM), %                    | 9.199             | 10.401            | 0.735             |
| **Noise Related Measurements**                                 |                   |                   |                   |
| Noise to harmonic ratio (NHR)                                  | 0.1253            | 0.1233            | 0.499             |
| Voice turbulence index score (VTI)                             | 0.383             | 0.037             | 0.612             |
| Soft phonation index score (SPI)                               | 15.992            | 25.702            | 0.237             |

P values were derived from Non parametric 2-related sample test. Boldface values indicate the statistical significance (p < 0.05).
help understand the physiology of vocal mechanism, even when no visually detectable lesion or tissue changes are present. For this purpose, a wide set of acoustic parameters measured by the MDVP analysis from a single vocalization was used. It was further presumed that, the more extensive the parameters used, the more likely the finding of the difference. As reported by Kent et al, “MDVP holds the promise of standardized and rapid assessment of voice; it is of particular interest as a tool for the characterization of a voice disorder”.

The present study evaluated the effect of vocal loading during one working day on acoustic parameters in professionally active fulltime female dubbing artists. Generally, professional voice users are subjected to symptoms of vocal loading and exhibit symptoms of functional (non organic) dysphonia. The comparison of different acoustic parameters of voice derived from speech signal before and after the vocal loading can significantly contribute to objective voice examinations and are useful in diagnosis of early stages of dysphonia in professional voice users. In the present study, after the dubbing session, we observed statistically significant deterioration in shimmer % and amplitude perturbation quotient, an indication of voice instability. Shimmer % gives information related to the short term period to period variability of peak to peak amplitude, while APQ gives information regarding long term variability of amplitude with a smoothing factor of eleven. From this result, it can be presumed that dubbing artists experience vocal fatigue along with associated compensation disturbances and difficulty in controlling regular pattern of intensity in phonation following the dubbing session. Studies in the literature indicate that amplitude perturbation measures get affected when there is vocal fold hyper adduction. Increased amplitude perturbation measures are also considered signs of pathological or functional disorders (subtle changes in vocal fold mucosa) of vocal folds. In the present study, however, it is difficult to predict the pathological changes depending on these measures alone, as voice signal is a complex product of the nonlinear interaction between the aerodynamic and biomechanical properties of the voice production system and contribution of the amplitude perturbation alone to identify the specific abnormalities of the glottal function is not very clear. However, this finding leads to the assumption that, voice use in dubbing can induce measurable changes in acoustic parameters of shimmer % and APQ.

CONCLUSION

Several studies in the literature have shown the usefulness of acoustic analysis of voice in predicting the dysphonic severity and effect of vocal loading. In the present study, when the acoustic voice characteristics were compared before and after dubbing sessions, statistically significant increase in shimmer % and APQ was observed during post dubbing sessions indicating voice instability. Hence, it can be presumed that acoustic analysis performed before and after the vocal loading during one working day will contribute to the understanding of impact of vocal loading in professional voice users. However, the underlying mechanism for these changes remains unclear and warrants continued investigation. Also, acoustic analysis of voice combined with other objective variables such as aerodynamic measurements and electroglottotographic measurements may improve the further understanding of vocal loading effects. Hence, large scale studies, including both genders, using more refined methods (phoniatric examination, aerodynamic measurements, self-reported voice problems, analysis of work ambience, quality of life measurement scales), to extensively study the nature of voice problems and factors influencing them are required to understand the effect of dubbing on the vocal mechanism and develop appropriate preventive measures.

References
Anti-N-methyl-D-aspartate receptor encephalitis
A diagnostic dilemma in Emergency Room


ABSTRACT

Introduction: Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a rare, potentially life threatening and acute form of encephalitis. It is caused by autoimmune IgG antibodies directed against N-methyl-D-aspartate (NMDA) receptors, resulting in a characteristic neuropsychiatric syndrome. The acute presentation of symptoms makes it difficult to diagnose, leading to delay in initiation of specific treatment.

Case Background: Presenting a case series of 2 patients who presented to the emergency department with fever, headache, vomiting and altered sensorium. Both were diagnosed and treated as meningoencephalitis. Due to waxing and waning of sensorium, we further evaluated the patients, They were found to have NMDA encephalitis. Early suspicion and prompt immunotherapy helped to resolve the symptoms.

Conclusion: Any patient presenting to emergency room with agitation and behavioral changes including self harming behavior shouldn’t be labeled psychiatric viral encephalitis unless all other causes have been ruled out. Such patients with orofacial dyskinesias should prompt us to evaluate them for autoimmune viral encephalitis from emergency room itself.

