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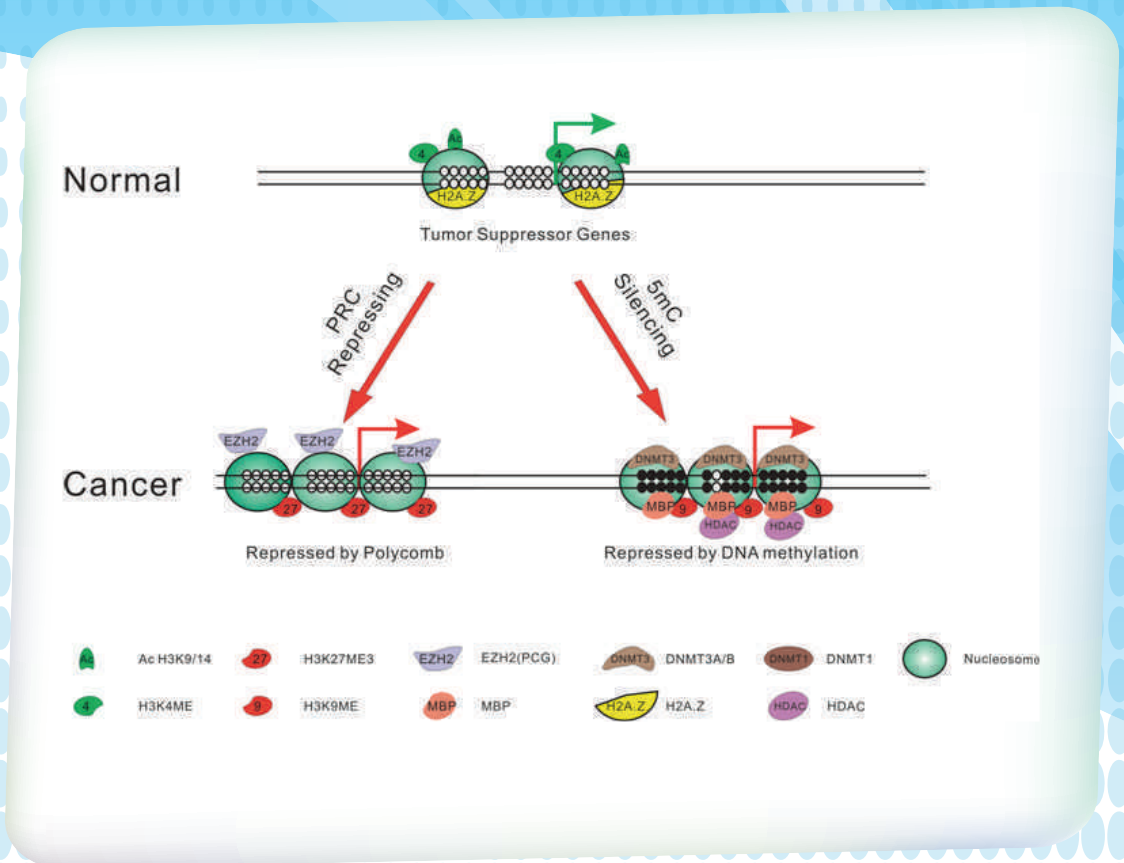
MEDICAL JOURNAL

In this issue



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Chettinad Health City

MEDICAL JOURNAL

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GLYCOMET GP **D RISE**

Editorial

Vanakkam.

This issue of the journal carries several commentaries, review articles and case reports.

A candid commentary discusses the issue of pain in the neonate and emphasises the need for providing pain relief in neonates undergoing invasive procedures.

Treadmill testing and its current role in the evaluation of ischemic heart disease are discussed in another commentary.

A review article on cerebro spinal fluid (CSF) dynamics outlines the different methods of estimating the CSF pressure and highlights the application in clinical practice.

Cancer is the emperor of all maladies[1]. The history of cancer is replete with several proven and unproven therapies. A review article on Epigenetics outlines a paradigm shift in cancer management.

Pigmented lesions of the oral cavity are outlined in another review article. The article also describes the differential diagnosis.

A brief article focuses on the interaction between the immune system and the male reproductive system. The article describes the condition disrupting the blood testes barrier, laboratory tests for anti sperm antibodies and the limitation of currently available methods of treatment.

Tempero mandibular disorders are one of the common causes of Oro facial pain of odontogenic origin. The condition is often difficult to diagnose and manage. A review article outlines the diagnosis and management of Tempero mandibular joint disorders.

A case report describes the deft removal of a difficult dumb bell skull base meningioma.

Another case report describes a child with Pierre Robin sequence.

Posterior reversible encephalopathy is detailed in another case report.

The pages of history take us to the life and times of the Saviour of mothers- Dr Ignaz Philipp Semmelweiss.

Medical updates are present throughout the journal to keep you informed of recent developments.

An interesting ECG is presented for diagnosis.

We hope you will enjoy going through the journal and give us your valuable feedback.

Dr. N. Pandiyan
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1) Siddhartha Murherjee – The Emperor of all maladies Scribner publications 16th Nov 2010

Commentary

Pain relief in Neonates: No Doubt it's a Duty

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Chettinad Health City Medical Journal 2014; 2(2): 28 - 30

Introduction

Pain is the most common complaint for which a patient presents to a physician. Pain management in neonate warrants special consideration because the present knowledge of developmental neuro-physiology has been enriched. With the advancement of various surgical techniques and improved peri-operative care, more and more sick neonates undergo surgery and optimum peri-operative pain management may improve outcome.

Why should pain in neonate be treated?

Neonates in a hospital are routinely subjected to various degrees of painful procedures from very early in their lives ranging from venipuncture to major surgery. Apart from ethical reasons and expectation of the parents, there are several long term and short term effects of poorly managed acute pain in neonate.

Neonates, even the premature ones feel pain and elicit stress response. This was first scientifically described in a landmark study by Anand et al[1] in 1987. Blunting the stress response with fentanyl was associated with improved outcome. Subsequently in 1992, Anand et al[2] showed that management of postoperative pain after cardiac surgery by potent opioids was associated with improved outcome. The stress response, activated by afferent neuronal impulses from the site of injury, was found to be greater in magnitude but shorter in duration in neonates compared with adults during the same surgeries. The stress response initiates a series of metabolic changes leading to catabolism of protein, fat and carbohydrate. In premature or sick infants, this might cause metabolic acidosis, hypoglycemia, hyperglycemia and electrolyte imbalances leading to increased morbidity and mortality[3].

Altered and heightened pain responses in subsequent painful procedures are most common long term effect[4] and this may persist till adolescent life. A proper analgesic regimen may prevent heightened pain response. Behavioral response may also be altered by stress exposure in the Neonatal Intensive Care Unit (NICU)[5]. Current consensus is that neonatal pain must be managed regardless of their age and severity of coexisting illness[6].

Neonates feel more pain than their older counterpart

Clinical and laboratory investigations of neonatal pain suggest that preterm neonates have an increased sensitivity to pain[7]. Anatomic studies have shown that the density of nociceptive nerve endings in the skin of newborns is similar to or greater than that in adult skin[8]. Lack of myelination was suggested as an argument to support the hypothesis that neonates are not capable of perceiving pain. However, nociceptive impulses in the peripheral nerves are conducted through unmyelinated (C- fibers) and thinly myelinated fibers (A-δ fibers)[9]. Lower pain threshold and the lack of inhibitory controls contribute to hypersensitivity in the most premature neonate. Repeated tactile stimulation leads to a significant lowering of the threshold (sensitization) in neonates up to 35 weeks postconceptional age[10]. The low pain threshold in preterm neonates is accentuated by an increased excitability of nociceptive neurons in the dorsal horn of the spinal cord after exposure to any painful stimulus (wind-up phenomenon). In neonate, prolonged activity in the nociceptive pathways may be perceived as chronic noxious stimulation.

Strategy

Appropriate pain management plan should be formulated and communicated to the parents to minimize their anxiety. Unnecessary laboratory investigations should be avoided to minimize pain associated with invasive procedures. Fasting period beyond the stipulated guidelines should not be extended to avoid unnecessary discomfort. Patient's present clinical conditions, presence of other co-existing medical illness, nature of the surgical procedure to be done and the area where the neonate will be managed in the postoperative period should be taken into consideration.

For blood sampling, heel is preferable, as it is less painful and mother should be encouraged to breast feed the baby whenever feasible or sucrose solution should be used. However topical local anesthetic cream (Eutectic mixture of local anesthetic; EMLA) may be used during venous/ arterial puncture and peripherally inserted central catheter (PICC) insertion in neonates aged more than 26 weeks and it is safe in single dose[11]. Neonates undergo a variety of surgeries ranging from simple herniotomy to major thoraco-abdominal

surgery. The analgesic regimen should also vary according the severity of surgical trauma and depends upon where the baby is being managed in the postoperative period.

The options of postoperative pain management range from simple analgesics like paracetamol to central neuraxial block like caudal or epidural. However, anesthesiologist should remember that a neonate is not a 'small child'. There is immense anatomical and physiological uniqueness in a neonate that affects the pharmacodynamics and pharmacokinetic characteristics of drugs to a considerable extent.

Paracetamol has long been known to be an effective analgesic in pediatric populations. Its efficacy in mild to moderate pain in neonate is now well documented[12]. It may be used in oral or per rectal route; however, for severe pain it may be used in intravenous route for its opioid sparing effects. But, at this moment, the use of intravenous paracetamol in preterm neonates with a postconceptual age (PCA) of less than 32 weeks may not be justified before further pharmacokinetic/ pharmacodynamic studies are conducted[13].

Robust data on use of NSAIDs in neonates are lacking till today. In the absence of prospective randomized controlled trials, at this time routine use of NSAIDs in neonates cannot be recommended[14].

Opioids are the mainstay of pain management following major surgery including in neonatal population. Morphine is the most commonly used opioid in the postoperative period and fentanyl is also being increasingly used. However, opioids exhibit narrow therapeutic window between analgesic doses and the dose that may cause respiratory depression. Neonates receiving opioids should have continuous pulse oximetry monitoring and should be managed in a setting where rapid intervention for airway management is possible, because respiratory-rate monitoring alone may be an inadequate predictor of impending apnea[15].

Epidural analgesia has been investigated as a modality of pain relief after major surgery. The most important consideration in central neuraxial block in neonates is the safety and possibility of in advertent injury to the developing spinal cord. Serious complications including neurologic injury has been reported in neonates and many authors have mentioned that only experienced pediatric anesthesiologist should perform central neuraxial block in neonate[16].

Conclusion

Despite various opinions regarding methods of optimum postoperative pain management in neonate, there is little doubt that neonates feel more pain than their older counterpart. Intravenous opioids with the use of morphine or fentanyl remains the most common modality of neonatal pain management and the role of paracetamol in decreasing opioid requirement seems to be promising. Though ketorolac appears to be safe, larger studies are required before its routine use can be recommended. Epidural analgesia/anesthesia when performed in experienced hand is quiet safe and poses several benefits over systemic opioids. Where technical and logistic feasibility is present, it may be a logical option as a part of balanced anesthesia technique.

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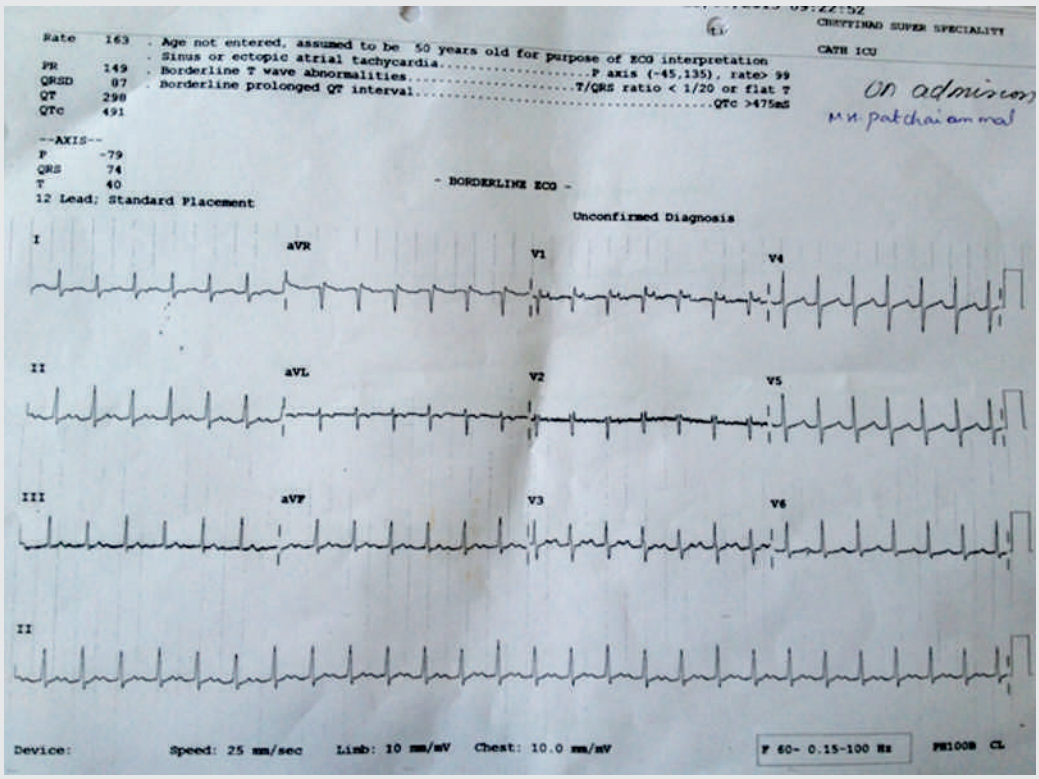
Diagnose the Condition

55 years old post menopausal female is known case of RHD – Severe MS, S/P CMV (2009), S/P BMV at CHRI on regular follow up, presented to us with complaints of Acute onset of palpitation. ECG taken taken is given below.



Answer in page no: 47

- **Dr. M.Chokkalingam,** Consultant Cardiology, CSSH

Commentary

Treadmill testing – Where does it stand today?

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Dr. Ganesh.N., did his undergraduation from PSG IMSR, Coimbatore, postgraduation from Government Medical College, Baroda. Further, he did his DM Cardiology from Grant Medical College and JJ Hospitals, Mumbai. He is a University Topper and Gold Medalist in DM Cardiology. He has published and presented many papers in National and International Journals. He is currently working as Consultant Interventional Cardiologist, Chettinad Super Specialty Hospital. His areas of interest include adult and pediatric interventions.

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Exercise testing is a cardiovascular stress test that uses treadmill bicycle exercise with electrocardiography (ECG) and blood pressure monitoring. Five decades ago Robert Bruce introduced cardiac exercise testing. Thereafter, treadmill testing has been a cornerstone of diagnostic procedures for coronary artery disease. Exercise stress testing, which is now widely available at a relatively low cost, is currently used most frequently to estimate prognosis and determine functional capacity, to assess the probability and extent of coronary disease. Exercise stress testing along with ECG and symptoms has been established as a major tool in the diagnosis and prognosis of cardiovascular disease, specifically coronary artery disease (CAD).

Treadmill test is performed frequently in patients with intermediate pretest probability (based on age, gender and symptoms) of coronary artery disease. Patients, who are stabilized after an episode of acute coronary syndrome (unstable angina or Non ST elevation MI) or myocardial infarction, are advised exercise testing to prognosticate, to prescribe the level of activity and the timing of coronary intervention. It is also used to evaluate patients after revascularization (coronary angioplasty or Bypass surgery) for the presence or absence of ischemia and to assess the exercise tolerance and prescribe activity. Patients suspected to have arrhythmias during exercise are evaluated by exercise testing. Exercise testing is also useful in evaluating children and adolescents with congenital heart disease and valvular heart disease to assess the exercise capacity and abnormalities of cardiac rhythm.

The parameters usually assessed are ST segment depression or ST elevation in leads without Q waves, development of angina, hemodynamic responses ST changes in recovery phase (table 1) angina pectoris, ventricular arrhythmias and inadequate response of blood pressure or heart rate to exercise (the latter is termed chronotropic incompetence) are the other important markers.

Increasing importance to recovery phase is being given; especially ST depression in the recovery carries almost similar diagnostic significance as that during the exercise. A study from the Cleveland Clinic group stressed on the time taken for the slowing of the heart rate during recovery, which indicates the vagal tone of the individual. Delayed heart rate slowing predicted poor outcome. Hence, heart rate recovery should be carefully monitored which adds further value to the test.

Table 1: Treadmill test variables

Diagnostic and prognostic treadmill test variables during exercise and recovery
Exercise variables
Maximal exercise capacity
ST-segment depression
ST-segment elevation
Angina pectoris
Inadequate blood-pressure response
Inadequate heart-rate response
Ventricular arrhythmia
Recovery variables
ST-segment depression
Delayed slowing of heart rate
Ventricular arrhythmia

Ventricular arrhythmia during the recovery phase carries more mortality risk than that during peak exercise. It also reflects the vagal tone as increased vagal activity during recovery is required to suppress the arrhythmia. Exercise duration, exercise hypotension, exercise hypertension, chronotropic incompetence, heart rate recovery are among the most important hemodynamic variables predicting future cardiac events even in the absence of ischemia[3].

Contraindications to testing include active angina or ischemia, heart failure, critical valvular heart diseases, severe hypertension, acute myocarditis or pericarditis. Elderly patients and patients with musculoskeletal problems cannot perform the test. The test carries the sensitivity and specificity of 57% and 72%. Baseline ECG changes of LVH, digoxin effect, bundle branch blocks, preexcitations greatly affect the interpretation of the test.

Pharmacological echocardiographic and radionucleotide stress testing are now widely available with better sensitivity and specificity[4]. These tests aredefinitely useful in patients who cannot exercise on

a treadmill and in those with precluding ECG changes as described, but are expensive and does not provide sufficient hemodynamic information compared to treadmill test. Despite the technical fallacies, treadmill test still holds its place in the current era as a diagnostic and prognostic tool.

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Swig a Little Wine, Keep Your Mind in Line

Drinking moderate amounts of alcohol (particularly red wine) is no longer frowned upon by the medical community. Several previous studies have shown that wine, when consumed in moderation, can reduce the risk of cardiovascular disease, prevent the damaging effects of sunburn and even, prevent cancer (due to the presence of resveratrol). Now in a new study published in BMC Medicine (Gea et al. BMC Medicine 2013, 11:192; http://www.biomedcentral.com/1741-7015/11/192), researchers from Spain, suggest that consumption of moderate amounts (2 to 7 small glasses per week) of wine significantly reduces the risk of depression. The study was carried out on 5005 individuals of both sexes between the ages of 35 and 80. The key word here is "moderation". All the benefits accrue only to those who practice moderation. Exceeding the limit of 7 small glasses per week may actually worsen the depression. Never overdo a good thing!

- Dr. K. Ramesh Rao

Invited Article

Epigenetics - A Paradigm shift in Cancer Management

Dr. Kurinji Pandiyan, Ph.D.

Kurinji Pandiyan completed her doctorate in Human Genetics and Molecular Biology from the Johns Hopkins School of Medicine, Baltimore, MD, USA. Her thesis research was conducted at Johns Hopkins University and at the University of Southern California, under the mentorship of Stephen Baylin, MD, and Peter Jones, PhD, DSc., distinguished professors in the field of cancer epigenetics. Kurinji's thesis work resulted in the development of a novel methodology to coordinately characterize nucleosome positioning and DNA methylation and is currently widely adopted by the field. Her graduate work has been published in several high-impact, peer-reviewed journals.

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Introduction

The importance of epigenetics was recognized decades ago by C.H. Waddington, when he coined the term and described it as "the causal interactions between genes and their products, which bring the phenotype into being" in 1942[1]. Although the definition of epigenetics has evolved over the decades that followed, the concept posited by Waddington as to the importance of epigenetics in controlling gene expression has withstood the test of time.

Currently, epigenetics is regarded as the study of mitotically and meiotically heritable changes in gene expression that are not caused by changes in the underlying DNA sequences[2]. A majority of these heritable modifications are established during embryogenesis and faithfully maintained through the divisions of somatic cells, allowing for the adoption of distinct cell identities despite identical genetic information. In our current understanding, epigenetic mechanisms of gene expression control include DNA methylation changes at CpG (cytosine followed by guanosine) sites, packaging of DNA into nucleosomes, octamers of histone proteins, and their positioning, modification of histone tails on the nucleosomes and the expression of small and large non-coding regulatory RNA species (Table 1)[3-6]. In concert, these define the epigenetic landscape of a cell, impact gene expression and hence cell state definition.

Epigenetic modification	Function
DNA methylation	Represses gene expression when present at gene promoters
Histone modifications	Can repress or activate gene expression depending on the mark
Histone variants	Some variants de-stabilize the nucleosome structure and activate gene expression
Nucleosome positioning	Represses gene expression when present at gene promoters
Regulatory RNAs	Generally repress of gene transcripts

Table 1: Components of the epigenetic machinery

All of these epigenetic mechanisms of control have been shown to go awry in cancer. Although it was originally believed that genetic changes are the primary causal events in tumorigenesis, it has now been established that some of the epigenetic aberrations seen in cancers can drive malignant potential[7,8]. These aberrations have been identified both at the individual gene level and on a genome-wide scale[9-11]. The prevalence of global epigenetic aberrations reinforces the concept that epigenetic disruption is truly a hallmark of cancer[12].

Since the identification of the first aberrantly hypermethylated gene promoters, numerous papers have observed these epigenetic changes in a multitude of genes that code for proteins with tumor suppressive function, such as cell cycle checkpoint proteins[13], DNA damage repair proteins[14] and adhesion proteins[15]. It is now widely accepted that promoter DNA hypermethylation results in turning off gene expression and locking genes in a repressed state. Global hypomethylation in tumors has also been implicated in destabilizing the genome and activating proto-oncogenes[16-18]. More recently, overexpression of the repressive polycomb group of proteins that administers the repressive trimethylation mark on the 27th lysine of histone H_3 has been implicated in tumorigenesi[s1]9. Alterations in the expression state of other components of the epigenetic machinery, such as chromatin remodelers, histone methyltransferases, demethylases, and deacetylases have all been observed in tumor[s]8. This indicates that the faithful inheritance of epigenetic processes is critical to the maintenance of the non-tumorigenic state

There is excitement revolving around the identification of epigenetic changes in fuelling carcinogenesis since these changes are potentially reversible by pharmacological intervention. Even though epigenetic states are heritable, they are dynamic and do not affect the primary DNA sequence in most situations, which makes them excellent targets for drug development. The vast quantities of data generated by recent genome-wide studies have established a picture of the

cancer epigenome, supporting the development of epigenetic therapies, the focus of which is currently on reverting aberrant gene silencing events. The last several decades has seen the emergence of numerous DNA methyltransferase inhibitors (DNMTi), histone deacetylases inhibitors (HDACi) and inhibitors antagonizing histone modifying enzymes. These drugs have been tested in both preclinical and clinical studies with encouraging results, predominantly in hematological malignancies [12,20-22].

Epigenetic Aberrations in Cancer

For decades it was believed that cancer was a disease of genetic mutations and that mutations and translocations were exclusively the causal events behind tumorigenesis[7]. Several studies have established that epigenetic silencing of tumor suppressor genes can cause and contribute to tumorigenesis (Figure 1)[9,23]. Epigenetic gene silencing has been shown to serve as a "second hit", resulting in the loss of function of genes that have one allele inactivated by mutations (eg. CDH1). There are also some genes that are rarely mutated and only silenced by DNA methylation (eg. SFRP1)[8,9]. More recently, it was found that genetic and epigenetic aberrations in cancer are not independent events and are, in fact, two sides of the same coin[8]. This notion arose from the unexpected finding that numerous components of the epigenetic machinery, such as DNA/histone methyltransferase enzymes and chromatin remodelers, harbor genetic disruption in cancers[8]. Abnormal expression of these genes or the presence of misfolded isoforms of the proteins results in the disruption of the epigenome and could trigger epigenetic alterations that lead to carcinogenesis[18]. Hence, a study of the aberrant cancer epigenome (Figure 1) is critical in order to understand the pathogenesis of cancer and the best ways to target it therapeutically. The following section describes the aberrant DNA methylation changes that have been observed in cancers.

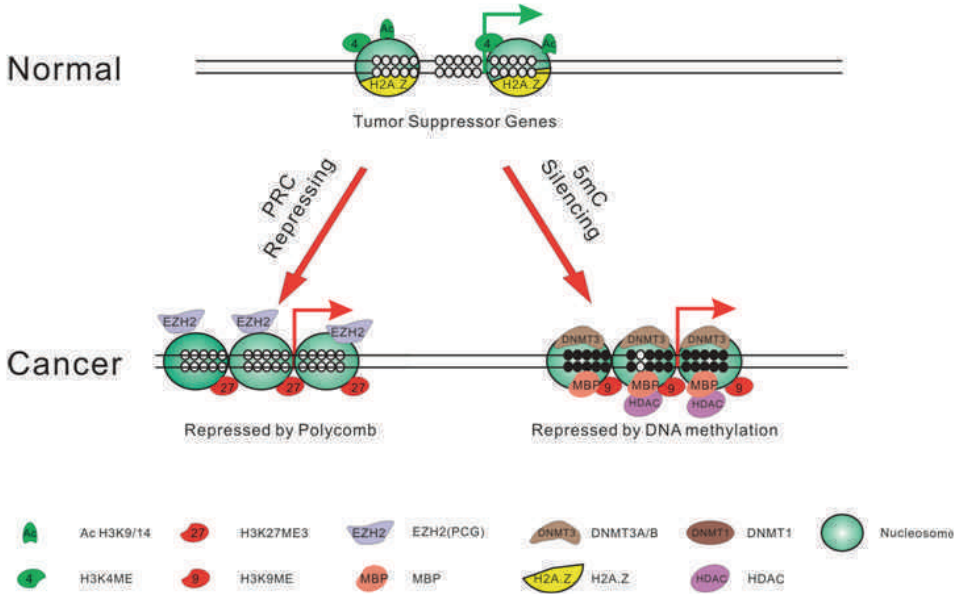

Figure 1: Aberrant epigenetic repression in cancer. *The above schematic depicts epigenetic repression in cancers that results from polycomb repression or from DNA methylation induced silencing. Red arrows on the genes represent transcription start sites (TSS); open circles represent unmethylatedCpG sites and filled circles represent methylated CpGdinucleotides. Tumor suppressor genes that are in an active configuration in normal cells are unmethylated, have nucleosomes with histone variants (e.g. H2A.Z) as well as histones with active marks (H3K4me3 and a nucleosome-depleted region (NDR) at the TSS, permissive for transcription. These tumor suppressor genes have been found as silenced by the polycomb H3K27me3 mark (applied by EZH2), independent of DNA methylation, or by DNA methylation (applied by DNMTs). Compounding of repression can occur when the methylated CpG sites recruit methyl-binding proteins (MBP). In turn, these recruit HDACs, that further repress chromatin by removing histone acetylation, as well as histone methyltransferases, that lock in methylation by applying trimethylation to H3K9. Nucleosome compaction is seen in both contexts of gene repression.*

The figure has been adapted from a recent paper12.

Aberrant DNA methylation in cancer

Disruption of DNA methylation patterns has been observed genome-wide in cancers. Key features of this disruption include global hypomethylation and promoter - specific hypermethylation[11,18,24]. Hypomethylation of repetitive elements such as those seen in regions of retrotransposon insertion can result in genomic instability and potential chromosomal translocations and breakage[16,24]. This is an understudied area and deserves more attention in the future. In contrast, focal hypermethylation at CpG island genes has garnered substantial interest. Studies have established that several tumor suppressor genes, encoding cell cycle regulators, DNA damage response genes, pro-differentiation factors as well as tumor suppressive microRNAs and other non-coding RNAs are found to be abnormally silenced by promoter DNA methylation[25-28]. A few examples of these well-studied tumor suppressor genes that have been found to harbor DNA hypermethylation in cancers include RB13, CDKN2A, MLH1, and BRCA1[11,29,30]. These genes are crucial to the maintenance of normal cellular physiology and their silencing could trigger tumorigenesis[31]. When differentiation inducing transcription factors are methylated, as seen frequently

for GATA4 and GATA5 in colon and gastric tumors, appropriate lineage specification is prevented[32]. A return of a stem cell signature in cancers has been frequently observed and could be a key driver of tumorigenesis[33].

Although it has been firmly established that DNA methylation patterns are disrupted in cancer, the field is a long way from understanding the mechanisms by which certain regions are targeted for hyper- or hypo-methylation. An initial hypothesis was that an aberrant increase in the levels of DNMTs could cause hypermethylation of genes[34]. This model does not explain the global hypomethylation that occurs in conjunction with the hypermethylation. Alternatively, recent studies have shown that certain genes have a predisposition for DNA hypermethylation due to the repressive H3K27me3 marks that they harbor in the embryonic state (along with the active H3K4me3 in the bivalent state) and in the adult stem cell state, a process that is potentially co-regulated by the polycomb group and DNMTs[35-38].The process by which a promoter that is repressed by the polycomb mark attains de novo DNA methylation has been termed "epigenetic switching", wherein the state of reduced epigenetic plasticity is locked into a state of irreversible silencing on application of DNA methylation[18,22,37]. It is unclear as to whether the DNA methylation machinery directly interacts with the polycomb machinery to induce silencing. There has been some evidence for this concept in recent studies that have uncovered interactions of EZH2[39] and CBX7 40 with DNMTs in cancer. It has also been demonstrated that the DNMTs themselves can achieve gene silencing without the application of DNA methylation, perhaps by acting as a scaffold for other repressive proteins[41].

Epigenetic therapy

The excitement surrounding the identification of epigenetic driver events in tumorigenesis is due to the relatively reversible nature of epigenetic aberrations. This is in contrast to genetic mutations that cannot be altered at the sequence level but, rather, can be compensated for by the use of inhibitors and protein substitutes to compensate for mutated proteins, depending on the consequences of the defect[42]. Since epigenetic changes are potentially erasable at the source, the research community has been triggered to develop a number of therapeutic measures to reverse the abnormalities. DNA methylation inhibitors have been the most widely studied and are currently the first line therapy for myelodysplastic syndrome (MDS). Drugs targeting other components of the epigenetic machinery are in development and have the potential to greatly impact cancer management[2].

DNA methyltransferase inhibitors

Without knowledge of the drugs' DNA demethylation potential, scientists at the Institute of Organic Chemistry and Biochemistry in Prague first synthesized 5-Azacytidine (AZA) and 5-aza-2 deoxycytidine (DAC), the rogue cytidine analogs that can replace cytidine in DNA. They were thought to be traditional chemotherapeutic agents and did in fact prove to induce cytotoxicity at high doses. The efficacy of these drugs, especially in liquid tumors such as acute myelogenous leukemia[43], was identified shortly thereafter. The demethylating effects of these drugs finally surfaced a few decades later when they were found to induce muscle differentiation in mouse embryonic cells[44,45]. It is now well established that the mechanism of action of these drugs involves incorporation into DNA following which DNA methyltransferases are covalently bound to these analogs and targeted for proteasomal degradation[46,47]. The loss of the DNMTs results in heritable global DNA demethylation and re-expression of genes that were aberrantly silenced by DNA methylation[12].

After years of clinical trials, the two DNMT inhibitors, AZA and DAC, have been approved by the Food and Drug Administration (FDA) for the treatment of myeloid malignancies[12]. Due to their high toxicity, these drugs were nearly abandoned years ago. Dose de-escalation has been key to the re-introduction of these drugs in the clinic and there remains continued interest in the ability of these drugs to induce sustained reprogramming of cancer cells[48]. The most effective demethylation induced by these drugs is at lower doses, since cell division and DNA synthesis is critical to their action[49]. AZA is also capable of directly incorporating into RNA, which has been shown to result in the disruption of cellular processes and, hence, inhibition of protein synthesis[50,51]. The schematic in Figure 2 depicts the action of DNA methylation in conjunction with other epigenetic therapies that have not been discussed in this review. Table 2 highlights select clinical studies that have shaped the understanding of these therapeutics.

Epigenetic Drug	Function	Disease targeted
Azacitidine	DNA methylation inhibitor	MDS/AML (2002-10)
Decitabine	DNA methylation inhibitor	MDS (2006-09), Refractory solid tumors (2009)
Azacitidine + Entinostat	DNA methylation inhibitor + histone deacetylase inhibitor	MDS/AML (2009)
Decitabine + Valproic acid	DNA methylation inhibitor + histone deacetylase inhibitor	Advanced leukemias (2007)

Table 2: Select clinical studies using epigenetic drugs

Numerous clinical trials are underway, attempting to expand the therapeutic reach of these drugs to solid tumors[2], wherein DNA hypermethylation is also observed. Despite encouraging results in myeloid malignancies, the results of treating solid tumors have been disappointing. A major cause of this is the inability of the drug to effectively reach the target tumor site, due to instability in aqueous solution. The drugs get readily hydrolyzed and become easily deaminated by cytidinedeaminase[52-55].

To circumvent this stability problem, other cytidine analogues with longer half-lives and improved aqueous stabilities have been developed. Zebularine is one such drug engineered to lack an amino group in the 4th position of the pyrimidine ring, which has rendered it less chemically labile and cytotoxic. The drug has proven effective in reactivating methylated tumor suppressor genes in breast cancers[56] and in vivo in MIN mice studies[57]. Another more stable version of AZA and DAC is their prodrug form, such as the analog S110. This is a dinucleotide with a 5-azacytosine ring that is more resistant to deamination. S110 is effective in re-expressing genes such as p16 in mouse models[58] and is the current focus of clinical trials in leukemias, under the umbrella of the Stand up to Cancer program.

A serious concern with the use of drugs that incorporate into DNA is potential mutagenic and DNA damage events that could result from the incorporation. Hence, another focus of the drug development community is to engineer non-nucleoside DNMT inhibitors, which are capable of targeting DNMTs for degradation without incorporating into DNA[18,59]. The few such inhibitors that have been developed to date, RG108 and MG98, have shown some promise in reactivating genes 12 by blocking the active site of DNMT1[60,61] but have limited potency in demethylation and, hence, have not been actively pursued for clinical applications[62].

Another concern in the use of these inhibitors is their lack of specificity in targeting the demethylation at tumor suppressor genes and the global hypomethylation that is induced as a result of usage. While it is possible that targeting of demethylation using zinc finger nucleases coupled with DNMT inhibitors is a future focus of drug development, the non-specificity of DNA methylation inhibition could, in fact, be a strength of the treatment since cancer is a multi-faceted disease with numerous epigenetic aberrations[2]. Finally, although demethylation is non-specific and genome-wide, the predilection for rebounding of methylation could be specific to some regions. Hence, regions with sustained demethylation coupled with chromatin opening may, in fact, be a lot less random than anticipated, and potentially be the drivers of therapeutic response post-therapy.

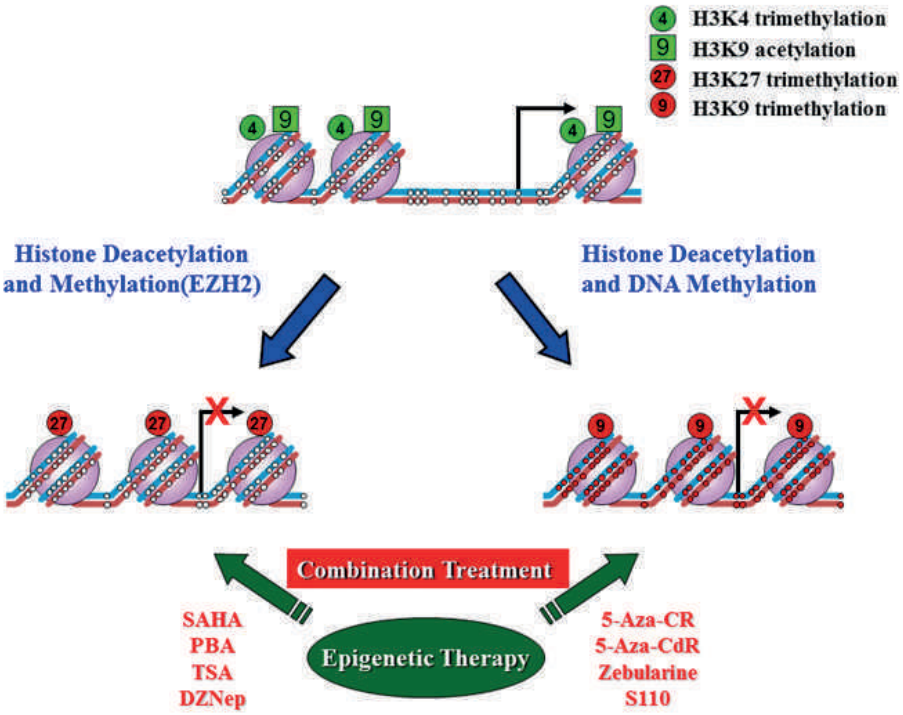

Figure 2: Epigenetic therapies can reverse aberrant epigenetic modifications in cancer. *Genes that are expressed in normal cells, such as tumor suppressor genes, have an open chromatin structure, consisting of an unmethylated promoter, active histone marks (marked in green) and a nucleosome-free region immediately upstream of the transcription start site. During tumorigenesis, genes can be silenced through one of the two silencing mechanisms: polycomb repressive complex (PRC) reprogramming and de novo DNA methylation. PRC mediated silencing can be reversed upon treatment with EZH2 inhibitors, such as DZnep. The de novo methylation mediated silencing can be reversed upon treatment with DNA methylation transferase inhibitors, such as 5-Aza-CdR, 5-Aza-CR, Zebularine, and S110. The therapeutic value of above reagents may be enhanced when combining with HDAC inhibitors, such as SAHA, PBA and TSA. Open and closed circles represent unmethylated and methylated CpG sites, respectively.*

Adapted from a recent paper 12

Conclusions

Epigenetic processes significantly impact and contribute to embryonic development, the maintenance of normal biological processes as well as in the initiation and progression of numerous diseases including cancer. Despite the outpouring of literature, we have but scratched the surface of this vast and important field of study. With rapidly advancing technologies, our ability to study epigenetic processes and changes has been better than ever before. This will allow us to dissect the intricacies of the epigenetic landscape and the tight control that is needed for maintenance of normal processes.

It is becoming increasingly important to obtain a holistic view of the field and to study different facets of the epigenome together, and not in isolation. In order to address this concern and to make the combined study of DNA methylation and chromatin accessibility readily available to clinical researchers and basic scientists alike we have developed a novel method, named AcceSsslble,to study DNA methylation and nucleosome positioning in a coordinate manner[63].

Epigenetic aberrations are prevalent yet potentially reversible with pharmacological interventions. Although, several epigenetic therapies have been developed and have shown some clinical promise, there are many unanswered questions that need to be addressed before epigenetic therapies in development can be translated from the bench to the bedside. As the paradigm has shifted in the usage of epigenetic modulators, from high cytotoxic doses to low reprogramming doses, the metrics for determining clinical trial efficacy and the regulatory barriers for drug approval also need to evolve. Future basic science, clinical and regulatory studies will, hopefully, address this burgeoning field of epigenetic therapy and allow for tailoring to meet individual patient needs, as an important component of personalized medicine.

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Review Article

Cerebrospinal Fluid Dynamics Study: Applications in Clinical Practice

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Abstract

The study of cerebrospinal fluid (CSF) dynamics is an important, yet, less well-known field. It has many important clinical applications, which include the disorders of CSF absorption. The methods of CSF dynamics measurement include Constant flow method, Constant pressure method, Bolus injection method, Radio-isotope dilution method, Phase contrast magnetic resonance imaging (MRI). The bolus lumbar injection method which has been improvised by the author is very useful for routine clinical application. The CSF dynamics study is very useful in the diagnosis and planning of treatment in normal pressure hydrocephalus, post-meningitic hydrocephalus, post-traumatic hydrocephalus and idiopathic intracranial hypertension.

Key words : Cerebrospinal fluid dynamics; Bolus lumbar injection method; Diagnosis of normal pressure hydrocephalus.

Introduction

The study of cerebrospinal fluid (CSF) physiology is an interesting and under-explored field. Disorders of CSF absorption like normal pressure hydrocephalus (NPH), post-meningitic hydrocephalus, post-traumatic hydrocephalus, idiopathic intracranial hypertension (IIH), etc., often pose a challenge in diagnosis and management decisions. The study of CSF dynamics helps in the diagnosis and planning treatment of these disorders.

Applied anatomy and physiology

The rate of CSF formation in humans is about 0.3–0.4 ml /min (about 500 ml day). Total CSF volume is 90–150 ml in adults. Potential sites of CSF formation include the choroid plexus, parenchyma of the brain and the spinal cord, and ependymal lining of the ventricles[1]. The fluid formed in the lateral ventricles escapes by the foramen of Monro into the third ventricle and then via the aqueduct into the fourth ventricle. From the fourth ventricle the fluid enters the subarachnoid spaces through the median foramen of Magendie and the two lateral foramina of Luschka. The absorption of the cerebrospinal fluid is a dual process. It is mainly through the arachnoid villi into the dural sinuses, and also through the perineural lymphatics (around ophthalmic, optic and vagal nerves) and via the capillary bed of the CNS[2].