Case 1

A previously healthy young female was referred to Emergency Department with confusion, agitation and occasional slurring of speech. She had a 10 days history of headache, vomiting, intermittent high grade fever and 3 days history of behavioral change and memory impairment prior to presentation. Headache was mainly in the fronto-temporal region with associated nausea and vomiting. Symptoms persisted and she got admitted in a secondary hospital. In view of clinical suspicion of meningitis/psychosis, she was referred to Amrita Institute of Medical Sciences (AIMS), Kochi.

On evaluation, patient was conscious, drowsy, hemodynamically stable with hyperventilation. There was involuntary dystonic posturing of both upper and lower limbs with perioral dyskinesias. There was no family or past history. Neurological examination on admission GCS: E4V5M3, optic fundus was normal, increased tone of upper limb, agitation, fluctuation in consciousness with loss of ability to speak or make eye contact, limb dyskinesias, orofacial dyskinesia (+), urinary incontinence, and self-harming behaviour (biting lips, knocking her head and arm on the bed), chewing movements, teeth grinding, and lip biting. Other neurological examination was within normal limits.

In view of fever with headache and altered sensorium, patient was provisionally diagnosed to have acute meningoencephalitis. Patient was empirically started on Inj. Ceftriaxone 2gm IV Q12H ,Inj. Crystalline penicillin15 lakh U IV Q8H, Inj Acyclovir 600mg IV Q8H , along with Inj. Dexamethasone 8mg Q8H and phenytoin.

Routine investigations showed total count 12.5K/uL. MRI Brain with contrast was done to rule out any structural lesions; none were found. Cerebrospinal fluid (CSF) analysis was done in view of meningitis which showed 155 cells - mononuclear cells with normal glucose and normal protein. CSF culture and also TB PCR came as negative.

Patient was also given a psychiatric consultation to rule out co-existing psychotic issues, as she was showing a waxing and waning consciousness level, self harming behavior and a negative CSF analysis for infective pathology. Later on, she started to show focal seizures mainly on the face for which an electroencephalogram (EEG) was done which showed a normal study in wakefulness.

In view of constellation of behavioral changes, cognitive impairment, orofacial dyskinesia, focal seizures, lymphocytic pleocytosis in CSF, negative culture reports, normal MRI brain and normal EEG, autoimmune encephalitis was suspected and paraneoplastic antibody panel, NMDA receptor antibody and Anti-voltage-gated potassium channel antibodies (anti-VGKC-Ab) were sent on the 3rd day.

Serum tested positive for NMDA type of glutamine receptor antibody by indirect Immunofluorescence.

A course of IV Methylprednisolone 1gm OD and Inj. Intravenous Immunglobulin (IG) (0.4g/kg) 25gm IV OD for 5 days was initiated in view of NMDA Encephalitis followed by oral prednisolone.

On the 4th post admission day, she started having tachycardia with hypertension and sweating on the face, possibility of autonomic instability was suspected and she was started on Inj Labetalol 50mg TID also.

Pelvic ultrasonography, computed tomography (CT) chest and abdomen was also done in view of association of anti-NMDAR antibodies with...
Amrita Journal of Medicine

Anti-N-methyl-D-aspartate receptor encephalitis
A diagnostic dilemma in Emergency Room

NMDA receptor antibody and VGKA antibodies were sent. Serum tested positive for NMDA type of glutamine receptor antibody by indirect Immunofluorescence. She was initiated on Intravenous Immunoglobulin (IG) (0.4g/kg) 25gm IV OD for 5 days

The association of anti-NMDAR antibodies with ovarian teratoma, other abdominal and thoracic tumors prompted pelvic ultrasonography, computed tomography (CT) chest and abdomen. CT abdomen showed probable right ovarian dermoid cyst.1.5 x 2 cm size. She was managed conservatively and discharged as she improved clinically.

Discussion
NMDA encephalitis is an acute form of encephalitis due to the autoimmune IgG antibodies directed against NMDA receptors resulting in a characteristic neuropsychiatric syndrome. It was first described in 20061. NMDA receptor encephalitis mainly affects women more than men and the prevalence is around 30% in young people below 18yrs2.

Our body is built in such a way to tackle all type of infections that hits our system. This important and sophisticated job is taken care by our immune system. Our immune system produces antibodies which will fight against offending foreign antigen. But, at times, these antibodies may react against the proteins of our own body which can result in autoimmune disease; when these reactions are against the proteins of the brain, it is called Autoimmune Encephalitis.

N-methyl-D-aspartate (NMDA) receptor is a protein of the brain which is considered as a fundamental neurotransmitter of the brain. NMDA receptors belong to ionotropic receptors family; it has high affinity to excitatory amino acid glutamate. They are found throughout the central nervous system.

Glutamate along with glycine and D-serine (co agonist) activates NMDA receptor which results in influx of calcium and sodium ions and efflux of potassium ion. There are two types of receptors, NR1 and NR2 subtypes bind glycine and glutamate, respectively. Influx of calcium ion into the post synaptase via the NMDA receptors will result in coupling of electrical synaptic activity to biochemical signaling via activation of Ca-dependent enzymes and downstream signaling pathways. At resting membrane potential NMDA receptor is blocked by magnesium ions via voltage dependent channel. When there is an adequate excitation of synapse, depolarization of the neuron occurs and Mg2+ is removed.

The NR1 and NR2 receptors of NMDA are distributed in forebrain, basal ganglia, cerebellum and spinal cord. In these patients, antibodies against NMDA receptors circulate within CSF and affect the areas responsible for personality, memory, movements and autonomic control. The role of the NMDA receptor in learning and memory is attributed to ability to regulate excitatory synaptic transmission through voltage-dependent magnesium block. This will result in change in personality, motor derangement and autonomic instability3.

NMDA encephalitis begins as a low grade fever, headache

EEG was done which was normal. CSF study showed normal opening pressure, elevated CSF protein level, normal sugar level and total count of 192 cells with mononuclear cells predominance. CSF cytology showed features suggestive of lymphocytic pleocytosis. We started her on Antiviral and 3rd generation cephalosporin was initiated empirically and supportive management.

In view of waxing and wanning of symptoms, autoimmune encephalitis was suspected and paraneoplastic antibody panel, As the suspicion for autoimmune encephalitis was considered and plan was to perform etiology workup.

Her routine blood workup showed raised white cell count. MRI Brain + Magnetic resonance venography with contrast showed features suggestive of T2 FLAIR hyperintensities in bilateral parahippocampal region and insular cortex likely representative of autoimmune/paraneoplastic/viral encephalitis.

Case 2
A 38 years young female with no co morbidities presented to Emergency Room with history of fever, headache and vomiting for past 3 days with 2 episodes of seizures on day of admission. She underwent CT brain imaging at local hospital which was apparently normal and started on Inj. Cefotaxim + Sulbactum, Inj. Mannitol with rest supportive management and referred to our hospital. On admission, she was afebrile, conscious but confused and papilloedema was noted on fundus examination in both eyes. Other neurological examination was within normal limits. Possibility of encephalitis was considered and plan was to perform etiology workup.

On examination, she was afebrile, conscious but confused and papilloedema was noted on fundus examination in both eyes. Other neurological examination was within normal limits. Possibility of encephalitis was considered and plan was to perform etiology workup.

Her routine blood workup showed raised white cell count. MRI Brain + Magnetic resonance venography with contrast showed features suggestive of T2 FLAIR hyperintensities in bilateral parahippocampal region and insular cortex likely representative of autoimmune/paraneoplastic/viral encephalitis.

Ovarian teratoma and other abdominal and thoracic tumors, which was normal.

Patient had perioral and limb dyskinesia which was managed with anticholinergics. Patient had few episodes of generalized tonic-clonic seizure (GTCS) which was managed with antiepileptics.

At the time of discharge, patient was on Ryles tube feed, could walk with mild support and was oriented in person and place.

EEG was done which was normal. CSF study showed normal opening pressure, elevated CSF protein level, normal sugar level and total count of 192 cells with mononuclear cells predominance. CSF cytology showed features suggestive of lymphocytic pleocytosis. We started her on Antiviral and 3rd generation cephalosporin was initiated empirically and supportive management.