There are two components in CSF circulation: (i) bulk flow (circulation) and (ii) pulsatile flow (back and forth motion). In bulk flow, CSF is produced by choroid plexus and absorbed by arachnoid granulations. The force, which provides CSF movement from the ventricular system to arachnoid granulation and CSF absorption, is caused by a hydrostatic pressure gradient between the site of its formation (slightly high pressure) and its site of absorption (slightly low pressure). In pulsatile flow, movement of the CSF is pulsatile and results from pulsations related to cardiac cycle of the choroid plexus and the subarachnoid portion of the cerebral arteries[3].

The CSF outflow resistance (Rout) is the most important parameter measured in the CSF dynamics study. Rout is the reciprocal of conductance (Cout) and reflects the CSF absorption at the arachnoidal villi. Rout measurement helps in the diagnosis and planning treatment of clinical disorders of CSF absorption.

Methods of Rout measurement

There are various methods of measuring Rout. The most important among them are: 1) Constant flow infusion (Katzman) method, 2) Constant pressure (servo-controlled) infusion method) and 3) Bolus injection (Marmarou) method. Radio-isotope dilution method and Phase contrast MRI (PC MRI) are also used in qualitative and quantitative study of CSF dynamics.

Constant flow infusion (Katzman) Method

The method of constant flow infusion was first introduced as a clinical tool in 1970 by Katzman and Hussey[4]. The method was later modified by others. Artificial CSF/saline is infused, usually through a lumbar or intraventricular needle, into the CSF space at a constant rate, and the corresponding rise in ICP/CSF pressure is registered and analysed. When ICP reaches

a steady state level (plateau), where the external input of artificial CSF added to the formation rate is equal to the absorption rate, the outflow conductance is given by Cout = Iext/ Pplateau – Pr where Iext is the rate of external infusion, Pplateau is the mean ICP on the new steady state plateau, and Pr is the resting pressure prior to infusion.

Constant pressure infusion method

The method of constant pressure infusion was clinically introduced by Ekstedt in 1977. When using the constant pressure infusion method, ICP is regulated to specific pressure levels, and the inflow of artificial CSF/saline needed to maintain that pressure is measured. This can be achieved with a peristaltic pump and a regulating system. Several predetermined pressure levels are employed, and on each pressure level mean ICP and net flow is determined. The flow is linearly dependent on ICP (given that the dural sinus pressure and the formation rate of CSF are constant), and thus Cout is assessed as the slope of the linear regression between flow and corresponding mean pressures[5,6].

Bolus injection (Marmarou) method

The bolus infusion test is based on a fast injection of a small volume of artificial CSF/saline and the study of the CSF pressure response to that injection developed by Marmarou[7,8]. The Madras Institute of Neurology (MIN) method devised by the author, is an improvised Marmarou's bolus lumbar injection method, using saline manometer made with easily available bed side material[9]. A saline manometer (if not readily available) is made using an intravenous set mounted on a meter scale and was filled with saline up to 11 cm of water with zero level corresponding to the level of the spine. Lumbar puncture is performed with 20G spinal needle and connected to the saline manometer through a three-way adapter. After the saline column stabilises the opening pressure (Po) is noted. A known volume of saline (rV), usually 5 or 10 ml is injected into the subarachnoid space through the three-way port at the rate of 1 ml/second. The peak pressure (Pp) reached after the bolus injection is noted. Once the saline column in the manometer starts falling gradually, after a fixed time ('t' in minutes), the pressure recording in the manometer (Pt) is noted. The CSF outflow resistance (Rout) is calculated using two step formula described by Marmarou[7,8].

I step: Pressure Volume Index (PVI) = rV/ log (Pp/Po)

II step: Rout = t.Po / PVI [log Pt (Pp - Po) / Pp (Pt - Po)] cm of water/ml/min.

This is converted into mm Hg/ml/min (cm of water/ml/min divided by 1.36).

Radio-isotope dilution method

This consists of injecting a radio-nuclide (I125,131, Tc99m) tagged to albumin or contrast agent into lumbar subarachnoid space and recording the radioactivity at various time intervals[10]. This is rarely used in clinical practice in the present day.

Phase contrast MRI

The PC MRI generates signal contrast between flowing and stationary nuclei by sensitising the phase of the transverse magnetisation to the velocity of motion. Before PC MRI data are acquired, the anticipated maximum CSF flow velocity must be entered into the pulse sequence protocol (velocity encoding (VENC). To obtain the optimal signal, the CSF flow velocity should be the same as, or slightly less than, the selected VENC. The mean VENC value is 5–8 cm/s for standard CSF flow imaging. In normal pressure hydrocephalus, significantly higher VENC values (20–25 cm/s) should be chosen owing to hyperdynamic CSF flow within the cerebral aqueduct. Quantitative CSF velocity and qualitative flow information can be obtained in 8 to 10 additional minutes in connection with routine MRI[11].

The constant flow infusion and the constant pressure infusion methods, though accurate, are difficult to perform in the routine clinical setting and are time consuming. Radio-isotope method is not widely used at present. The PC MRI is not yet widely and routinely available. The MIN method of bolus lumbar injection is a very simple bedside test, which can be performed with easily available equipment and has a good accuracy and useful for routine clinical application.

Clinical Applications

Communicating hydrocephalus is a fairly common clinical problem. This is due to a defect in the CSF absorption, which is mainly in the arachnoidal villi. The causes of communicating hydrocephalus are varied. The commonest of them are normal pressure hydrocephalus (NPH), post-meningitic hydrocephalus and post-traumatic hydrocephalus. All these situations may be mimicked by atrophic ventriculomegaly, either due to age related, post traumatic or post-meningitic causes. This might confuse the neurosurgeon in the decision making regarding shunt. Hence, in addition to the clinical and radiological parameters which may be dubious, there is a need for a fool proof investigative tool to determine the indications for shunt in these patients. A defect in the CSF absorption results in early increase in CSF outflow resistance. The increase in Rout precedes the clinical and radiological manifestations in patients with communicating hydrocephalus. The increase in Rout also often precedes the increase in intracranial pressure or subarachnoid CSF pressure as determined by measuring the opening pressure (Po) by lumbar puncture. Hence the measurement of Rout is likely to help in the early diagnosis of patients suitable for shunt in communicating hydrocephalus. The normal value of Rout in Indian population ranges from 3.82 to 9.7 mm Hg/ml/min, with a mean of 6.09 mm Hg/ml/min11. Rout value of 18 mm Hg/ml/min is kept as threshold for diagnosis and predicting good outcome following shunting in NPH[12,13]. Similarly elevated Rout is also helpful in the diagnosis and predicting good outcome following shunt in post-meningitic and post-traumatic hydrocephalus[9].

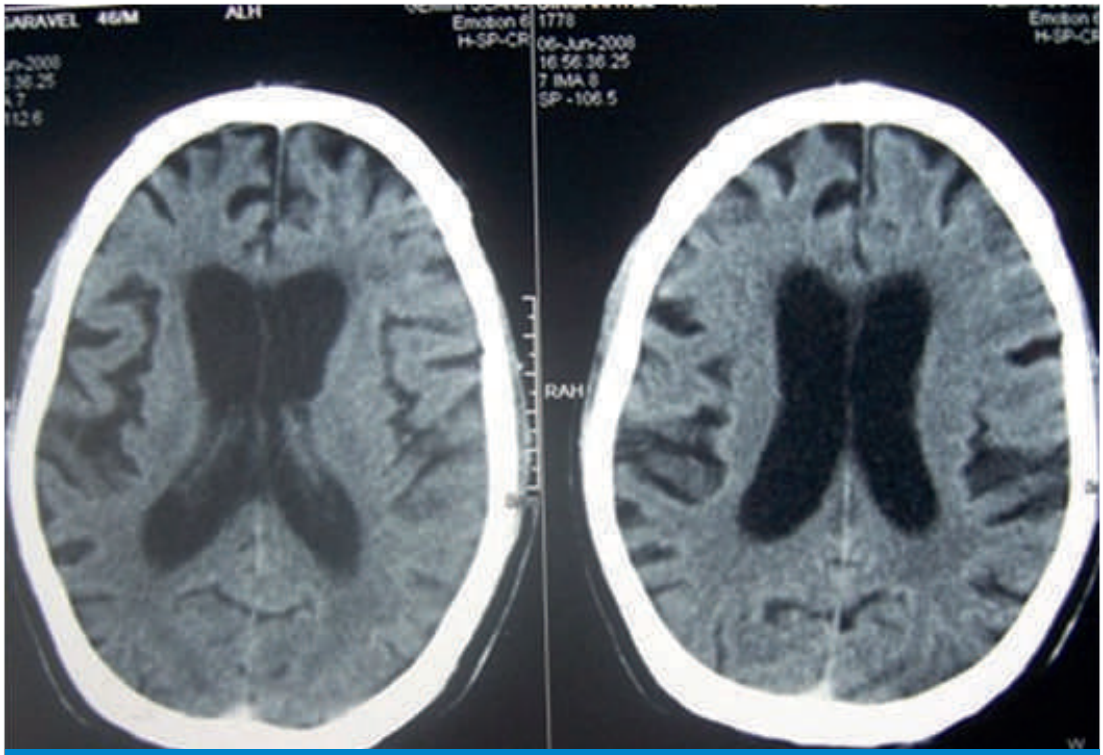

Fig 1:

Idiopathic intracranial hypertension (IIH), also known as benign intracranial hypertension and pseudotumour cerebri, is another clinical condition due to derangement of CSF absorption. This condition also poses diagnostic problem, as it may be mimicked by other conditions. Rout is grossly elevated in IIH. Single measurement of opening pressure after lumbar puncture is not a very reliable yardstick in the diagnosis of IIH. Hence Rout measurement is very useful in the establishment of diagnosis of IIH[9,14].

Clinical Vignette

A 45-year-old man was admitted with history of difficulty in walking and memory disturbances since 8 months. Neurological examination revealed slow gait with gait ataxia and moderate dementia with normal bladder function.

CT Brain (Fig.1) showed ventriculomegaly without periventricular lucency and some degree of cortical atrophy. The differential diagnosis in this patient would be either NPH or Alzheimer's dementia, since the clinical and CT pictures were not clear cut. The treatment and prognosis are completely different in both these conditions and hence precise diagnosis is mandatory. It is in such a situation that the CSF dynamics study is of immense help. CSF dynamics study (Bolus lumbar injection – MIN method) was performed in this patient, which showed opening pressure (Po) of 17cms of H_2O, which is only mild increase and not very conclusive. But CSF outflow resistance (Rout) measurement showed a value of 21.97 mm Hg/ml/min, which is an enormous increase. This conclusively established the diagnosis of NPH and the patient underwent ventriculo-peritoneal shunt surgery. He started showing very good clinical improvement in 10 days and near normal gait and memory at the time of discharge. This is an example to show the value of CSF dynamics study in establishing the diagnosis of an eminently treatable condition, namely, NPH.

Conclusion

The field of CSF dynamics study is fascinating. The MIN bolus lumbar injection method is a reliable, simple method of measurement of Rout, which can be used for routine bedside application. Rout measurement is very useful in establishing the diagnosis and planning treatment in the various disorders of CSF absorption, namely, NPH, post-meningitic hydrocephalus, post-traumatic hydrocephalus and IIH.

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EZH2 Makes it Easy

EZH2 is an enzyme (Histone-lysine N-methyltransferase) that is encoded by the EZH2 gene in humans. It directly controls the expression of some 1200 genes. In a new study done at the University of Illinois, the researchers used bio-informatics techniques to show that the level of expression of these genes correlated with biological behaviour (aggressiveness) of breast cancer. In the study published online in Molecular and Cellular Biology (Molecular and Cellular Biology, 2013; DOI: 10.1128/MCB.00426-13), the researchers altered the expression EZH2 gene in breast cancer cell lines with small molecule RNA inhibitors. Depending on the degree of inhibition, the level of expression of controlled genes varied and allowed the researchers to develop an analysis pipeline that would prove useful in stratifying breast cancer patients based on aggressiveness. The authors feel that EZH2 may make it easy to predict the prognosis in breast cancer and also in deciding therapy. The small molecule RNA inhibitor used in this study has the potential to become a therapeutic agent.

- Dr. K. Ramesh Rao

Review Article

Immune Mediated Male Infertility

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Abstract

This brief review focuses on the interaction between the immune and the reproductive systems. Conditions disrupting the blood testis barrier, laboratory tests for diagnosing antisperm antibodies and the currently available methods of treatment are discussed.

Introduction

Antigens associated with spermatozoa are never exposed to the immune system of the male unless the 'blood testis barrier' is breached. Spermatozoa are antigenically different both from the male who produces them and the female who receives them.

Immune Privilege and the Blood Testis Barrier

During the perinatal period the immune system learns how to recognize the 'self' from the reproductive'non self antigens'. Antigens produced after this period are not recognized as self by the body. At the time of puberty germ cells differentiate to produce mature spermatozoa. This process of Spermatogenesis results in the expression of new sperm antigens. These antigens are not recognized by the body as 'self'. Due to testis being immune privileged, germ cell antigens do not trigger immune response.

The sperm antigens are not exposed to the immune system due to the existence of the blood testis barrier. This barrier is morphologically defined as a series of tight junctions[3] formed by adjacent Sertoli cells. This divides the seminiferous epithelium into a basal compartment where the developing germ cells have free access to the vascular and immune system, and an adluminal compartment just above the barrier which represents the region isolated from the immune system. This adluminal compartment is where spermatogenesis takes place. The Sertoli cells might contribute to maintenance of immune privilege by the production of immunosuppressive proteins into the surrounding environment[4]. Breach in the blood –testis barrier leads to the exposure of spermatozoa antigen(s) to the immune system and production of Antisperm Antibodies (ASAB).

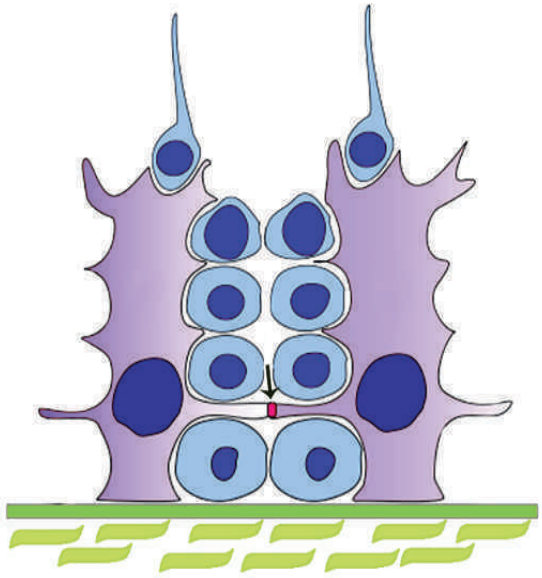

Fig1: Arrow shows the blood testis barrier formed by adjacent Sertoli cells

Pathophysiology of Sperm Antigens: The New Antigens

The acquisition of sperm surface antigens is a complex process. The addition or alteration of sperm surface antigens is thought to occur in the seminiferous tubules and the epididymis[5].Labelling of intact spermatozoa with I125 has revealed 300 different proteins[6]on the sperm surface of the spermatozoa. Although a few antigens like PH-20, Fertilin, CD59, CD52, HE2, HE4, have been identified[7], their exact function and characteristics are not known. In a study done by Claudia et.al.,[8](2001)highly enriched sperm proteins were separated by 2D gel electrophoresis from the seminal plasma of 20 infertile patients who showed ASABs. A total of 18 antigens were identified. Six of the recognized proteins were isolated and identified as Heat shock protein 70, heat shock protein 60, inactive

form of caspase 3, ER60, and 2 subunits of the proteasome. The highest rates of binding of the ASABs was seen with caspase 3 (90%) and ER 60 (95%) in all samples.Further studies are required to characterise and identify sperm membrane antigens responsible for impairing fertilisation.

Conditions that disrupt the blood testis barrier leading to generation of ASABs include testicular trauma[9], varicocele[10], testicular torsion[11], testicular tumour11, vasectomy[12]. Furthermore, Shibahara et al[11](2003) have reported other conditions associated with ASABs, which include spinal cord injury, mumps orchitis, congenital absence of vas and unexplained infertility.

In a study done by Mahdi et. al.,[13] (2011)in 45 infertile women, antisperm antibodies were found in both the cervicovaginal secretions (62.2%) and sera (64.4%) as compared to the control group of 30 fertile women who showed antisperm antibodies value of 3.3% each in the cervicovaginal and sera respectively. The precise mechanism by which antibodies impair sperm egg interaction is unclear. The antibodies may directly bind with the spermatozoa and inhibit motility, or may indirectly cause the release of cytokines from the spermatozoa and impede cell function and also reduce cervical mucus penetration[14]. Some antibodies of the IgA category are known to reduce fertilization rate when bound to the head[11], while IgM antibodies when bound to the head and tail caused the most significant reduction in fertilization rates[11]. This indicates that the ASABs exhibit diversity and heterogeneity.

Laboratory tests for diagnosing antisperm antibodies

Immune infertility in men may present in three ways. 1. It may manifest by the presence of sperm antibodies in the serum, semen or on the surface of sperm. 2. It may manifest by agglutination of spermatozoa in the semen. 3. It may also manifest by a reduction in the ability of the affected sperm to penetrate normal cervical mucus. Fertilization failure in an IVF program and a negative sperm penetration assay may be due to immune infertility. Diagnostic test currently used for evaluating immune infertility are 1. Sperm agglutination test; A. Gel agglutination test; B. Tray agglutination tests; C. Tube slide agglutination test. 2. Indirect immunofloresence. 3. Mixed erythrocyte spermatozoa antiglobulin reaction test. 4. Enzyme linked Immunosorbent assay. 5. Immuno bead test. Currently used tests include the Immuno bead test, Mixed Agglutination Reaction test (MAR).

Mixed Agglutination Reaction test: This test is performed by mixing semen with immunoglobulin G or IgA coated latex beads or red blood cells, and IgG or IgA antiserum on a microscopic slide. If antibodies are present the sperms will form clumps with the coated latex beads, if antibodies are absent the sperms will swim freely. A level of binding greater than 50% is considered significant[15]. This test is useful for detecting direct antibodies in men.

Immunobead test: this test is performed by combining IgG or IgA coated latex beads and washed sperm on the slide. The sperm is washed with media and Bovine serum albumin. Post wash the sperms are placed on slides with IgG or IgA coated latex beads. If antibodies are present the beads will attach directly to the sperm. This test provides more information than the mixed agglutination reaction. The results provide the number of sperms bound by beads and the specific locations were the bead is bound to the sperm. Unlike the MAR test this test can be used to detect ASAB's in the women's serum, follicular fluid, or cervical mucus. A level binding greater than 50% is considered to be of clinical significance[15].

The Immunobead tests, MAR tests and, ELISA have an inherent problem. They do not identify the antibody that is clinically relevant. Only subsets of patients with ASABs have agglutinating and cytotoxic antibodies[16].These tests are unable to determine the number of antibody and antigen molecules involved in binding. These tests only give us ASAB titres; however which of these ASAB's are of clinical significance cannot be determined by these tests[17]. Also these tests do not give information regarding the specific antigens to which antibodies bind and their subsequent impact on spermatozoa function. ASABs have the ability to bind against multiple antigens on the spermatozoa surface[17], which of these antigens are important clinically is still a subject of research. There is a pressing need for developing antigen specific tests which will help us categorize the patients based on sperm functions, and help us in adopting less radical treatment protocols. A series of assays would be more reliable than a single assay[18].

Treatment

Treatment of immune mediated infertility is unsatisfactory. Currently available methods are

1) Barrier contraception – particularly condom, reduces the exposure of female partner to sperm and may reduce ASABs titres. In a case report by Franken[19], a couple with no apparent cause of infertility apart from high ASABs in the women's sera were advised use of condoms for 6 months. The antibody titres were monitored; antibody levels fell after 7 months of therapy. However there was no concomitant increase in the pregnancy rate.

2) Steroid administration[20]-several centres around the world use steroids along with IUI, the most common regimen followed was 20 mg of methyl prednisolone for days 1-10 of the female partner's follicular phase, followed by 5 mg daily for days 11 and 12[20].Continuous treatment with steroids for a period of 6 months may improve pregnancy rate and semen parameters[20]. Steroids reduce the antibody titre by immunosupression. The rationale of steroid therapy is to obtain a proportion of antibody free sperm which would be available for fertilization. However long term use of steroids is associated with the risk of developing diabetes mellitus, hypertension, hypogonadism, steroid psychosis, osteoporosis and harmful changes in the cholesterol levels. Bilateral aseptic necrosis of the femoral head has been reported with intermittent

high dose steroid therapy[21].Due to the doubtful efficacy of steroids along with their long term adverse effects, the use of steroids has come down in favour of ART. However not all patients can afford ART, so steroids may have clinical value and more studies are required on their efficacy and adverse effects

3) In Vitro sperm processing / washing techniques – no invitro sperm processing technique has been able to disrupt the antigen-antibody complexes bound to the sperm surface[22]

4) ART- may help overcome immune mediated infertility. IUI helps to overcome cervical mucus penetration impairment. The pregnancy rate of IUI is variable from 0% to 64%. Nevertheless a good result can be obtained when moderate sperm auto immunisation is present[23]. The effectiveness of IUI is not just the cost factor, but in cases of moderate sperm immunisation the proportion of antibody free sperms in the semen, and its meeting the egg is favoured in a well timed cycle[23]. ICSI is favoured over conventional IVF-ET in case of IUI failure[23]. ICSI has been claimed as the primary treatment choice in immunological mediated infertility, as it overcomes any interference of ASAB with sperm-zona binding, progression of the sperm and ultimately the fertilizing ability[23].