In view of waxing and wanning of symptoms, autoimmune encephalitis was suspected and paraneoplastic antibody panel, As the suspicion for autoimmune encephalitis was high, Inj. Methylprednisolone 1gm was also started.
NMDA Encephalitis is considered as a paraneoplastic syndrome because of its association with teratoma of ovaries. They are also associated with mediastinal teratomas, sex-cord stromal tumors, small-cell lung cancer and testicular teratomas. NMDA encephalitis is associated with tumors in <5% in male and around 20 – 57% in females. This is because the tumor stimulates production of NMDA receptor antibodies. Patients diagnosed to have NMDA Encephalitis should undergo USG abdomen & pelvis or MRI abdomen & pelvis as a part of initial workup itself. They should also be periodically reviewed for at least two years after the first episode. A study by Dalmau et al. on 100 patients diagnosed to have NMDA Encephalitis showed that 59% of the patients had a tumor, most commonly ovarian teratoma, Median age of the group was 23 years and 91% were women.

CSF analysis usually shows lymphocytic pleocytosis, increased protein concentration, normal glucose, oligoclonal bands and high IgG index, electroencephalogram frequently shows focal or diffuse slow activity during episodes of dyskinesias or abnormal movements. MRI findings are less predictable and may show small areas of FLAIR abnormalities in cerebral cortex (outside the medial temporal lobes), sometimes involving cerebellum and brainstem; transient enhancement of overlying meanings. The diagnosis of NMDA encephalitis is confirmed by the detection of NMDA receptor antibodies in serum and CSF.

The differential diagnosis of anti-NMDA receptor encephalitis includes acute psychosis, viral and autoimmune causes for encephalitis, the latter involving classic paraneoplastic antigens or cell membrane antigens. The most commonly encountered viral causes include herpes simplex virus and human herpes virus-6 (HHV-6). Although varicella zoster virus and cytomegalovirus screening is frequently included in CSF testing, these viruses are rarely responsible for viral encephalitis. Immunocompromised individuals, particularly those having undergone bone marrow or stem cell transplantation, are more susceptible to infection with HHV-6. Arboviral encephalitis and rabies should also be considered.

**Most Common Differential Diagnosis**
1. Acute Psychosis
2. Viral Encephalitis
3. Meningitis
4. Hypoglycemia
5. Encephalopathy

First line management for NMDA encephalitis is immunotherapy consisting of Steroids (Methylprednisolone 1.0 g intravenously per day for 5 days), Intravenous immunoglobulin therapy (0.4 g/kg intravenously per day for 5 consecutive days each month) and Plasmapheresis. Second line immunotherapy involving anti-CD20 monoclonal antibodies (Rituximab) and Cyclophosphamide. Combination therapy of steroids and IVIG has also found to be effective. Most patients with tumors have got excellent outcome with tumor resection and prompt and aggressive immunotherapy. Independent of the treatment used, slow improvement have been noticed in most cases.

Titulaer et al in their study found that 53% of patients showed symptom improvement with first line immunotherapy or tumor removal within four weeks of treatment. Out of the patients who received first line immunotherapy, 97% showed good outcome at 24 month follow-up. Patients who did not benefit with first line therapy received second line therapy, 81% showed good outcome in 24 month follow up. Predictors of good outcome were early treatment and lack of ICU admission.

Recovery from NMDA Encephalitis is typically slow; more than 75% of patients recover but relapses are quite common, especially in patients with undetected or recurrent tumors. Mortality rate is 4%. Some of these patients may have an occult tumor. However, spontaneous recovery has also been described in a few patients after several months of severe symptoms. Recovery is mainly observed by declining antibody titers. In a few patients whose CSF was obtained during neurological improvement, the decrease of CSF antibody titers was substantially slower than that of serum titers.

**Conclusions**
Any patient presenting to emergency room with agitation and behavioral changes including self harming behavior should not be labeled psychiatric viral encephalitis unless all other causes have been ruled out. Patients with lymphocytic pleocytosis in CSF study is managed most of the time as viral/TB encephalitis. But even in India, there is a high incidence of autoimmune encephalitis. Patients with negative CSF C&S, TB PCR and HSV PCR with orofacial dyskinesias and waxing and waning of consciousness should prompt us to evaluate them for autoimmune encephalitis from Emergency room itself.

**References**
2. Sarosh R Irani, Angela Vincent “NMDA-Receptor Antibody Encephalitis”, the encephalitis society.


Combined Central Retinal Artery & Central Retinal Vein Occlusion In Secondary Anti-Phospholipid Syndrome (APS)


ABSTRACT
Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by either vascular thrombosis (arterial or venous) or pregnancy morbidity due to the presence of abnormal antibodies circulating in the blood. It is a hypercoaguable condition with systemic features depending upon the organ affected. Ocular involvement occurs in up to 80 - 90 % of APS in the form of amaurosis Fugax, retinal artery occlusion, retinal vein occlusion, optic neuropathy etc. Even though central retinal arterial obstruction (CRAO) and central retinal venous obstruction (CRVO) have been noted independently in APS (primary and secondary), combined CRAO and CRVO is one of the rarest presentation in APS. We hereby report a case with the above rare combination as the initial presenting complaint in a 38 year old lady with secondary APS.

INTRODUCTION
The Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by either a history of vascular thrombosis (one or more clinical episodes of arterial, venous, or small vessel thrombosis in any tissue or organ) or pregnancy morbidity in association with the presence of antiphospholipid (aPL) antibodies. These antibodies, namely, anticardiolipin (aCL) antibodies, lupus anticoagulant (LA), or antibodies against beta2-glycoprotein 1 (anti-b2GPI) either of IgG or IgM isotype have been recently established as the laboratory criteria for the diagnosis of definite APS. APS is prevalent in 2-4% of general population and 50% of them are due to primary etiology. Among the secondary causes, the most common one is systemic lupus erythematosus (SLE); 23% of cases develop APS. It is a hypercoaguable condition & thrombosis can occur anywhere in the body including nervous system, kidney, liver skin & eye. Almost all cases of APS have bilateral ocular involvement while monocular presentation can also occur. Studies on ocular manifestations as the initial presentation in APS have not been done, as only a few such instances have been reported worldwide. Among ocular manifestations, retinal artery or venous occlusion has been well described. But combined arterial and venous obstruction as an initial presentation in APS is very rare. Combined central retinal arterial obstruction (CRAO) and central retinal venous obstruction (CRVO) is an uncommon retinal vascular disease that leads to relatively sudden loss of visual acuity. This combined entity includes the clinical features and characteristic retinal changes of both CRAO and CRVO. It is well distinguished from isolated CRAO or CRVO. The pathophysiology of the disease and thrombosis as the cause of the obstruction is not well defined. Affected eyes typically have a poor outcome and tend to develop severe complications, such as rubeosis iridis and neovascular glaucoma. Unfortunately, no treatment capable of reversing the visual loss has so far proved effective.

CASE REPORT
A 38 year old housewife from Kochi presented to us with complaints of painless loss of vision of her left eye as she got up from sleep. She did not have any history of eye pain, trauma to eye, redness or watering, fever, symptoms of raised intracranial tension, no focal neurological deficits, rashes, joint pain, alopecia, recurrent oral ulcers or genital ulcerations, edema, cough, palpitation or breathlessness. No hematuria or frothy urine was reported. There was no h/o animal bite.

She gave history of 3 abortions: during 1st pregnancy, spontaneous abortion at 7th month, during 3rd pregnancy, an intrauterine death at 6th month and during 4th pregnancy, spontaneous abortion at 2nd month. In her 2nd pregnancy, she gave birth to a live male child.

On initial examination, she was noted to be anaemic. Her left eye was completely blind with absent light perception and direct light reflex (in-direct reflex was present). Left fundus showed a ‘splashed tomato’ appearance with multiple superficial & deep hemorrhages involving all the quadrants, unclear disc margins with dilated & tortuous veins. All these features were suggestive of CRVO. In addition to the above mentioned findings, retina was very pale & there was presence of cherry-red spot which was suggestive of CRAO. Ophthalmology evaluation and florescent fundus angiogram showed delayed arterial fill.

*Dept. of Internal Medicine,
** Dept. of Ophthalmology, AIMS, Kochi.
ing and choroidal ischemia (suggestive of CRAO) and retinal capillary non-perfusion (suggestive of CRVO). These confirmed our clinical findings.

Initial blood investigations showed pancytopenia (Hb-7.14, PCV-22.8, total WBC count-3.01, platelets-21300) and raised ESR (62). aPTT was 50/32, which was not corrected even after mixing study suggestive of no factor deficiency. PT – INR was normal.