Conclusion

Though there are several tests to detect ASABs, the exact significances of these tests are not known. Besides there is no satisfactory way to treat these couples. There seems to be conflicting evidence with respect to ASABs affecting pregnancy and miscarriage rates. Since there seems to be no satisfactory way to treat these couples in out-patient clinics, ART seems promising. It should be recognised that Immunosuppressive therapy has its own risk in the long term. Intrauterine artificial insemination with husband's spermatozoa has been suggested as an appropriate therapy[23] but the pregnancy rate has been variable. Immune mediated male infertility and ASABs remains a controversial area[24]. Although introduction of assisted reproduction has helped overcome this condition, it has however, raised numerous questions as how to prevent an increase in titres of specific ASABs More work is still needed to understand the cellular interactions between the male gametes and the immune system.

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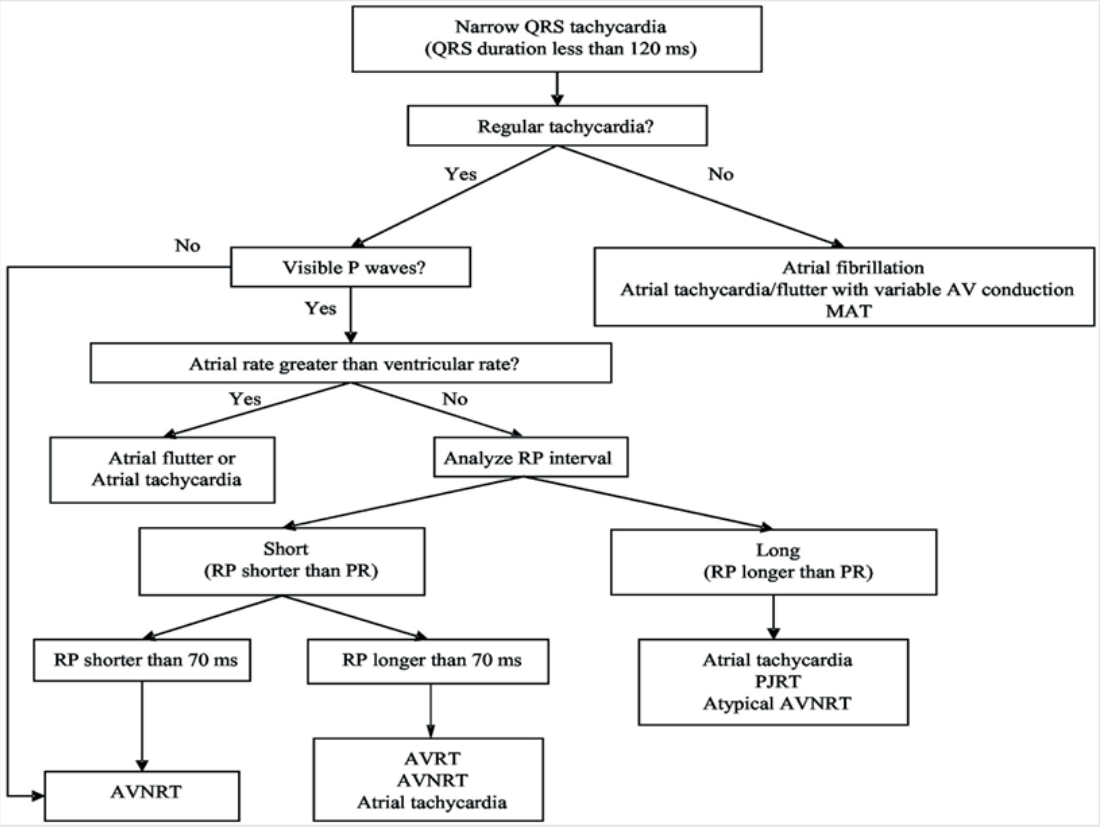
Answer to : **Diagnose the Condition**

ECG shows narrow QRS tachycardia which is regular.RP interval is longer than PR interval. Hence diagnosis could be either 1.Atypical AVNRT 2.Paroxysmal Atrial Tachycardia 3.PJRT. Inview of her previous H/O RHD ,possibility of tachycardia arising from atria is more. SVT got reverted with INJ.Verapamil.



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Review Article

Pigmented Lesions Of The Oral Cavity-Review And Differential Diagnosis

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Abstract

Pigmented lesions are commonly found in the mouth. Such lesions represent a variety of clinical entities, ranging from physiologic changes to manifestations of systemic illness and malignant neoplasm. Evaluation of patient presenting with a pigmented lesion should include a full medical and dental history, extra oral and intra oral examinations and in some cases biopsy and laboratory investigations.

Key words : Diagnosis, Differential diagnosis, Oral cavity, Pigmentation disorders.

Introduction

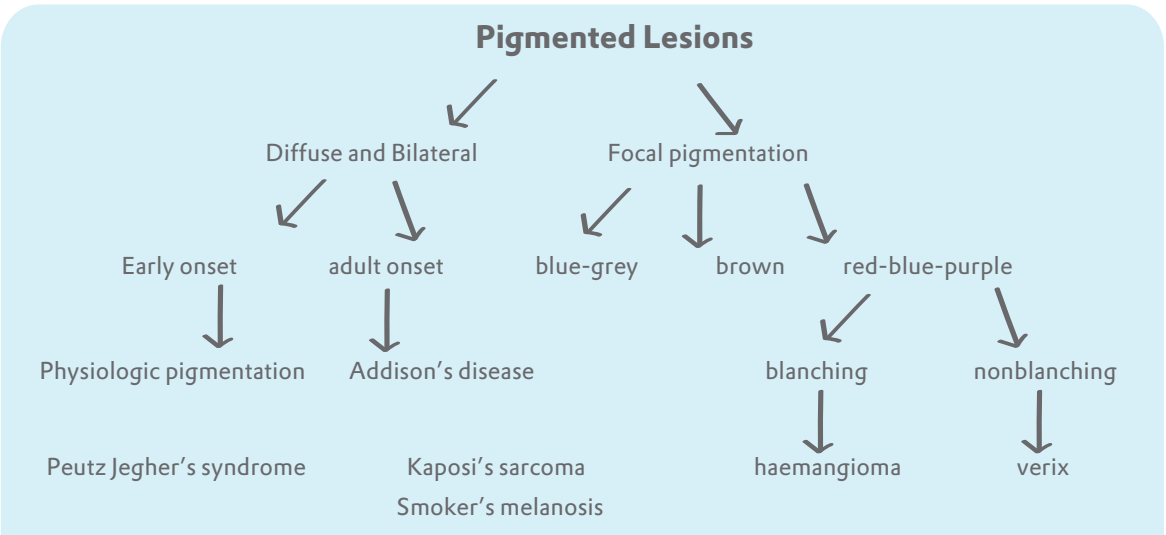
Pigmented lesions are commonly found in the mouth. Such lesions represent a variety of clinical entities, ranging from physiologic changes (racial pigmentation) to manifestations of systemic illness (Addison's disease) and malignant neoplasm (Kaposi's sarcoma).

Oral pigmentation may be exogenous or endogenous in origin. Exogenous pigmentations are commonly due to foreign body implantation in the oral mucosa. Endogenous pigments include melanin, haemoglobin and carotene. Melanin is produced by melanocytes in the basal layer of the epithelium and is transferred to the adjacent keratinocytes via membrane bound organelles called melanosomes. Melanin is also synthesized by nevus cells, which are derived from the neural crest cells and are found in the skin and mucosa. Pigmented lesions caused by increased melanin deposition may be brown, blue, grey or black depending on the amount and location of melanin in the tissues[1].

Diffuse and bilateral pigmentation

a) Physiologic pigmentation

It is common in the African, Asian, and Mediterranean populations[2]. It is due to greater melanocyte activity rather than a greater number of melanocytes. Physiologic pigmentation develops during the first two decades of life. The colour ranges from light to dark brown (Fig.1.1).The attached gingiva is the most common intraoral site of such pigmentation where it appears as a bilateral, well demarcated, ribbon-like dark brown band. The pigmentation is asymptomatic and no treatment is required.



Differential diagnosis of oral & Pigmentation

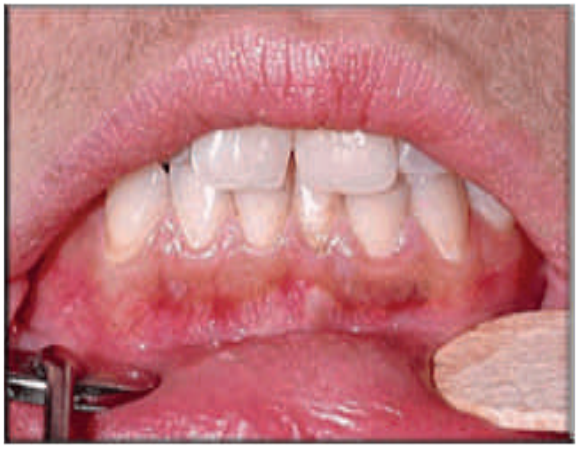


Fig.1.1: Physiologic pigmentation due to increased keratinisation

b) Addison's Disease

It is due to progressive bilateral destruction of the adrenal cortex by autoimmune disease, infection or malignancy. Oral involvement presents diffuse brown patches on gingival, buccal mucosa, palate and tongue which may resemble physiological pigmentation (Fig.1.2). Oral mucosal pigmentation associated with Addison's disease develops and progress during adult life and accompanied by weakness, nausea, vomiting, abdominal pain, constipation, weight loss and hypotension. Addison's disease can be fatal if left untreated. Management includes treatment of the underlying cause and corticosteroid replacement therapy.

Fig 1.2: Diffuse pigmentation of the gingiva seen in Addison's disease

c) Drug – Induced Pigmentation

The pathogenesis of drug-induced pigmentation varies depending on the causative drug. Chloroquine (Fig.1.3) and other quinine derivatives are used in the treatment of malaria, arrhythmia and arthritis. Mucosal discolouration with this drug occurs as blue grey or blue black pigmentation in the hard palate[3].

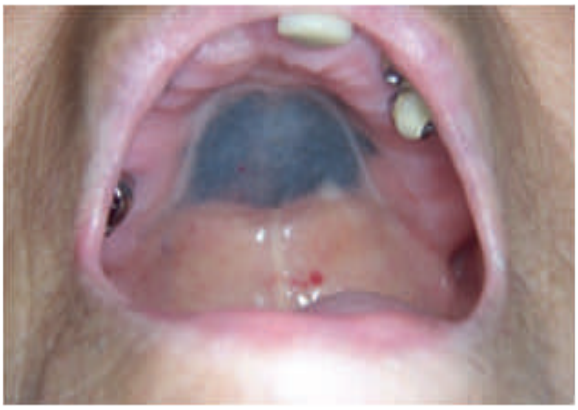


Fig.1.3: Bluish Grey pigmentation of the hard palate caused by antimalarial drug chloroquine.

d) Smoker's Melanosis

Smoking may cause oral pigmentation in light skinned individuals and accentuate the pigmentation of dark skinned persons[4]. Smoker's melanosis occurs in up to 25% of the smokers[5]. Women are more commonly affected than men, which suggest a synergistic effect between the female sex hormone and smoking. The brownish black lesions occur mostly on the anterior labial gingiva followed by buccal mucosa (Fig1.4). Smoker's melanosis usually disappears within three years of smoking cessation. Biopsy should be performed if there is surface elevation or increased pigment intensity or the pigmentation is in unexpected site[4].

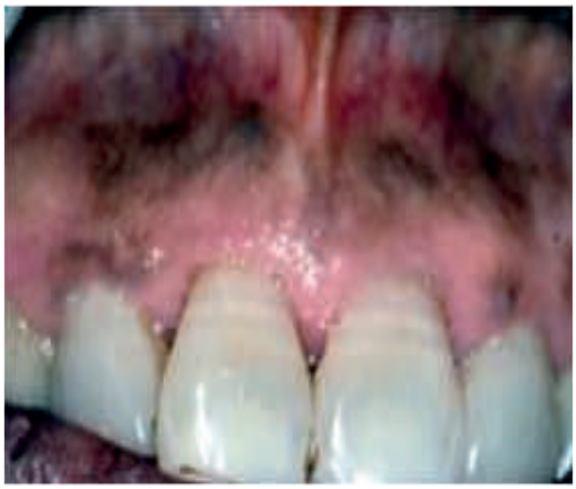


Fig.1.4: Brownish black hyperpigmentation of gingiva in smoker's melanosis.

e) Focal pigmentation Hemangioma

It is a benign proliferation of the endothelial cells that line the vascular channels. Haemangioma regresses as the patient ages, but vascular malformation persists throughout life. In the oral cavity tongue is the most common site of occurrence (Fig1.5). The lesion may be flat or slightly raised and colour varies from red to bluish purple depending on the type of vessels involved.

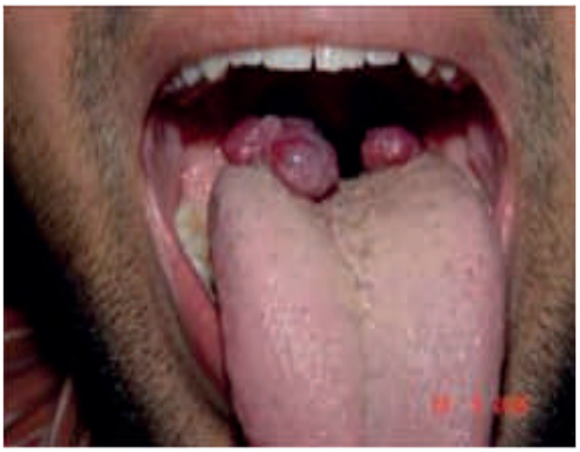


Fig. 1.5: Haemangioma of the tongue

f) Varix And Thrombus

Varices are abnormally dilated veins seen mostly in patients older than sixty years of age. The most common intra oral location is the ventral surface of the tongue where it appears as multiple bluish purple, irregular and soft elevations that blanch on pressure (Fig1.7). If a varix contains a thrombus, it presents as a firm bluish purple nodule that does not blanch on pressure. Thrombi are more common on the lower lip and buccal mucosa (Fig1.6).

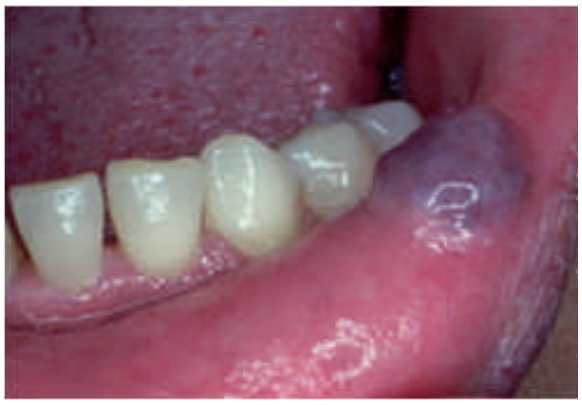


Fig.1.6: Thrombus present on the lower lip

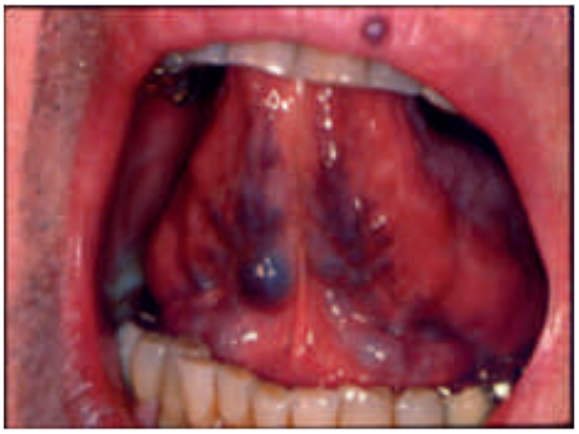


Fig.1.7: Varices present on the dorsum of the tongue.

g) Hematoma And Other Hemorrhagic Lesions

Hematomas, purpuras and echymoses are caused by extravasations of blood into the soft tissues. They appear as non blanching flat or elevated pigmented lesions (Fig1.8). They may occur spontaneously in certain systemic conditions such as idiopathic thrombocytopenic purpura or they may result from trauma. The colour produced by the degradation of haemoglobin to bilirubin varies among red, purple, blue and bluish black depending on the length of time. The colour gradually returns to normal, but takes upto two weeks. If hemorrhagic lesions occur in the absence of recent trauma, the patient should be investigated for platelet disorders and coagulopathies.

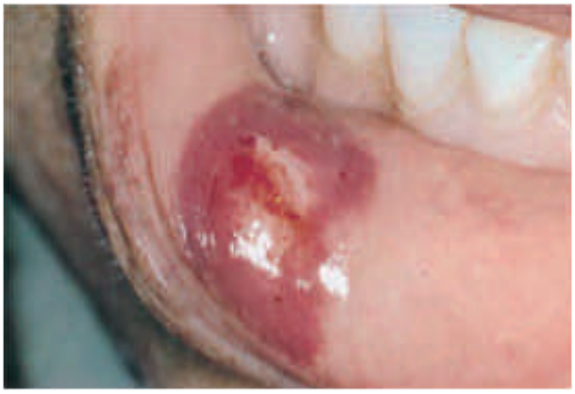


Fig.1.8: Hematoma of the lower lip.

h) Amalgam Tattoo

It is one of the most common causes of intra oral pigmentations. It presents clinically as a localized flat, blue-grey lesions of variable dimensions (Fig1.9). The gingival and alveolar mucosa are the most common sites of involvement. In some cases, when the amalgam particles are large enough, they can be seen in intraoral radiographs as fine radio-opaque granules. In these circumstances the diagnosis of amalgam tattoo can be made on the basis of the clinical and radiographic findings.

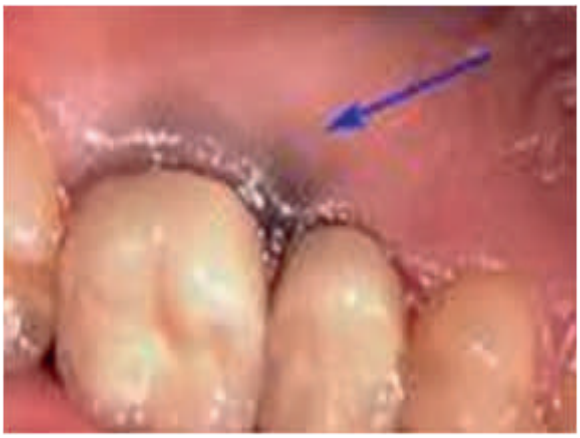


Fig.1.9: Blue grey hyperpigmentation of amalgam.

i) Pigmented Nevi

Pigmented nevi are rare causes of focal oral pigmentations. They present either brown or blue lesions (Fig1.10). As such they are classified as Junctional, Intradermal or Intramucosal and Compound nevi. These nevi may represent precursor lesions to oral mucosal melanoma. Thus these lesions should be excised and submitted for histopathologic examination[5].

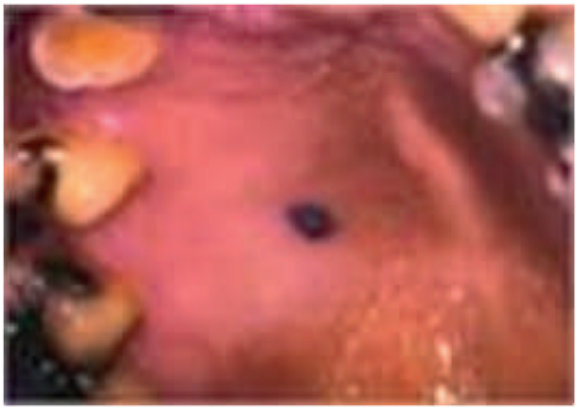


Fig.1.10: Blue nevi present on the palate.

j) Oral Melanoma

It is characterised by proliferation of malignant melanocytes along the junction between the epithelial and connective tissues as well as within the connective tissues. The most common site is the palate which occurs in about 40% of the cases followed by gingiva. Clinically, oral melanoma may present as an asymptomatic, slow growing brown or black patch (Fig.1.11) with asymmetric and irregular borders with ulceration, bleeding, pain and bone destruction.