VDRL was positive, TPHA was negative. Anti Cardiolipin was positive IgM positive – 13.8 (0-11MPLu/ml), IgG positive – 97.4(0-23GPLu/ml), LUPUS anticoagulant – positive, 02-glycoprotein– negative 3.42(0-5). Her ANA (IFA) showed speckled pattern and Anti-ds DNA – positive 51(0-30IU/ml)

Table 1
Clinical and laboratory criteria for diagnosis of antiphospholipid syndrome

Clinical criteria
1. Vascular thrombosis
2. Pregnancy morbidity
   • One or more deaths of normal fetus at or beyond 10th week of gestation
   • One or more premature births of normal neonate before 34th week of gestation from eclampsia, pre-eclampsia or placental insufficiency
   • Three or more consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded

Laboratory criteria
1. Lupus anticoagulant
2. Elevated anticardiolipin antibody
3. Elevated anti-02-glycoprotein antibody

Note. At least 1 of both criteria is need for definitive classification. Laboratory results must be present on 2 or more occasions separated by no less than 12 weeks but no more than 5 years.

When both clinical and laboratory parameters were combined, we arrived at a final diagnosis of APS based on criteria in table 1. But only 3 out of 11 criteria of SLE (Pancytopenia, ANA, Anti-ds DNA) were present. So a final diagnosis of APS secondary to probable SLE was considered.

She was initially pulsed with steroid (methyl prednisolone) for 5 days, followed by oral prednisolone. Along with that, she was anticoagulated with LMWH (low molecular weight heparin, Enoxaparin) which was followed by oral anticoagulation with warfarin (INR maintained strictly between 2-3). At the time of discharge, her left eye was still completely blind. She was advised regular follow up in Medical and Ophthalmology Departments.

After 3 months, antibodies were repeated again which showed Anti cardiolipin Positive IgG 63.2 (0-23GPLu/ml), Lupus anticoagulant positive & even anti-02-glycoprotein which was negative initially was also positive 26.0(0-15) and diagnosis of APS was confirmed. Vision in her left eye started improving gradually. She was able to perceive finger movements by 3 months; visual acuity improved to 6/60 by 7 months.

DISCUSSION
Antiphospholipid syndrome is an acquired thrombophilic disorder in which autoantibodies are produced to a variety of phospholipids and phospholipid-binding proteins.

These antibodies include anticardiolipin antibodies, b-2-glycoprotein-1 antibodies, and lupus anticoagulant. The characteristic pathologic finding in the APS is a bland thrombosis with minimal vascular or perivascular inflammation. This change is not specific for the APS, as it also occurs in a variety of other disorders including the hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura, systemic sclerosis (scleroderma), and malignant hypertension. Larger vessels, both arteries and veins, may develop in situ thrombosis or be sites from or into which emboli originate or lodge.

The diagnostic criteria require one clinical event, i.e. thrombosis or pregnancy complication, and two positive blood tests spaced at least 3 months apart. These antibodies are: lupus anticoagulant, anti-cardiolipin and anti-02-glycoprotein-I.

The term “primary antiphospholipid syndrome” is used when APS occurs in the absence of any other related disease. APS however also occurs in the context of other autoimmune diseases, such as systemic lupus erythematosus (SLE), in which case the term “secondary antiphospholipid syndrome” is used. In rare cases, APS leads to rapid organ failure due to generalized thrombosis; this is termed “catastrophic antiphospholipid syndrome” (CAPS) and is associated with a high risk of death.

Ocular manifestations, as already mentioned, occur in 90% cases of APS. Unlike other autoimmune disorders, APS is more of a hypercoagulable condition.

Therefore, the ocular manifestations are mainly due to thrombosis rather than vasculitis which is more common in other autoimmune disorders like rheumatoid arthritis, Sjogrens syndrome etc.. It can affect choroid, retina & optic nerve. According to a multicenter study done in Europe, including 100 APS patients, the most common ocular manifestations included Amaurosis Fugax, retinal artery & vein thrombosis, isolated retinal hemorrhages and cotton wool spots, and retinal neovascularization & optic neuropathy. APS can affect any part of eyes. (Table 2)
The reason for the ocular manifestations in APS with SLE can be due to both thrombosis and vasculitis. But in APS, it is more of hypercoaguable state; most of the systemic manifestations or presentations are due to thrombotic phenomenon. Also, it is very unlike for a vasculitis to cause unilateral loss of vision as has been reported in all the 4 cases.

The main treatment is anticoagulation. We started our patient on LMW heparin & later bridged with oral Anticoagulant-Warfarin. Anticoagulation is of the utmost importance because these individuals are prone for recurrent thrombotic events in future. Also, as in our case, there can be the additional benefit in the form of gradual improvement in vision. Even though she might not regain her total vision, at least her quality of life has improved.