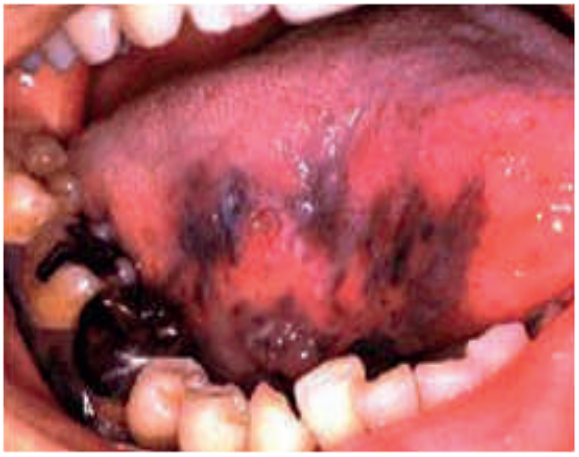


Fig.1.11: Oral melanoma of the tongue.

Conclusion

An algorithm of the pigmented lesions of the oral cavity is seen from physiologic changes to manifestations of systemic illness.

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Culprit is Not the Age but a Protein!

The progressive loss of memory that afflicts the old is often considered to be an early sign of Alzheimer's. But age-related memory loss and Alzheimer's are two distinctive and clinically identifiable entities. They affect different parts of hippocampus: while Alzheimer's affects entorhinal cortex, the age related memory loss is due to changes in dentate gyrus. In a new study published online in the journal Science Translational Medicine (Sci Transl Med 28 August 2013 5:200ra115. DOI:10.1126/scitranslmed.3006373), the researchers from Columbia University Medical Centre (CUMC), analysed dentate gyrus and entorhinal regions in the post-mortem brain samples of eight individuals and found that age related memory loss was associated with decline in a histone binding protein RbAp48 in the dentate gyrus. When the researchers genetically inhibited RbAp48 gene in transgenic mice, the latter manifested memory deficits similar to those observed in the age related memory loss. The researchers feel that this study provides a conclusive evidence for separating age related memory loss as a distinct entity, apart from opening up opportunities for its therapeutic intervention.

- Dr. K. Ramesh Rao

Review Article

Diagnosis & Management of Temporomandibular Joint Disorders - What the Medical and Dental practitioners should know

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Abstract

Temporomandibular disorders (TMD) are one of the most common causes of facial pain after odontogenic origin. The temporomandibular disorders (TMD) are of multifactorial etiology and characterized by multiplicity of clinical signs and symptoms, making its diagnosis and management very difficult for the clinician. TMD should be considered in the differential diagnosis of headache and orofacial pain in the absence of specific attributable organic cause. Scientific evidence shows that noninvasive methods are preferred in the management of TMD. These include occlusal, behavioral, physical and pharmacological treatment. Practitioners of medicine and dentistry have the responsibility of diagnosing and managing people with TMD or refer them to an appropriate health care professional based on the nature and etiology of the problem.

Key words : TMD, Temporomandibular disorders, headache, facial pain, diagnosis

Introduction

Historically, dentistry has been geared primarily to the diagnosis and treatment of odontogenic pain (pulpal and periodontal). However dentists come across orofacial pain originating from various other structures such as sinuses, ear, muscles, bones, nerves(neuralgia), blood vessels(migraine headaches) and temporomandibular joint(TMJ), which may be referred to dental structures and vice versa. It can stem from simple causes to life-threatening diseases and it can cause great suffering for patients.

Apart from the odontogenic causes, temporomandibular joint disorders are one of the most common causes of orofacial pain[1] .The temporomandibular joint has a close anatomical and functional association with the structures of the head, neck and face and any disturbance in the joints, can produce symptoms which may be referred to any of these structures. It can be from dental and non-dental source of origin including psycho-somatic disorders and therefore it is important that dentists, physicians, ophthalmologist, oto-laryngologist, surgeons, orthopedicians, psychologists and neurologists possess a fundamental knowledge of the TMJ disorders and consider it in the differential diagnosis of orofacial pain.

The diagnostic process for temporomandibular disorders (TMD) is complicated by the multifactorial etiology and multiplicity of clinical signs and symptoms characterizing such disorders. However, proper diagnosis and management or referral of patients with these disorders as speedily as possible to the appropriate therapist is an important aspect of the quality of care provided by health care professionals.

The purpose of this article is to review the basic anatomy, function and disturbances of the temporomandibular joint, its diagnosis, differential diagnosis and clinical management.

The Temporo-Mandibular Joint

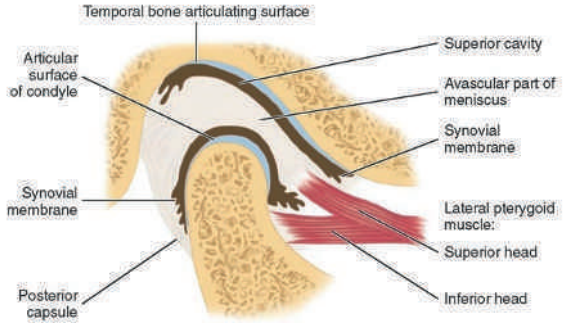
The temporomandibular joint commonly called "TMJ" is an important joint that connects the mandible to the skull and regulates mandibular movement. It is one of the most complex joint in the body, performing multiple vital functions. It lets the mandible move up and down, side to side, forward and backward as a person does wondrous things as speaking, biting, chewing, swallowing, smiling, laughing, and frowning. It is a bicondylar joint in which the condyles, located at the two ends of the mandible, function at the same time.[2]

The joint Anatomy

The normal human skull possesses 2 temporomandibular joints (TMJs) that connect the skull to the lower jaw bone (the mandible) so as to allow the mouth to open and close.

The TMJ is a gliding joint, formed by the condyle of the mandible and the squamous portion of the temporal bone. The articular surface of the temporal bone

consists of a convex articular eminence anteriorly and a concave articular fossa posterior. The articular surface of the mandible is formed by the superior surface of the condyle. Articular surfaces of the mandible and temporal bone are separated by an articular disc, which divides the joint cavity into 2 small spaces.



Articular Disc

The articular disc, also known as the meniscus, is a biconcave, fibrocartilaginous structure, which provides the gliding surface for the mandibular condyle, resulting in smooth joint movement. The articular disc has 3 parts—a thick anterior band, a thin intermediate zone, and a thick posterior band. When the mouth closed, the condyle is separated from the articular fossa of the temporal bone by the thick posterior band. When the mouth is open, the condyle is separated from the articular eminence of the temporal bone by the thin intermediate zone. The articular disc distributes the heavy masticatory forces to the condyle, articular eminence and the fossa.

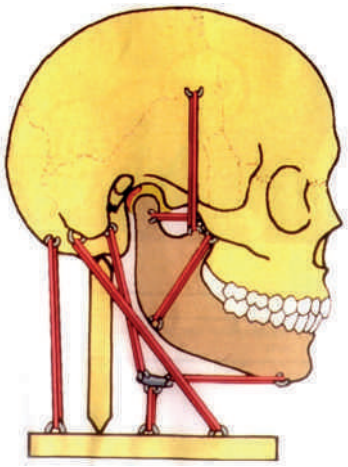
The lateral ligament, sphenomandibular ligament and stylomandibular ligaments restricts the movements of the mandible and protects the joint. The various movements of the mandible are brought about by the muscles of mastication and the supra-hyoid group of muscles.

All these structures including the dentition form an integral part of the masticatory system.

Uniqueness of the TM Joint

- The TMJs are 2 joints, formed by 3 bones and their functions are interdependent.
- The articulating surfaces of the TMJ are covered by a fibrous connective tissue; this avascular and non-innervated structure has a greater capacity to resist degenerative change and regenerate itself than the hyaline cartilage of other synovial joints.
- They are synovial joints with both rotatory and translatory movements possible.
- The articular disc completely divides the joint space into separate upper and lower joint compartments.
- The functions of the joints are not only influenced by the muscles and ligaments, but also by the teeth and their alignment.

Design of the Masticatory System



The mandible is connected to the maxilla, cranium, clavicle, hyoid and spinal column through trapezius, Sterno-cleido-mastoid, suprahyoid group of muscles including digastric muscle, muscles of mastication and various ligaments. The design and functioning of the masticatory system is a complex one and requires a balanced function of muscles, ligaments, bones and teeth. Each movement is precisely co-ordinated, programmed and orchestrated[3,4].

Relationship to Adjacent Structures

All organs in the head-shoulder region are strongly networked via muscles and nerves by a complex biological feed-back mechanism.

Organs in the head-shoulder region:

- Masticatory organ (teeth, mandibular joints, chewing muscles)
- Organs of swallowing (swallowing muscles)
- Alveolar organ, Periodontium (Mechano -sensors)
- Organ of speech (speech muscles)
- Hearing organ (ears)
- Organ of sight (eyes)
- Olfactory organ (nose)
- Central nervous system (brain, impulse network via sensors an

The temporo mandibular joint has a close anatomical and functional association with these structures.d nerves)

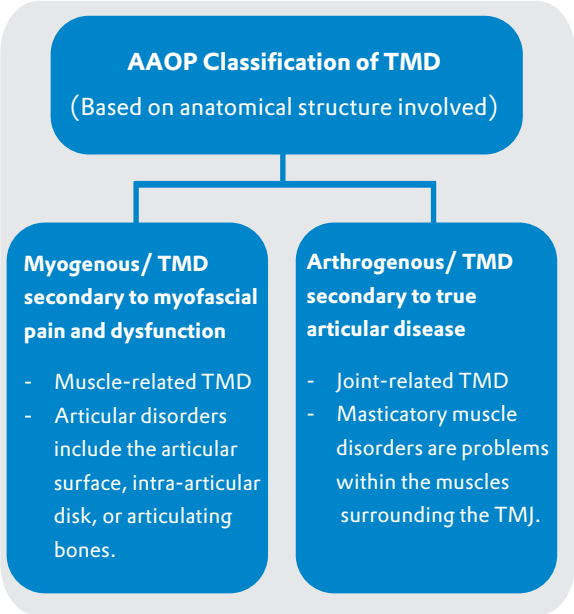
The Temporomandibular Joint Disorder

In the past, many physicians addressed this condition as TMJ disease or TMJ syndrome. TMD was also previously known under the eponymous title of Costen syndrome, after Dr. James Costen, an oto-laryngologist, who elucidated many aspects of the syndrome as it relates to dental malocclusion.

Today, a much more comprehensive view of this condition exists, and the term temporomandibular disorder (TMD) is the preferred term according to the

American Academy of Orofacial Pain (AAOP) which defines TMD as " a collective term embracing a number of clinical problems that involve the masticatory musculature, Temporomandibular joint and associated structures or both."

As a group these conditions have no common etiology or biological explanation and comprise of a heterogeneous group of health problems whose signs and symptoms overlap.



Most often, these 2 types often coexist in one patient, making diagnosis and treatment more challenging.

Myogenous type is a more common form of TMD and in its pure form lacks apparent destructive changes of the TMJ on radiograph. The causes of the symptoms (i.e., pain, tenderness, and spasm of masticatory muscles) are muscular hyperactivity and dysfunction due to multiple etiologies such as bruxism and daytime jaw clenching and malocclusion of varying degree and duration. Psychological factors may also play a role.

Arthrogenous TMD can be further specified as disk displacement disorder (more common), chronic recurrent dislocations, degenerative joint disorders, systemic arthritic conditions, ankylosis, infections, and neoplasia.

Etiology

The etiology of TMJ disorders remains unclear, but it is likely multifactorial. Capsule inflammation or damage and muscle pain or spasm may be caused by abnormal occlusion, parafunctional habits (e.g., bruxism [teeth grinding], teeth clenching, lip biting), stress, anxiety, or abnormalities of the intra-articular disk.

In recent years, many of the theories about the development of TMJ disorders have been questioned. Abnormal dental occlusion appears to be equally common in persons with and without TMJ symptoms and occlusal correction does not reliably improve the symptoms or signs of TMJ disorders. Parafunctional habits have been thought to cause TMJ microtrauma or masticatory muscle hyperactivity; however, these habits are also common in asymptomatic patients. Although parafunctional habits may play a role in initiating or perpetuating symptoms in some patients, the cause-and-effect relationship remains uncertain[4,5].

There is some evidence to suggest that anxiety, stress, and other emotional disturbances may exacerbate TMJ disorders, especially in patients who experience chronic pain. As many as 75 percent of patients with TMJ disorders have a significant psychological abnormality. Recognition and treatment of concomitant mental illness is important in the overall approach to management of chronic pain, including pain caused by TMJ disorders[5,6].

Genetic variations in the gene coding for catecholamine-O-methyltransferase (COMT), a gene that relates in to some aspects of pain sensitivity has also been implicated[6].

The other classifications of Etiology of TMD are

I. Dental and Non-Dental causes

II. Predisposing factors, Initiating factors, Perpetuating factors

Predisposing factors – factors that increase the risk of developing TMD. E.g.

- Systematic factors(degenerative, endocrine, infectious, metabolic, neoplastic, neurological,vascular and rheumatological diseases)
- Psychological factors (Anxiety, depression)
- Structural factors (change in synovial fluid viscosity, increased intra-articular pressure)
- Genetic factors.

Initiating factors – factors that cause onset of the disorder. E.g. Trauma, parafunctional habits such as bruxism, clenching

Perpetuating factors – factors that interfere with healing and complicate management of the disorder. E.g. Mechanical and Muscular stress, metabolic problems.

Epidemiology

Sex Predilection

Temporomandibular disorder primarily affects women with a male-to-female ratio of 1:4. This could possibly be due to the presence of estrogen receptors in the TM joint[7,8,9].

Age

Even though it is common in adults and adolescents, the highest incidence is among young adults; especially women aged 20-40 years.

In epidemiologic studies, up to 75 percent of adults show at least one sign of joint dysfunction on examination and as many as one third have at least one symptom. However, only 5 percent of adults with TMJ

symptoms require treatment and even fewer develop chronic or debilitating symptoms.

Symptoms of Temporo mandibular disorder

- Soreness of Muscles of mastication
- Attrition of teeth and sensitivity
- Hypermobility of teeth
- Pain in the joints
- Clicking in the joints
- Crepitation in the joints
- Difficulty in opening of mouth
- Open lock of the mandible

Apart from these symptoms, If a person suffers from any of the following symptoms without any specific or organic cause, then the possibility of Tempo mandibular disorder could be considered.

- Headaches in the temple region
- Pain in the area of forehead and eyes
- Pain in the back of the head, possibly extending to the shoulders and neck
- Fullness in the ears
- Tinnitus
- Pressure on the eyes, sensitivity to light
- Dizzy spells, vertigo, nausea
- Lack of concentration

Temporomandibular disorders can cause these disturbances due to its anatomic proximity and functional associations to these structures. The trigeminal nerve, which is one of the main nerve supply to the TMJ and facial region, is a complex cranial nerve that can cause headaches when over stimulated by the muscles surrounding it[10].

Diagnosis

Medical History

A comprehensive, chronological medical and dental history of the patient is essential for diagnosis of the problem and to decide about further investigations and treatment plan.

Observation

- Forward head posture (this has been shown to displace the condyles posteriorly)
- Jaw malocclusion, abnormal dental wear, and poor dentition
- Visible clenching or spasm of the ipsilateral neck musculature

Physical Examination

Joint range of motion: Evaluation of jaw opening and closure as well as lateral deviation bilaterally. Normal range of motion for opening is 5 cm and lateral mandibular movement is 1 cm. Patients with TMD usually have reduced opening.

Palpation: The TMJ is best palpated laterally as a depression below the zygomatic arch and 1-2 cm anterior to the tragus. The posterior aspect of the joint is palpated through the external auditory canal. The joint should be palpated in both open and closed positions and also both laterally and posteriorly. While palpating, the examiner should feel for muscle spasm, muscle or joint tenderness, and joint sound. The muscles palpated as a part of complete TMJ examination are masseter, temporalis, medial pterygoid, lateral pterygoid, and sternocleidomastoid. In isolated myofascial pain and dysfunction, joint tenderness and joint click are usually absent.

Diagnostic Classification

An abbreviated version of the diagnostic classification system developed by the American Academy of Orofacial Pain is shown in Table 1 TMJ disorders are separated into two main categories based on the anatomic origin of the problem: articular disorders and masticatory muscle disorders. Accurate recognition of the origin of pain, either intra-articular or muscular, may help the dentst recommend an initial therapy; however, it is not clear which noninvasive therapies work best and varies.

TABLE 1

Diagnostic Classification of TMJ Disorders[1]

Articular disorders of the TMJ	Masticatory muscle disorders
Ankylosis	Local myalgia (unclassified)
Congenital or developmental disorders	Myofascial pain
Aplasia, hyperplasia, or hypoplasia of the cranial bones or mandible	Myofibrotic contracture
Neoplasia of the TMJ or associated structures	Myositis
Disk derangement disorders	Myospasm
Articular disk displacement with or without reduction	Neoplasia
Fracture of the condylar process	
Inflammatory disorders like Synovitis, Capsulitis, Polyarthritides including the TMJ	
Osteoarthritis	
TMJ dislocation	

Differential Diagnosis

The differential diagnosis for orofacial pain is listed in Table 2. TMJ disorders can cause referred pain, particularly undifferentiated headache. Some studies have shown that as many as 55 percent of patients with chronic headache who were referred to a neurologist were found to have significant signs or symptoms of TMJ disorders. Educating patients on self-care techniques and referral for noninvasive treatment should be considered in patients with chronic undifferentiated headache or headache that is not responding to standard treatment.

TABLE 2
Differential Diagnosis of Orofacial Pain

Condition	Symptoms	Signs
Dental pathology		
Tooth abscess	Pain with chewing over affected tooth	Visible tooth decay; fluctuance along gum line; pain with palpation over the tooth
Wisdom tooth eruption	Dull ache behind posterior molars	Tenderness to palpation over emerging tooth
Infection or inflammation		
Herpes zoster and postherpetic neuralgia	Prodrome of pain followed by vesicular rash	Vesicular rash in dermatomal distribution, not crossing midline
Mastoiditis	Fever; otalgia	Postauricular erythema and swelling tenderness over mastoid process
Otitis externa	Pruritus, pain, and tenderness of the external ear	Erythema and edema of external auditory canal
Otitis media	Fever; malaise; otalgia	Tympanic membrane dull, bulging, erythematous; loss of landmarks on tympanic membrane
Parotitis	Fever; malaise; myalgia; pain over parotid gland	Tenderness and induration over parotid gland
Sialadenitis	Pain and swelling of involved salivary gland	Tenderness, induration, and/or erythema of salivary gland; usually unilateral
Trigeminal neuralgia	Paroxysmal, unilateral lancinating pains in trigeminal nerve distribution	Examination generally normal
Cluster Headache	retro-orbital or sinus pain , Episode, last 6 to 8 weeks, long pain free	Rhinorrhea, nasal congestion and lacrimation from the involved side
Migraine Headache	Unilateral dull, throbbing pain	Unrelieved by a diagnostic block
Tumors	Weight loss, History of cancer	Unusual response to treatment, pain may become diffuse or paresthesia can occur

Diagnostic Testing

Diagnostic testing and radiologic imaging of the TMJ have uncertain usefulness and generally should only be used for the most severe or chronic symptoms. Local anesthetic nerve blocking can be helpful in differentiating whether orofacial pain originates from the TMJ capsule or from associated muscular structures. Sensory innervation of the TMJ is delivered primarily through the auriculotemporal branch of the third division of the trigeminal nerve. Patients who do not experience pain relief from diagnostic nerve blocking should be evaluated for other causes of orofacial pain[11, 12].

Laboratory Studies

If a systemic illness is suspected to be the cause of temporomandibular disorder (TMD), lab work is required. WBC count may be done if infection is suspected. Rheumatoid factor (RF), ESR, antinuclear antibody (ANA), and other specific antibodies should be checked if rheumatoid arthritis, temporal arteritis, or a connective tissue disorder is suspected. Uric acid should be checked for gout. Arthrocentesis may be required to demonstrate specific crystals.

Imaging Studies

Conventional radiography is the most utilized imaging study. It is simple, evaluates bony structures, and in most cases it is sufficient. It involves specific techniques and views such as modified Schuller views of each TMJ, both open mouth and closed mouth. Radiographic findings in TMJ depend on the etiology of TMD; in cases like rheumatoid arthritis, plain films show erosions, osteophytes, subchondral bony sclerosis, and condylar-glenoid fossa remodeling[13, 14].

Dynamic high-resolution ultrasonography allows for visualization of the morphological elements and the functions of the TMJ, articular disk, mandibular condyle, and lateral pterygoid muscle[15,16].

CT scans can explore both bony structures and muscular soft tissues. Of interest, there is utility with cone beam computed tomography (CBCT). The patient is scanned with the mouth open and closed. Specifically, CBCT can aid in the diagnosis of osteoarthritis, rheumatoid arthritis, synovial chondromatosis, and neoplastic disorders.