The occurrence of ocular events is very common in APS. So APS should always be ruled out in individuals who present with sudden loss of vision secondary to a vascular phenomenon in which no definite cause can be identified. Even though combined CRAO & CRVO is an extremely rare presentation of APS, the possibility should always be kept in mind as it is a treatable condition, leading to improvement of the patient’s vision like in our case. But more studies are required in this field for final acceptance. Also, as studies have already showed, 23% of SLE patients develop APS in future. Hence, we suggest checking for APS antibodies in patients with SLE, as early diagnosis and initiation of anticoagulant therapy can prevent thrombo-vascular complications.

The long-term prognosis for APS is determined mainly by recurrent thrombosis, which may occur in up to 29% of patients, sometimes despite antithrombotic therapy.

### Table 2

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Unclear Vision, Transient Diplopia, Transient Field Loss, Amaurosis Fugax, Photopsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjuctiva</td>
<td>Telangiectacias, Aneurysms, Episcleritis</td>
</tr>
<tr>
<td>Cornea</td>
<td>Keratoprecipitates, Limbal Keratitis</td>
</tr>
<tr>
<td>Vitreous</td>
<td>Haemorrhage, Cells</td>
</tr>
<tr>
<td>Optic Nerve</td>
<td>Disc Oedema, Anterior Ischemic optic neuropathy</td>
</tr>
<tr>
<td>Retina</td>
<td>Arterial or Venous Occclusion, venous Tortuosity, Aneurys cotton wool spots, vasculitis, vascular sheathing, Macular Serous Detachment, acute Retinal Necrosis</td>
</tr>
</tbody>
</table>

These conditions typically occur in the elderly; APS patients may experience them earlier in life.

Usually either CRAO & CRVO occur separately. But combined CRAO & CRVO is very rare. Only 3 cases have been reported worldwide. The first one was a 27 yr old described by Fitzpatrick in English Medical Literature in whom SLE & APS was detected only after the initial ocular event. The second was reported by Durukan: a 23 yr old female who was already a diagnosed case of SLE & APS developed 5 days postpartum. She had stopped prophylactic heparin 3 weeks before the event. The third case was reported by Chang from school of medicine, Taipei, which was a case of 35 yr old female who was already a diagnosed case of SLE on prophylaxis (poor compliance) reported with sudden unilateral loss of vision. In our case, it was a 38 year old who presented with combined CRAO & CRVO, fitting into the criteria of APLA. APLA can be primary or secondary. Among secondary, SLE is the most common cause. Our patient only satisfied 3 out of 11 criteria for SLE. But SLE is an evolving disease, so in future she may develop its other manifestations.

In the above reported cases 1 & 2, there was complete loss of vision and no recovery at all. In case 3, there was almost complete recovery of vision only to have subsequent similar episodes. However, in our case there has been slow recovery; after 7 months of the event, her visual acuity improved to 6/60 from being completely blind.

**REFERENCE**


8. Oosting JD, Derksen RHWM, Bobbink IWG, Hackeng TM, Bouma BN, Groot PG. Antiphospholipid antibodies directed against a combination of phospholipids with prothrombin, protein C, or protein S: an explanation for their pathogenic mechanism?


INSTRUCTIONS TO AUTHORS

The Amrita Journal of Medicine publishes original manuscripts, meta-analyses and reviews, debates, interesting clinical cases, guidelines and consensus statements of clinical relevance and letters relating to all fields of medical and surgical specialities.

We reserve the right to copy or edit accepted manuscripts, reviews, letters and editorials. Corrected proofs will be sent to the corresponding author for final approval. The editors and publishers are not responsible for the opinions expressed by contributors to the Amrita Journal of Medicine.

ABSTRACT: A Structured abstract of not more than 250 words should accompany each original article, systematic review or meta analysis. Abstracts for original contributions should be divided by individual headings into paragraph entitled; Objectives, Methods, Results and Conclusions.

Case reports should include a brief abstract describing the case (s) and literature review. Reviews must have an abstract included, which can be unstructured. Editorials need not include an abstract. Abbreviations or references to figures or tables should not be utilised in the abstract.

ORIGINAL ARTICLES: All original manuscripts should include the following:

Abstract: Structured abstract as described above.

Introduction: The specific aim(s) and a priori hypothesis need to be stated.

Methods: must include sufficient information to judge the quality of the work, including statistical analysis and study power where appropriate.

Results: Please do not duplicate results present in the text and tables.

Discussion: Consider including a brief statement of the major findings, the meaning of the study including possible explanations and implications for clinicians, the findings in relation to other studies and consideration of important differences in results, the strengths and weaknesses of the present study, and what are now the unanswered questions and future research needs.