Magnetic resonance image (MRI) should be used as the study of choice if an articular or meniscal pathology is suspected and an endoscopic or surgical procedure is contemplated, or in the case of traumatic TMD17.

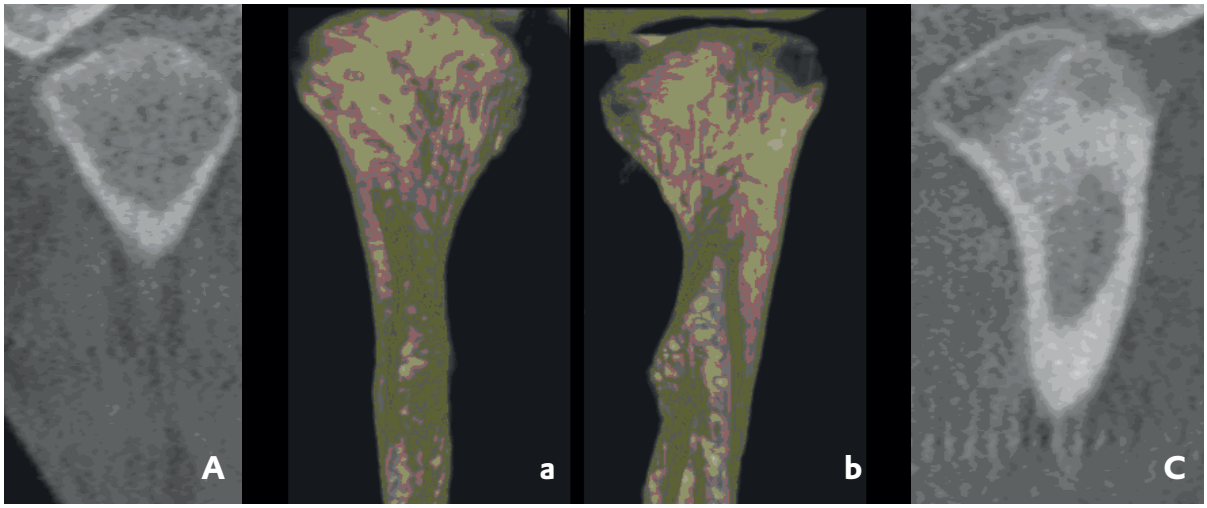


Fig - CBCT and reconstructed image of condyles

Fig: A a - Shows normal condylar morphology,

Fig: B b - shows erosion on condylar head

Other Tests

Quantitative analysis of occlusal strain and stress can be helpful by using photoplastic phenomenon of some polymers. Results of strain analysis can help harmonize static and kinematic occlusal patterns by detecting and eliminating prematurities and interferences. Stress analysis helps to understand the temporomandibular mechanical relationship[17].

Procedures

Diagnostic arthroscopy is an invasive diagnostic approach and should be used mainly in patients suffering from internal TMJ derangements recalcitrant to conservative measures. MRI is suggested to be obtained prior to arthroscopy[18].

Treatment

The signs and symptoms of TMD improve for most of the patients over time with or without treatment. As much as 50 percent of the patients improve from TMD symptoms in one year and almost 85 percent improve completely in three years. Interventions that change the anatomy of the joint, invade the integrity of the joint space, or manipulate the jaw have the potential to cause harm and have not been shown to improve symptoms. Therefore, self-care and noninvasive treatments are good options and should be attempted before invasive or permanent therapies, such as orthodontics or surgery, are recommended[19,20].

Self - Care

There is little evidence to suggest that any TMJ disorder treatment modality is superior to any other, although it is generally accepted that self-care and behavioral interventions should be encouraged for all patients, regardless of which therapies are considered. Providing a few simple exercises, behavioral instructions, and reassurance are important steps when treating the average patient with new or intermittent symptoms.

Noninvasive Therapy

Many noninvasive therapies are commonly used for the treatment of TMJ disorders. The disciplines of medicine, dentistry (occlusal splint therapy, replacement of missing teeth, correcting malocclusion), physical therapy, and psychology can provide effective treatment in different clinical situations.

Pharmacotherapy

The indicated classes of pharmacologic agents include analgesics, anti-inflammatory agents, corticosteroids, anxiolytics, muscle relaxants and antidepressants. Non-opiate analgesics are effective for mild to moderate acute pain associated with TMD, and opioid narcotics are considered for short-term use in only controlling acute severe pain. Additionally, tricyclic antidepressants appear to be effective in the control of chronic orofacial pain of non-inflammatory origin, independent of their effects on mood, with daily doses smaller than those typically used in the treatment of depression.[17] Several available therapies are listed in Table 3. Because most patients with TMJ disorders improve with or without treatment, these conservative therapies should be encouraged before invasive treatments are considered.[21, 22, 23]

TABLE 3

Noninvasive Therapies for TMJ Disorders

Alternative therapies

- Acupressure
- Acupuncture
- Hypnosis
- Massage

Dental procedures

Occlusal splint therapy, replacement of missing teeth, correcting malocclusion, Occlusal adjustments

Medical interventions

- Intra-articular corticosteroid or anesthetic injection
- Myofascial trigger-point injection
- Pharmacologic treatment
  - Acetaminophen
  - Anxiolytics
  - Benzodiazepines
  - Muscle relaxants
  - Nonsteroidal anti-inflammatory drugs
  - Tricyclic antidepressants

Physical therapy modalities

- Biofeedback
- Iontophoresis
- Superficial or deep heat
- Therapeutic exercise
  - Lateral jaw movement
  - Protrusive jaw movement
  - Resisted closing
  - Resisted opening
  - Tongue-up exercise
- Transcutaneous electrical nerve stimulation

Psychological interventions

- Cognitive behavior therapy
- Relaxation techniques
- Stress management

Surgical treatment

Surgery is indicated only in specific articular disorders, usually in cases that do not respond to conservative treatment, and when the patient's quality of life has been significantly affected[1,25,22] Surgical management may vary from closed surgical procedures, such as arthrocentesis and arthroscopy, to more complex open joint operations, such as arthrotomy, disk repositioning, diskectomy and condylotomy.[24,25,26]

Conclusion

Medical and dental practitioners should consider temporomandibular Joint disorders as a possible cause in the diagnosis of oro-facial pain including headaches, shoulder and neck pain, vertigo and associated pain, blurring of vision, disorders of hearing, nausea, vomiting, and disturbances in concentration, in the absence of any specific, attributable or organic cause.

While orofacial pain and headache secondary to jaw muscle function and dental structures ideally be managed by dentists, pain in the head and neck region unrelated to it should be should be referred to an appropriate medical care specialists for management.

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Blueberries and Diabetes

Results of three longitudinal cohort studies published in BMJ (BMJ 2013;347:f5001) appear to suggest that eating whole fruit is associated with reduced risk of developing type 2 diabetes. But fruit juice does not appear to have similar effect. The researchers took a look at the diets of more than 1,87,000 Americans. Three servings per week of blueberries, grape, raisins, apples and pears significantly reduced the risk. Replacing fruit juice with blueberries could reduce the risk of developing type 2 diabetes by 33%, with grapes and raisins by 19%, apples and pears by 13% and with any combination of whole fruit by 7%. The beneficial effects are probably related to high levels anthocyanins in many of these fruits. Besides, most fruits also have variable content of antioxidants, fibre, phytochemicals and other nutrients. The UK government recommends eating five portions of fruit and vegetables every day.

- Dr. K. Ramesh Rao

Case Report

Dumb Bell Skull Base Meningioma

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Abstract

Meningiomas are the most commonly occurring benign tumors of the brain. Meningiomas occurring in the base of the skull account for 10 % of them. Microsurgical excision of meningiomas in skull base is technically demanding because of the close association of the major blood vessels and vital brain areas. Here we present an interesting skull base meningioma which has a dumbbell component.

Key words :Meningioma-Dumb bell- Dura-skull base

Case Report

A 38 yr old female patient presented with progressively increasing left sided headache associated with occasional vomiting for the past 6 months duration. On examination patient was conscious oriented and she had early papilloedema. No other neurological deficit. MRI of the brain with contrast showed 5 cm well circumscribed contrast enhancing lesion occurring the left temporal base with another dumbbell component of 4 cm size in the frontal lobe.MRI also showed the classic dural tail sign which is characteristic of Meningioma (Fig 1,2).

Under ETGA and hypotensive anaesthesia, patient was placed in supine position and face turned to right side, a left fronto temporo parietal scalp incision made. Temporalis muscle was separated from the bone and the zygomatic arch exposed. With high speed drill left fronto temporo parietal craniotomy and zygomatic osteotomy was performed. Both the frontal and and temporal part of the skull base exposed. Dura was opened along the margin of the tumor and the dura was devascularised from the surface of the tumor. The tumor was firm and very vascular in nature (Fig 3). With meticulous microsurgical technique and microscope the tumor was debulked. Tumor –brain interface was dissected along the arachnoid plane. Then the tumor was detached from the dura of the base of the frontal and temporal bone. There was a dumb bell component of the tumor going to the frontal lobe which was attached through a small pedicle. With meticulous dissection the tumor was removed in total along with involved dura without damaging the underlying brain parenchyma. Dura was reconstructed with the temporalis fascia and closed in water tight fashion. Temporalis muscle was reattached and the boneflap and zygomatic bone was replaced and fixed with mini plate and screws. Post operative period was uneventful (Fig 4). Histopathology confirmed it as Grade I meningioma. Three month follow up MRI showed no residual lesion (Fig 5).

Discussion

Meningioma comprise about one fourth of all primary tumors of the central nervous system (CNS). It is the most common primary intracranial neoplasm and the most diversified in histologic patterns among all primary tumors of the CNS. Meningioma arise from Arachnoidal cap cells. Meningiomas, as defined by the World Health Organization (WHO), are "meningothelial (arachnoid) cell neoplasms, typically attached to the inner surface of the dura mater," and these tumors fall into WHO grades I, II, and III. Meningioma is essentially a tumor of adulthood, with a peak incidence in the sixth decade of life. These tumors are twice as common in women. Atypical and anaplastic meningiomas, however, show a male predominance. Childhood meningiomas occur more often in males. Meningiomas associated with neurofibromatosis type 2 (NF2) tend to occur in younger individuals and with equal distribution between males and females. With the exception that papillary meningiomas are more common in children, meningiomas are rather uncommon in children and almost never occur in infants. When these tumors occur in children, however, they are more often infratentorial, intraventricular, or intraparenchymal than in adults.

Meningiomas are most commonly dural-based tumors in the brain and, less commonly, the spinal cord. Rare cases occur as intraventricular and pulmonary tumors. Most meningiomas are intracranial extra-axial tumors. About half of these tumors occur in the falcine and parasagittal locations, and they are often firmly affixed to the sagittal sinus. The majority of the remainder occur in the skull base. Meningiomas are slow-growing tumors, and smaller ones often remain asymptomatic throughout life. For the larger and symptomatic tumors, symptoms result from local compression and peritumoral edema. Headache and newly onset seizures are the most common initial manifestations. For the rare tumors that arise in the ventricles, hydrocephalus is often part of the clinical picture.

Tumors that arise in the cranial base have a strong tendency to invade the surrounding osseous and nonosseous tissue, and they can be surgically challenging[1]. Invasion of the cranial base and adjacent structures could cause a spectrum of manifestations, ranging from cranial nerve palsy, symptoms related to involvement of the sinuses and the orbit, dental complaints,and masses in the forehead. Cranial base meningiomas are more likely to recur[2], but this probably reflects the difficulty in total surgical resection rather than the biological nature of these tumors.

Contrast-enhanced MRI is the most sensitive method for detecting meningiomas. Meningiomas enhance strongly and often homogeneously. About half of patients have an area of dural enhancement, or so-called "dural tail." Histologically, the dural tails may be composed entirely of hypervascular, presumably reactive tissue, but not meningioma tumor cells. Management of meningiomas are entirely complete surgical excision of the tumor along with the involved dura and involved bone. Recurrence of the meningioma occur depending upon the extent of removal.(SIMPSON S GRADING)

Conclusion

Skull base meningiomas usually erode the adjacent bone and encircle the adjacent neurovascular structure, thus posing challenge in removing completely. Only with very good anatomical knowledge and meticulous neurosurgical skills they can be removed appropriately without damaging the adjacent normal brain[3,4,5].

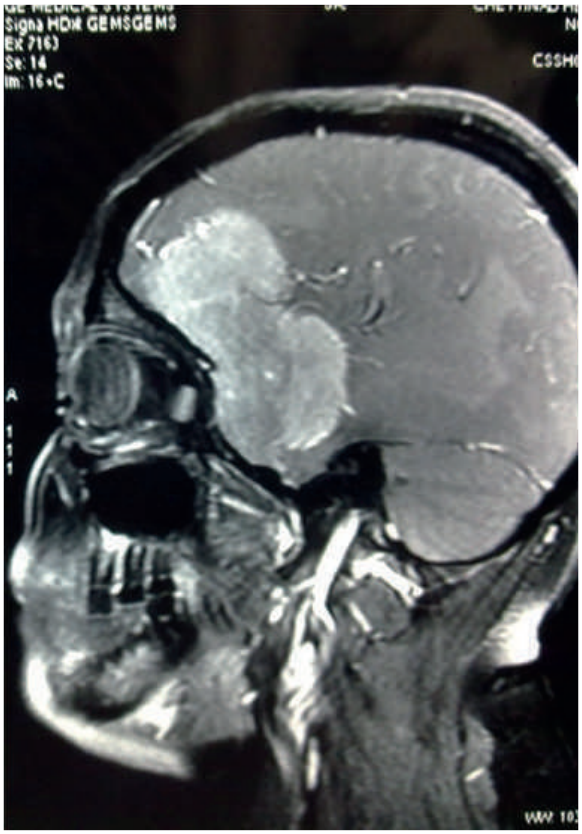

Fig 2 - Mri Sagittal Showing Basal Meningioma With Dumb Bell Component

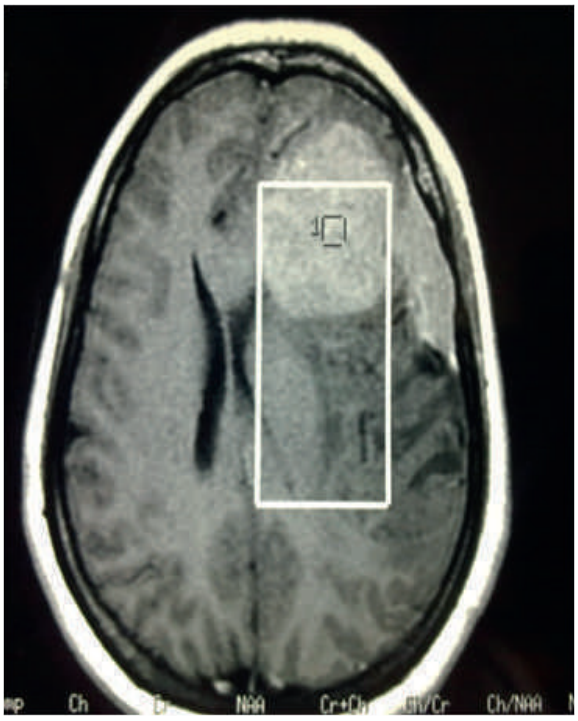

Fig 1 - Mri Brain Axial Showing Dural Based Lesion With Frontal Dumb Bell Component

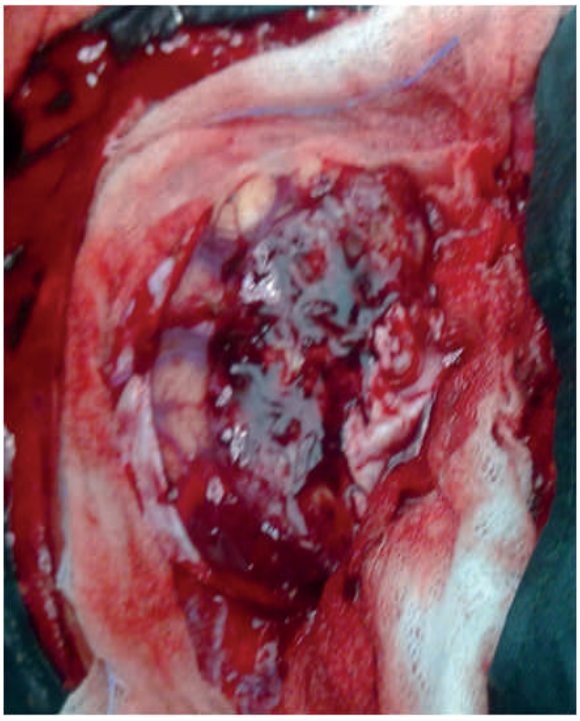

Fig 3 - Intra Operative Pic Showing Brain Dura & Tumor

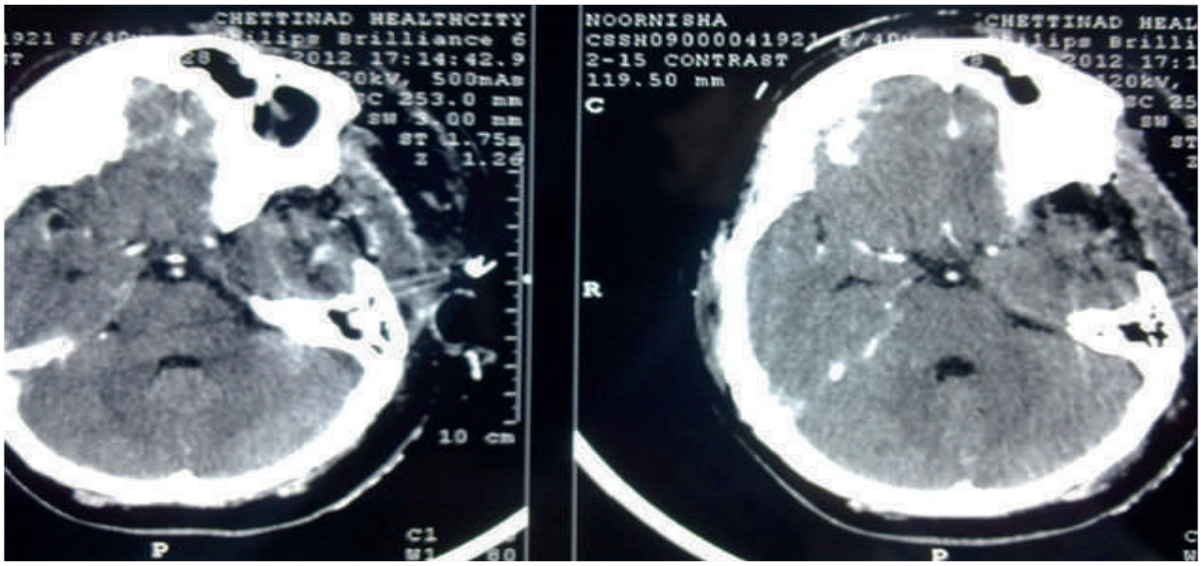

Fig 4 - Post op ct brain showing complete excision

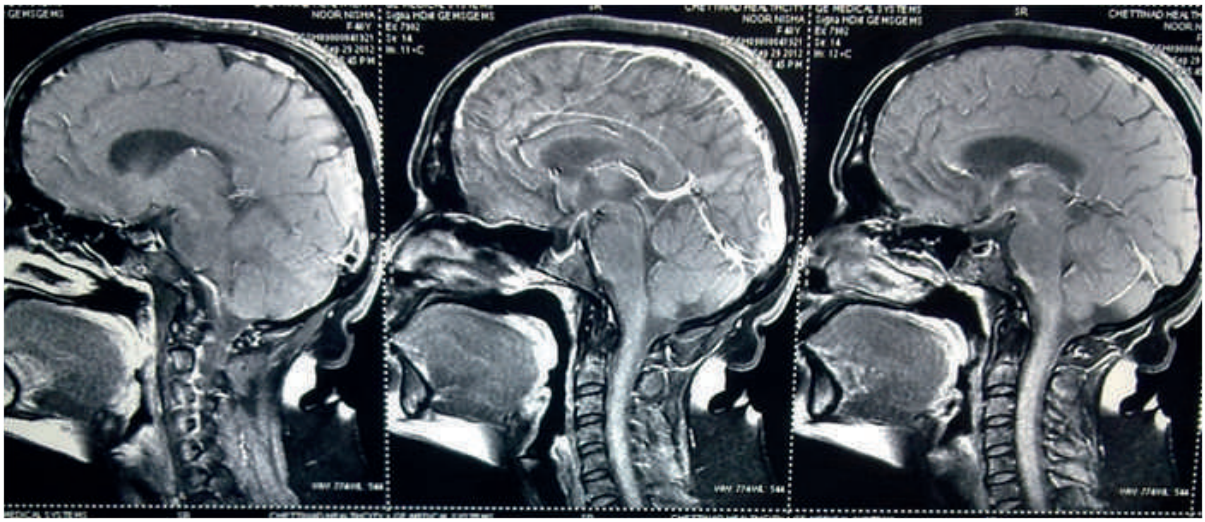

Fig 5 - Two Month Follow Up Mri Showing No Residual Lesion

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Case Report

Variant of Pierre Robin Sequence Requiring Prolonged Tracheostomy

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Abstract

Pierre Robin sequence (PRS) or anomalad, a well-recognized presentation, is the association of the first branchial arch malformation. It presents with a classic triad of micrognathia, glossoptosis, and cleft palate. Presenting here is a neonate with features of Pierre Robin sequence with syndactyly of fingers and toes and congenital heart disease [ASD with PDA], which also needed tracheostomy on day 16 of life and decannulation done after 7 months.

Key words : Pierre Robin, Tracheostomy

Introduction

Pierre Robin Sequence is considered to be a nonspecific anomalad which may occur either as an isolated defect or as a broader group of malformations[1]. It presents with a classic triad of micrognathia, glossoptosis, and cleft palate. In 1923 French physician Pierre Robin introduced the term 'glossoptosis' in association with micrognathia. He later reported an association with cleft palate in 1934 and this constellation of findings was termed as syndrome[2].

PRS is a clinically well-defined subgroup of the cleft lip-palate population with an unknown etiology, often observed as a part of other Mendelian syndromes, such as Stickler's syndrome, velocardiofacial syndrome, and Marshall's syndrome[3].

Recent studies on genetics have shown that that the association of dysregulation of the genes SOX9 and KCNJ2 may be involved in PRS, evidenced by a familial translocation with a breakpoint located in the gene empty region between SOX9 and KCNJ2, and by reduced expression of SOX9 and KCNJ2 in non-translocated patients with PRS[4].

Case details

Here is a live term male baby second born to a non consanguineously married couple. Mother is an elderly[39 yrs], multigravida with history of three spontaneous abortions. There was no h/o oligohydramnios. Baby was born by lower segment caesarean section indication being previous section, baby cried immediately after birth with birth weight of 2.4kg and on examination had features like low set ears, micrognathia, retrognathia, rudimentary tongue, glossptosis, U shaped cleft palate suggestive of Pierre Robin sequence[Fig 1] and also syndactyly of second and third fingers and toes were noted[Fig2]. On auscultation there was systolic murmur and the baby was managed in the Neonatal intensive care unit. Investigations like ultrasound abdomen and cranium, infantogram done was normal, echocardiography showed ASD [0.6mm] with PDA[0.5mm]. Karyotyping was normal. As baby had respiratory distress and was not maintaining saturation even in prone position required intubation frequently, hence tracheostomy was done on day 16 of life, metabolic parameters were corrected, intravenous antibiotics given and Nasogastric feeds with expressed breast milk started on day 2 of life and baby was discharged on day 36 of life with tracheostomy and nasogastric tube in situ. The mother was trained regarding the maintenance of both the tubes and was called for follow up. She was on follow up, baby was growing well and tracheostomy site was clean, hearing evaluation done at 3 months by otoacoustic emission test was normal, there were no orthopedic problems and at the age of 7 months tracheostomy tube was removed, and now the baby has no respiratory distress and has gained weight accordingly, development is according to age except language milestones where only cooing is present [no monosyllables], no history suggestive of any obstructive sleep apnea and surgery for cleft palate is being planned followed by speech therapy.

Discussion

Pierre Robin Sequence is a congenital abnormality characterized by the presence of a combination of mandibular hypoplasia, glossoptosis and often labio palatine clefting[5].

A relatively small number of patients with clefts of palate are not of the multifactorial inheritance[6]. These patients usually make up approximately 3% of child population and present with one or more additional structural abnormalities[7].

- Three pathophysiological theories exist to explain the occurrence of Pierre Robin sequence[8].

  The mechanical theory: This theory is the most accepted. The initial event, mandibular hypoplasia, occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves. This theory explains the classic inverted U-shaped cleft and the absence of an associated cleft lip. Oligohydramnios could play a role in the etiology since the lack of amniotic fluid could cause deformation of the chin and subsequent impaction of the tongue between the palatal shelves.

- The neurological maturation theory: A delay in neurological maturation has been noted on electromyography of the tongue musculature, the pharyngeal pillars, and the palate, as has a delay in hypoglossal nerve conduction. The spontaneous correction of the majority of cases with age supports this theory.

- The rhombencephalic dysneurulation theory: In this theory, the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis.

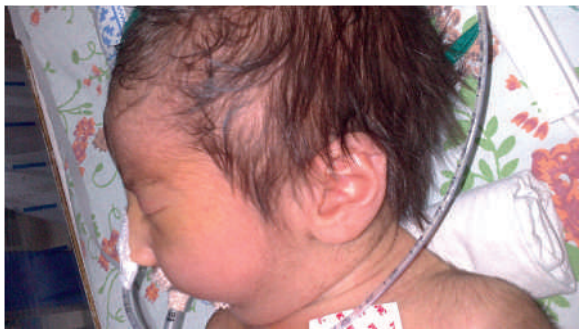

Fig 1: Facial Profile of Pierre Robin Sequence

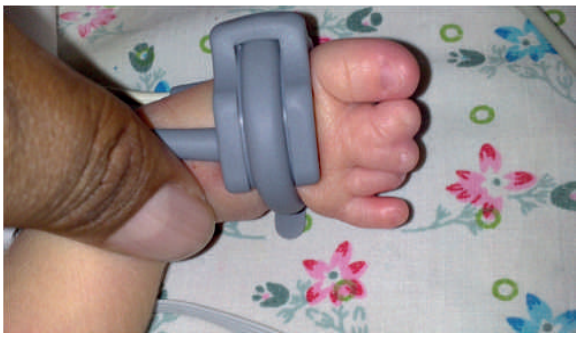

Fig 2: Syndactyly of right toe

The tongue is usually of normal size, but the floor of the mouth is shortened. Obstruction of the air passages may occur particularly on inspiration, and usually requires treatment to prevent suffocation. The infant should be maintained in a prone or partially prone position so that the tongue falls forward to relieve respiratory obstruction. When positioning alone fails, tongue base airway obstruction may be relieved by placement of a nasopharyngeal airway (NPA) without anesthesia. Some patients may require endotracheal intubation or rarely tracheostomy. Surgical procedures include tongue-lip adhesion (TLA), mandibular distraction osteogenesis (MDO), and tracheotomy[9]. Mandibular distraction procedures in a neonate can improve mandibular size, enhance respiration, and facilitate oral feedings[10]. Sufficient spontaneous mandibular growth may take place within a few months to relieve the potential airway obstruction. Often the growth of the mandible achieves the normal profile in 4 – 6 years. The feeding of infants with mandibular hypoplasia requires great care and patience but can usually be accomplished without resorting to gavage. Dental anomalies usually require individualized treatment[9]. The palatal cleft interferes with nursing and causes regurgitation of food through nose. Infection of the nasopharynx is frequent. Otitis media may result in 30- 40% of the afflicted, leading to hearing impairment or permanent deafness[1]. Bronchitis and pneumonia can complicate the local infections. In general, prognosis is good in majority of cases and death from PRS is thought to be the result of poorly controlled combined effects of obstructive apnea and failure to thrive.

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Case Report

Posterior Reversible Encephalopathy Syndrome

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Abstract

Posterior reversible encephalopathy syndrome is one of the causes of convulsions in the postpartum period. It is a neurological condition which affects men and women and occurs in pregnancy both antepartum and postpartum. Herein we analyze two cases that presented in postpartum period with PRES and their management. We analysed patients who presented at a tertiary level medical college hospital with convulsions who were in pregnancy or Puerperium from 2007 to 2013. In this period we had 4315 deliveries in our hospital. . We found that we had 18 cases of convulsions complicating pregnancy & puerperium giving us an incidence of 0.417%. Of these 12 were cases of eclampsia and 6 were cases of non-eclamptic convulsions. Of these six, 2 were cases of Posterior Reversible Encephalopathy Syndrome.

Key words : Posterior reversible encephalopathy syndrome (PRES)

Introduction

Posterior reversible encephalopathy syndrome is a neurological condition which is characterized by headache, nausea, vomiting, seizures, visual disturbances and altered sensorium. PRES can occur in pregnancy, both in antepartum and postpartum period. It is also seen in paediatric age group and adults, both men & women. PRES usually affects the cerebral white matter, but grey matter also can be affected. We analysed patients who presented at a tertiary level medical college hospital with convulsions who were in pregnancy or Puerperium from 2007 to 2013. In this period we had 4315 deliveries in our hospital. We found that we had 18 cases of convulsions complicating pregnancy & puerperium giving us an incidence of 0.417%. Of these 12 were cases of eclampsia and 6 were cases of non-eclamptic convulsions. Of these six, 2 were cases of Posterior Reversible Encephalopathy Syndrome.

Case1: 32 year old Para2Live2Abortion1 both Lower segment caesarean sections was brought on Post operative day-9 with history of one episode of convulsion (tonic clonic) at home which was preceded by complaints of severe headache for one week and blurring of vision for one day. Patient had one episode of vomiting and there was no history of fever. Previous menstrual history -3-4/30 days, regular. Married for 6 years, Non consanguinous marriage.

Obstetric history

1st pregnancy - Full term lower segment caesarean section, indication - Cephalo pelvic disproportion, wt-3.450kg, no Antenatal or postnatal complications.

2nd pregnancy -Dilatation and curettage done at 50days of amenorrhea.

Present pregnancy - Full term lower segment caesarean section, indication-previous LSCS with cephalopelvic disproportion.

On examination: Patient was conscious and oriented to time, place and person, afebrile, pedal edema present, no neck rigidity, Pupils equally reacting to light, Cardiovascular system and respiratory system were found to be essentially normal, BP on admission -164/90mmHg. Per abdomen-uterus well contracted and retracted, Deep tendon reflexes-brisk, clonus-negative, plantar- flexor, no motor or sensory deficit. No further convulsions noted after patient was brought to the casualty

Patient was further investigated and the reports are as follows: Urine: albumin-nil, sugar-nil, microscopy-pus cells-1-3cells/ high power field, epithelial cells-1-2 cells per high power field. Blood: Hemoglobin-10.8 g/dl, Packed cell volume-33.6%, Total leukocyte count -6600cells /cmm, Differential count- Neutrophils -61%, Eosinophils -1.3%, Basophils-0.7%, Lymphocytes -31.4%, Monocytes-5.6%, Mean corpuscular volume-84. 8fL, Mean corpuscular hemoglobin- 27.2PG, Mean corpuscular hemoglobin concentration-32.1g/dl, RBC distribution width-11.7%, Platalet-2.51 lac/cmm, Blood urea nitrogen-6mg/dl, creatinine-0.65mg/dl, uric acid-4.3mg/dl, total protein-6.1g/dl, albumin-3.5g/dl, globulin-2.6g/dl, Albumin/Globulin ratio-1.3:1, bilirubin total-0.2mg /dl, bilirubin direct-0.03mg/dl, AST-26U/L, ALT- 41U/L, alkaline ne phosphata se -122U/ L, gam ma glutamyltransfera -22U/L, Bleeding Time -2mtsoosecs, Clotting Time-5mts30secs, Anti nuclear antibody (ELISA)-0.26(negative), Anti phospholipid antibodies-ies- IgG-0 .17, IgM-0 .15, Activ ated par t ial thrombopla stin time- control-29, test-

Prothrombin time-control- 12.6sec, test-13.3sec, INR-1.05, HIV/HCV/RPR - Non reactive, HbsAg - negative. MRI brain-axial T2/axial T2 FLAIR images (fig-1): white matter hyper intensities noted in bilateral parieto occipital and right frontal lobes. Mild tortuosity of both optic nerves noted more on the right side. Impression- features suggestive of posterior reversible encephalopathy syndrome.

Pt treated with Pritchard's regime (Magnesium sulphate regime) and Tablet Nifidipine. The patient recovered and was discharged normotensive and is on follow up with no sequelae.

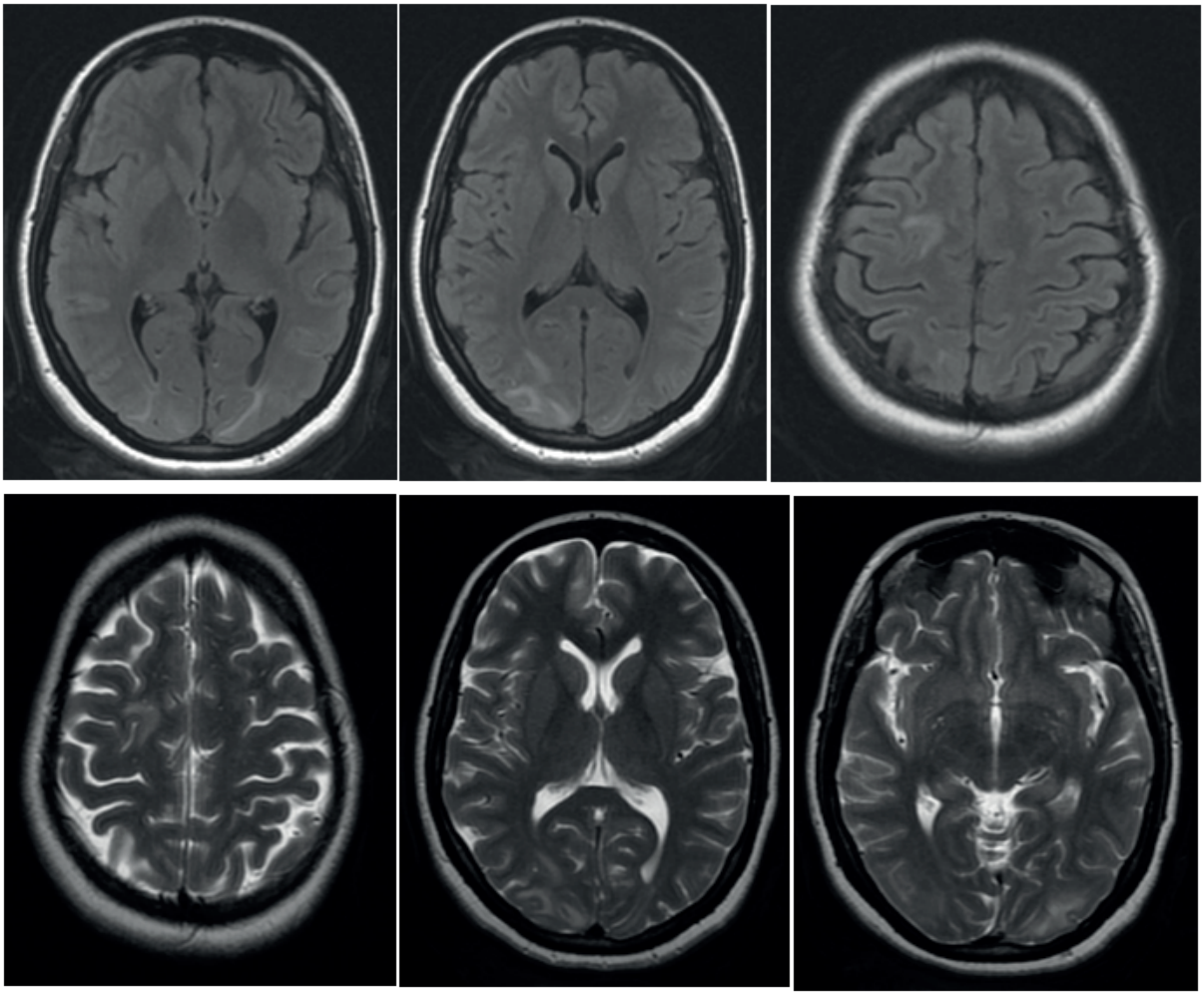

Fig-1: AXIAL T2 & AXIAL T2 FLAIR images:

Showing hyper intensities of white matter in the parietal, occipital and frontal lobes

Case2: 24 year old Para2Live2 both full term normal vaginal deliveries was brought on 4th post natal day with history of one episode of convulsion(tonic clonic) at home which was preceded by intense headache. Patient had no history of fever/vomiting/visual disturbances. Patient had delivered a girl baby weighing 2.98kg, Apgar score-8/10.

Previous menstrual cycle: 3-4/25 days, regular.

Married for 4 years, consanguineous marriage.

Obstetric history

1st pregnancy - Full term normal vaginal delivery, boy 3 yrs, alive and healthy

Present pregnancy- Full term normal vaginal delivery, girl baby four days old, alive and healthy.

On examination: Patient was conscious, oriented to time place & person, afebrile, no neck rigidity, Pupils equally reacting to light, pedal edema present, BP on admission was190/106 mm Hg. Cardiovascular system and Respiratory system were found to be normal. Per abdomen: soft and uterus involuting. Central nervous system: deep tendon reflexes-brisk, clonus negative, plantar –flexor, no motor or sensory deficit. Patient had the second episode of convulsion in the casualty. Pritchard's regime was started. Papilledema was ruled out after an Ophthalmologist' opinion Neurologist opinion was obtained and was advised to continue the same treatment and to investigate for the cause of hypertension.

Patient was further investigated and the reports are as follows:

Urine: albumin-nil, sugar –nil, Pus cells1-2cells per high power field, Epithelial cells-2-4cells per high power field, Blood: Hemoglobin-12.5g/dl, Packed cell volume- 37.7%,Total leukocyte count-13100cells/cubicmm.

Differential count: Neutrophil76.9%, Lymphocyte-16.1%, Monocytes-3.6%, Basophils-1%, Eosinophils-2.4%, Mean corpuscular volume-90fL, Mean corpuscular hemoglobin-29.8PG, Mean corpuscular hemoglobin concentration-33.1g/dl, RBC distribution width-10.2%, Random blood sugar-116mg/dl, Blood urea nitrogen-13mg/dl, uric acid- 5.5mg/dl, total protein-6.6g/dl, Albumin-4.1g/dl, Globulin-2.5g/dl, SGOT-21U/L, SGPT-41U/L, Serum alkaline phosphatase-160U/L, Gamma glutamyltransferase -21U/L, Bilirubin total- 0.2mg/dl, bilirubin direct-0.05mg/dl, sodium143mEq/L, potassium 4.5mEq/L, HIV/HCV/RPR-Non reactive, HbsAg- negative, blood group- O positive, MRI- axial T2 and axial T2 flair images(fig-2): hyper intensities noted in bilateral occipital and parietal lobes, no signal intensity changes noted in gradient or diffusion weighted images, signal intensity changes noted in left optic nerve. Impression: features suggestive of Posterior reversible encephalopathy syndrome [PRES].

Patient treated with Pritchard's regime and Tablet Nifidipine. Patient became normotensive & recovered completely.

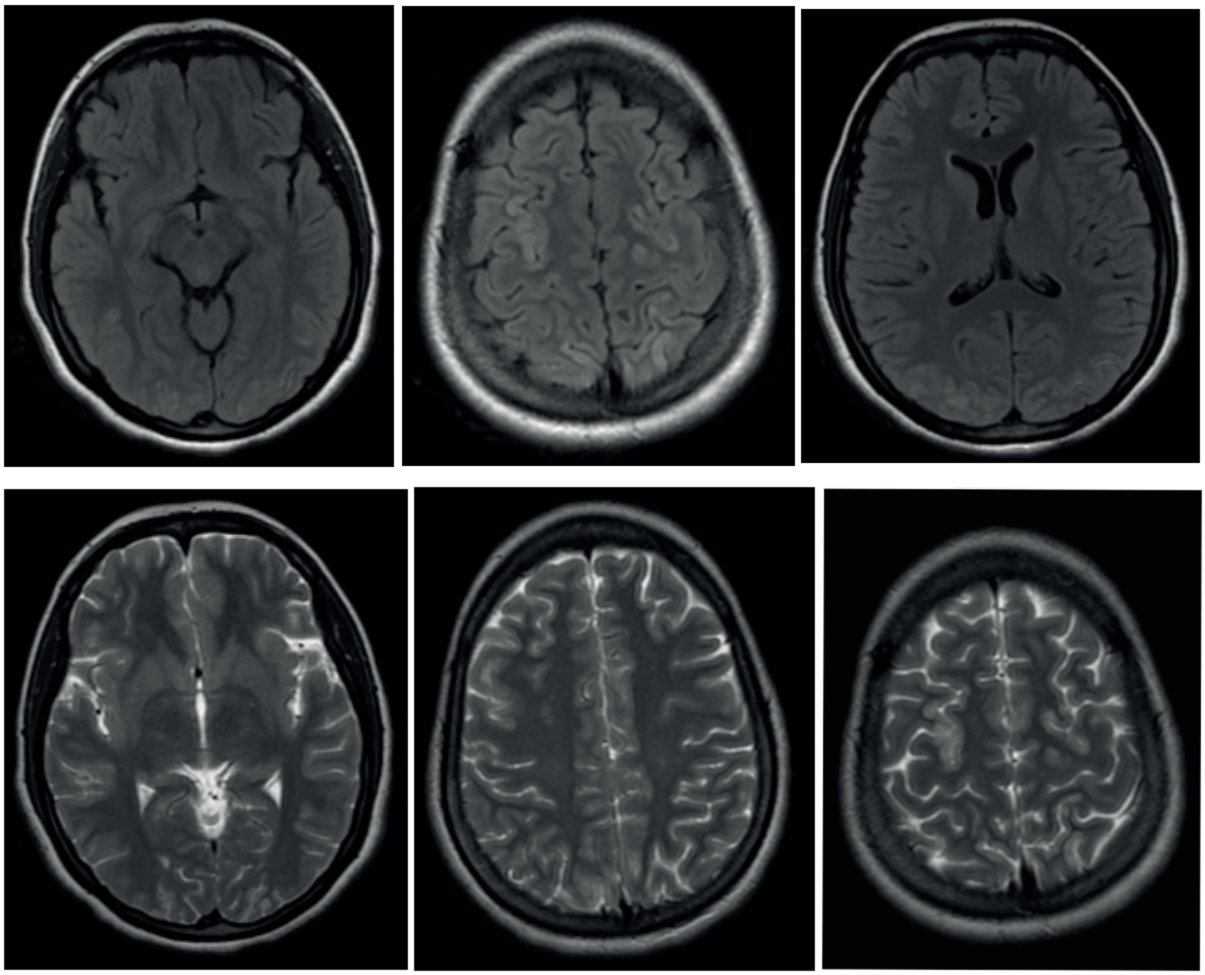

Fig-2: AXIAL T2 & AXIAL T2 FLAIR images:
showing hyper intensities in the bilateral parietal and occipital lobes.