Authors are required to include in addition to a structured abstract, a separate paragraph with 4-8 bullet points under the heading: what is known on the subject and what this research adds. This information will be included as a table at the end of the article, and is to be aimed at simply explaining the study’s importance and knowledge gained from it to those who are non-experts in the particular fields.

RANDOMIZED CLINICAL TRIALS (RCTs): RCTs are encouraged and will be fast tracked in the review and publishing schedule. Randomised clinical trials must all reports their data in accordance with CONSORT (Consolidated Standards of Reporting Trials) statement. This ensures that you provide enough information for editors, peer reviewers, and readers to see how the trial was performed and to judge whether the findings are likely to be reliable. Please provide the following, as described in the CONSORT statement:

Five extra sub head section in the main text of the paper: Protocol, assignment, masking, participant flow and follow up, analysis.

A completed checklist for editors and reviewers (not for publication) showing that you have described 21 key points in your report.

All RCTs must meet CONSORT guidelines, and include the CONSORT checklist with submissions. We may choose not to use all of the sub headings in the published version of the paper for reasons of readability.

For further enquiries please visit: http://www.consort-statement.org/

SYSTEMATIC AND CLINICAL REVIEWS: Reviews of systematic and clinical topics are encouraged for publication... Include a brief methods section on how the information was found. An abstract must be included. Inclusion of illustrations to illustrate teaching concepts is strongly encouraged. Review should be not longer than 2500–3000 words, excluding references, tables and illustrations.

CASE REPORTS: Selected case reports will be considered but should write to represent new clinical observations, new method of treatment or interesting cases that carry a message to the reader for diagnosis or treatment of patients. Case reports must be short and focused, and consist of not more than 1500 words excluding references. An abstract should accompany the report.

EDITORIALS: Editorials must consist of not more than 1000 words excluding references.

DEBATES: They must be written by different authors for the pros and cons, and will be crisp and short in nature, consisting of not more than 1000 words excluding references.

LETTERS TO THE EDITOR: Letters to the editor will be considered if they are written on published articles or reviews. Letters must be submitted within three months of the original or review articles. Letters should be not more than 400 words, should cite the previous article that appeared in the Amrita Journal that is being discussed, and should include not more than 5 other references.

REFERENCES: All the references should be numbered consecutively and be listed according to the order in which they are referred to in the text of the manuscript. The references should be typed double-spaced and abbreviations of Journals must conform to those used in Index Medicus of the National Library of Medicine. The format should conform to the example listed below.

References to an article with 3 or less authors:

1. Thise ND, Rotterdam H, Dieterich D. Cytomegalovirus esophagitis in AIDS: Diagnosis by Endoscopic biopsy. Am J Gastroenterol 1991;06:1123-6

References to an article with more than 3 authors:


Reference to a book:


Reference to a chapter in a book:


TABLES: Each table should have an appropriate title, self-explanatory, and should not duplicate the text. The data should be logical and well organised so that it can be used to compare or classify related items. Tables should be numbered consecutively in Arabic numerals beginning with 1.

ILLUSTRATIONS: Colour illustrations are allowed, and will not usually attract a cost to authors.

One set of original illustrations should be mailed. All the illustrations of graphs, artwork, and photographs should be numbered in consecutive Arabic numerals and submitted. A label should be affixed to the back of each illustration with the name of the senior author, manuscript title, figure number and an arrow indicating the top of the figure. The legend(s) of all figures should be typed double spaced on a separate sheet of paper. When appropriate, arrows should be placed on photographs and drawings to indicate the portions to which reference is made. In the legends for photomicrographs, the magnification and stain utilized should be included.

RAPID COMMUNICATIONS: Rapid communications are welcomed and are guaranteed rapid decision and publication if accepted.

INVESTIGATION INVOLVING HUMAN SUBJECTS: All clinical research papers submitted which involves human or animal subjects must be accompanied by evidence of Institutional Review Board or Ethics Committee Review. The date the project was approved, when available, should be included.

MEASUREMENTS: All measurements should be in metric units.
Value Driven Leadership through

- Quality that is Infinite
- Service that Cares
- Hardwork that Endures

Making Positive Difference to lives across the globe

Alkem Laboratories Ltd.
Alkem House, Senapati Bapat Marg, Lower Parel, Mumbai - 400 013, Tel: 022 39829999