Discussion

Posterior reversible encephalopathy syndrome is a neurological condition which is characterized by headache, nausea, vomiting, seizures, visual disturbances and altered sensorium. PRES can occur in pregnancy, both in antepartum and postpartum period. Cases of PRES have been reported in children and adults, men & women. PRES usually affects the cerebral white matter, but grey matter can also be affected. Parietal and occipital regions are most commonly involved; sometimes the lesions can extend into basal ganglia, brain stem and cerebellum.

Seizures in pregnancy are usually considered to be manifestations of eclampsia. Eclampsia is defined as occurrence of convulsions or coma with hypertension, proteinuria and or pedal edema during pregnancy between 20 wks of gestation and 48hrs postpartum without any pre existing neurological disorders. Seizures occurring beyond 48hrs but less than 4 wks after delivery is accepted as late postpartum eclampsia. The causes for postpartum seizures or altered sensorium other than eclampsia include cerebral infarction, hemorrhage, hypertensive encephalopathy, cerebral venous thrombosis, cerebral malaria, meningitis, intra cranial tumors and many others[1].

Etiology : The common causes of posterior reversible encephalopathy syndrome are hypertension,

eclampsia, renal failure, following organ transplantation, use of immunosuppressive and cytotoxic drugs like Cyclosporin A, Interferon alpha, intravenous immunoglobulins, Cisplatin, Tacrolimus etc,. Immunological disorders like Systemic lupus erythematosis, Porphyria, Behcet's syndrome, Polyarteritis nodosa are some rare causes of posterior reversible encephalopathy syndrome.

Pathogenesis : The pathogenesis of PRES is thought to be due to failure of cerebral auto regulation and endothelial dysfunction. Increase in blood pressure causes disruption of brain's normal auto regulation of cerebral blood flow. This disturbance of auto regulation produces dilatation of cerebral arterioles with opening up of endothelial tight junctions and leakage of plasma cells into the extra cellular space causing cerebral edema. Vasogenic edema occurs if cerebral white matter is affected. The cerebral white matter is composed of myelinated fibres in a cellular matrix of glial cells, arterioles and capillaries due to which there can be fluid accumulation leading to vasogenic edema. There is deficiency of adrenergic innervation of cerebral blood vessels, mainly in the posterior cerebral area, so it is affected the most.[2]

Clinically, PRES is characterized by seizures, headache, altered sensorium, and visual defects like blurring of vision, hemianopia and even cortical blindness. Seizures are of generalized tonic clonic type and can be single or multiple. Hypertensive encephalopathy presents with the same clinical features as PRES. So, the complete diagnosis can only be arrived in conjunction with radiological evidence.[3] In PRES, T2 weighted MR images and T2FLAIR images show hyper intense lesions in the cerebral white matter mainly in the parieto occipital region, sometimes grey matter can also be affected. Hypertensive encephalopathy shows all the features of PRES along with empty sella and optic nerve hydrops.

PRES is reversible if the blood pressure is controlled and treated early. Anti epileptic therapy is not needed. Controlling the blood pressure can reverse all the clinical effects and MRI abnormalities of PRES. If not treated in time, patients may develop irreversible neurological deficits, vision loss and the condition may even be fatal.

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Cure for Effects of Dangerous Decibels?

Noise pollution induced damage is an almost unavoidable consequence of modern living. Paradoxically, most of the noise is produced by those seeking pleasure (loud music), or politics (loud speakers) or comfort (machinery). Until now, how noise induced the hearing loss had not been fully explained. Now in a study conducted on mice (FASEB J. 2013 Sep;27(9):3730-40. doi: 10.1096/fj.13-232892. Epub 2013 May 31), researchers from Oregon Hearing Research Centre have demonstrated that perivascular resident macrophages (PVM/Ms; a hybrid cell type with characteristics of both macrophages and melanocytes) are damaged by noise leading to decreased production of pigment epithelium derived factor (PEDF) and increased leakiness of endothelial cells. The key event appears to be the down-regulation of PEDF. The latter is necessary for the integrity of interstitial-blood barrier. Breach of the latter leads to hearing loss. The researchers have shown that the delivery of PEDF to damaged ear can reverse the situation. Now that we have a solution, the noise pollution may become worse.

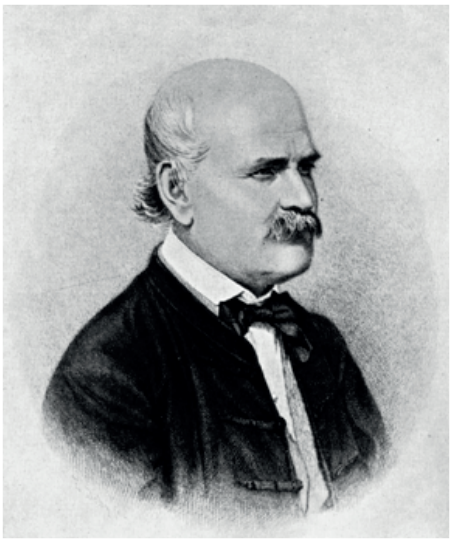
- Dr. K. Ramesh Rao

From the Pages of History

Ignaz Philipp Semmelweis (July 1, 1818 – August 13, 1865)[i] , [ii],[iii] "Saviour of Mothers"

Dr. Ramesh Rao, Professor and HOD, Dept. of Pathology, Chettinad Hospital and Research Institute, Chennai, India

Chettinad Health City Medical Journal 2014; 2(2): 69 - 69



Being ahead of your time is not always rewarding as you are likely to be misunderstood. If you question the prevalent dogma in uncompromising and non-conciliatory manner, you are likely to be ridiculed and ostracised. History of science is replete with records of such unfortunate thinkers. Ignaz Philipp Semmelweis was one such who paid heavily for his ideas.

Semmelweiss was born on 1st of July, 1818 in Taban (present day Budapest), Hungary to a wealthy Jewish family. Initially he wanted to study law but for some unexplained reason took up medicine. In 1944, he obtained his master's (Magister) degree in medicine from University of Vienna. Having failed to obtain an appointment in internal medicine clinic, he decided to specialise in Obstetrics. One of his teachers was Karl von Rokitansky.

On 1st of July 1946, he joined as assistant at First Obstetrical Clinic of the Vienna General Hospital (equivalent to chief resident). In those days Vienna General Hospital used to run two maternity clinics with admissions on alternate days. These clinics were run on similar lines except for one difference: the first clinic was used for training medical students while the second clinic was used for instruction of nurses only. Even outsiders knew that the first clinic had a high maternal mortality rate (~13%) due to high incidence of puerperal fever (childbed fever). In comparison, the second clinic had a mortality rate of around 3%. Most women used to beg to be admitted to second clinic.

This worried Semmelweis. He decided to investigate why there is such a high mortality in the first clinic. At around the same time, one of his close friends died of a fever similar to puerperal fever which developed after he sustained a wound while performing autopsy. This prompted Semmelweiss to connect cadaveric contamination with puerperal fever.He hypothesized that he and medical students carried the "cadaverous particles" from autopsy room to the patients they examined in first clinic. This also explained why there was lower death rate in the second clinic as the midwives were not involved in autopsies or surgery.

As a corrective measure, he made hand-washing with chlorinated lime (hypochlorite solution) compulsory before examining patients in first clinic. This simple but revolutionary procedure brought the mortality rate dramatically down to the level observed in second clinic. But he was a shy man. He did not initially publish his findings. But many of his students tried to popularise his ideas. There was lot of resistance and ridicule from his colleagues. Among those who opposed his ideas was influential Rudolf Virchow. As the germ theory of disease was still unknown and "miasma" (bad air) was considered to be the cause of disease, nobody wanted to accept the ideas of an expatriate. Semmelweis was forced to leave Vienna. However, he achieved similar success in many other hospitals he worked. He published his observations finally in 1861 in the book "The Aetiology, Concept and Prophylaxis of Childbed Fever."

By then he had developed a nervous disorder (probably post-traumatic stress disorder). He was admitted in mental asylum in 1865 where he was severely beaten up by guards and confined to a darkened cell. He died two weeks later of internal injuries and sepsis similar to puerperal sepsis that he tried to eliminate from clinical practice. He was only 47 years old.

Recognition came only after Louis Pasteur acknowledged Semmelweis's contribution when he proposed the germ theory of disease. Semmelweis is now universally recognised as the pioneer of antisepsis.

i- http://www.sma.org.sg/smj/4701/4701ms1.pdf
ii- http://en.wikipedia.org/wiki/Ignaz_Semmelweis
iii- http://explorable.com/semmelweis-germ-theory

Abstracts from the Chettinad National Fertility Colloquium September 2013

Chettinad Health City Medical Journal 2014; 2(2): 70 - 72

1) Dr.Asha Benziger, Chettinad Health City, Kelambakkam, Tamil Nadu,India.

A PROSPECTIVE STUDY ON THE IMPACT OF RADIOFREQUENCY ELECTROMAGNETIC WAVES (RF - EMWs) EMITTED BY CELL PHONE DURING CALL ATTENDED MODE ON THE SEMEN SAMPLE

Aim: To assess the motility of the spermatozoa after exposure to RADIO FREQUENCY ELECTROMAGNETIC WAVES (RF-EMWs) emitted by the cell phone during the call attended mode from different directions.

Type of Research Study: Prospective Single Blind Study.

Study Place: Central Animal facility, Department of Reproductive Medicine.

Materials & Method: 30 normozoospermic men were randomly selected, during January to May 2013. Semen samples were collected soon after ejaculation, sperm concentration and motility were noted.The remaining sample were taken in 4 vials.The samples were exposed to RF EMWs at 4 places {1st -incubator (the control), 2nd- front of the mobile, 3rd- back, 4th-antenna} 2.5 cm away from the mobile. During the call attended mode the mobile generated power density of an average of 63.57 - front side,70.5 - back side,103.5 - antenna side respectively which was measured by FIELD STRENGTH METER. After 1hr, the 4 samples were re-analyzed.

Results: There was statistically significant decline in percentage of progressively motile sperms in all the exposure groups compared to the control group.

Conclusion: Impact was highest in the group exposed from antenna, followed by the behind and front respectively. Awareness regarding the hazards of cell phones on the man's fertility has to be created among the public.

Dr.Indumathi, Institue of Reproductive Medicine, MMM, Chennai, Tamil Nadu, India.

2) **A COMPARATIVE STUDY OF THE OUTCOME OF THE INDIVIDUALIZED GnRH ANTAGONIST STIMULATION PROTOCOL (EARLY INITIATION) WITH THE FIXED ANTAGONIST PROTOCOL IN IVF/ICSI – ET CYCLES**

Objective: To compare the outcome of the individualized (early initiation) GnRH antagonist stimulation protocol with the fixed antagonist stimulation protocol in IVF/ICSI- ET cycles.

Design: A prospective observational study.

Setting: Tertiary care Assisted Reproductive Unit.

Patients: All women who underwent a fresh embryo transfer following IVF/ICSI after controlled ovarian hyperstimulation (COH)using either an individualized (early initiation) antagonist protocol(Group – A) or a fixed antagonist protocol (Group-B). The number of patients included in the study were 144,out of which 84 were in group A and 60 in group B.

Outcome Measures: Clinical pregnancy rate (CPR), Ongoing pregnancy rate (OPR). No. of oocytes retrieved. No. of M2 oocytes. Fertilization Rate. Implantation Rate

Results: The clinical pregnancy rate was 41.7% and 40%, the ongoing pregnancy rate was 29.4% and 33.3% in group A and group B respectively which was statistically not significant. There was no significant difference in the number of oocytes retrieved, M2 oocytes and fertilization rate though the implantation rate was 19.3% and 18.8% in group A and group B respectively. 19 patients out of 25 in group A and 18 patients out of 24 in group B had delivered. Among the remaining number of the clinically pregnant patients, the pregnancies are ongoing.

Conclusion: Our present study showed differences in the clinical pregnancy rate, the ongoing pregnancy rate, fertilization rate and the implantation rate though not statically significant. Further randomized studies are required to study the effect of elevated LH levels in the follicular phase before planning early initiation of GnRH antagonist administration
in antagonist cycles.

Keywords: Fixed protocol, individualized protocol, clinical pregnancy, ongoing pregnancy rate.

Dr.S.S.Gayathri Devi, , Chettinad Health City, Kelambakkam, Tamil Nadu,India

3) **THE CORRELATION BETWEEN ENDOMETRIAL THICKNESS AND OUTCOME OF PREGNANCY IN AN ASSISTED REPRODUCTIVE TECHNOLOGY PROGRAMME – RETROSPECTIVE OBSERVATIONAL STUDY**

Aim: The aim of our study is to evaluate the endometrial thickness on the day of hCG administration during ART cycle and to assess the correlation between endometrial thickness and ART/ET outcome.

Material & Methods: From January 2010 to December 2011, 60 patients undergoing assisted reproduction cycles were taken retrospectively for pregnancy outcome in relation to endometrial thickness. The study was done in the Reproductive Medicine department. The protocol used for pituitary down regulation was short flare protocol. Division into four groups was made depending on the thickness: group 1 ≤8 mm; group 2: >8 to ≤11 mm; group 3: >11 to < =14 mm; group 4>14mm.

Results: A total of 60 patients were investigated in this study.The overall clinical pregnancy rate was 33.33%.The endometrial thickness on the day of hCG administration ranged from 7.1mm to 18mm. Most pregnancies were in the endometrial thickness range of 8-14 mm. (67.1%)All the pregnancies occurred with grade I embryos.

Conclusion: In conclusion, when a thinner endometrium (≤7 mm) without triple-line endometrial pattern coexists in a couple undergoing ART/ICSI, cryopreservation is recommended. No case with endometrial thickness < 7 mm was observed. A thicker endometrium (>14 mm) did not have an adverse effect on the clinical outcome. Endometrial thickness and pattern, when both are analysed, is more valuable than the separate analyses. All pregnancies in this study occurred with grade I embryos. Hence embryo quality plays an important role than endometrial thickness.

4) Dr.Mariano, Christian Medical College, Vellore, Tamil Nadu,India

DOES SERUM PROGESTERONE LEVEL ON THE DAY OF HUMAN CHORIONIC GONADOTROPIN ADMINISTRATION AFFECT CLINICAL PREGNANCY RATES IN FRESH EMBRYO TRANSFER CYCLES? : A RETROSPECTIVE COHORT STUDY

Aim: To determine whether serum progesterone level on the day of human chorionic gonadotropin administration affects clinical pregnancy rate in fresh embryo transfer cycles.

Material & Methods: Retrospective cohort study of all IVF cycles at the Reproductive Medicine unit from January 2011 to December 2012

Results: Patients were categorized in to high progesterone - > 1.5 ng/ml ,altered P4/E2 ratio -> 1 and results were analysed based on this.

Protocol	Total no.cycles	ET	Overall clin.preg	P4- > 1.5 ng/ml	P4</= 1.5 ng/ml	P4/E2 ratio -> 1	P4/E2</= 1	N=
Antogonist	315	289	136/289 47%	3/17 17.6%	133/272 48.9%	5/24 20.8%	131/265 49.4%	289
Long agonist	188			2/7 28.5%	80/181 44%	6/20 30%	74/168 44%	188
Ultra long	49			2/7 28.5%	10/42 23.8%	5/18 27.7%	12/31 27.7%	49
Short protocol	43			1/5 20%	8/38 21%	1/6 16.7%	8/37 21.6%	43

Conclusion:The clinical pregnancy rates are significantly lower in the fresh embryo transfer cycles in which the progesterone levels on the day of hCG trigger are > 1.5 ng/ml, or the progesterone/estradiol ratio is >1.

5) Dr.Ramesh Raja, Chettinad Health City, Kelambakkam, Tamil Nadu,India

A PILOT STUDY : IMMOTILE SPERMATOZOA IN SEMEN SAMPLE – RESTING OR IMMOTILE?

Objective: To observe the immotile spermatozoa over a period of time in semen samples to find out if they are immotile or resting. Type of study: Pilot study

Study place: Reproductive Medicine Department

Materials & Methods: Data collected during January 2012 to October 2012. After routine semen analysis was done according to WHO 2010 criteria, the immotile spermatozoa in the each semen sample was observed for about 5minutes and recordings noted down at 2 minutes and 5minutes.

Results: In 111 patients,498 immotile spermatozoa were observed continuously for 5 minutes and found 1. At 2 minutes (7% became Progressively motile and 8% became Non progressively motile). 2. At 5 minutes (3% became progressively motile and 7% became non progressively motile).

Conclusion: We observed that some immotile spermatozoa at a point of time may become motile later on. These spermatozoa may be resting spermatozoa which may resume motility later on. This is a pilot study and we are looking at more samples to see if spermatozoa regain motility after some time.

Key Words: Immotile Spermatozoa , Resting Spermatozoa, Spermatozoa Motility.

6) Dr.Ranjani, Chettinad Health City, Kelambakkam, Tamil Nadu,India

LEUCOCYTOSPERMIA –DOES IT MEAN ANYTHING?

Objective:To find out the significance of leucocytospermia in patients with round cells > 5 mill/ml in routine semen analysis attending infertility clinic.

Type of study: Retrospective study

Setting: Dept of Reproductive Medicine.

Data collection: Data of patients who came for routine semen analysis and had round cells > 5 mill /ml from August 2009 - July 2011 was taken. The data of patients leucocytes >1 mill/ml was checked for semen culture reports and intervention with antibiotic treatment, if any was noted and analysed.

Results: Among the 2447 patients who came for semen analysis 196 had round cells >5 mill/ml. After leucoscreen test 39 had leucocytes >1 million/ml. Among them 23 had semen culture done.Only seven had culture positive.16 had no growth of any pathogens out of which 1 had significant growth, and 2 had moderate growth and was put on antibiotics. 4 of the patients had very low growth and were not treated with antibiotics. Patients who were put on antibiotics were asymptomatic except for one patient who complained of burning micturition. His urine culture was also positive for the same organism.

Conclusion: According to this observational study leucocytospermia was not associated with clinical symptom or bacteriospermia as the culture yielded no growth or insignificant growth of any organisms in majority of the patients. Larger study is required to see if leucocytospermia is an indicator of infection in the male and whether leucocytospermia does mean anything to us in male infertility.

7) Dr.Sumi Thomas, Christian Medical College, Vellore, Tamil Nadu,India

CHROMOSOMAL ABERRATIONS IN COUPLES WITH RECURRENT MISCARRIAGES – AN EXPERIENCE OF 479 COUPLES AT A TERTIARY CARE CENTRE IN INDIA

Aim:To evaluate the contribution of chromosomal abnormalities in causing recurrent miscarriages.

Materials & Methods: Retrospective study of 479 couples who attended the Reproductive Medicine unit with history of recurrent miscarriage from 2002 to May 2013.

Results:There were totally 479 couples (958 individuals) out of whom 69 (7.2%) individuals were detected to have chromosomal aberrations. 21 (2.1%) individuals had translocations, 34 (3.9%)had numerical abnormalities, 4 (0.4%)with inversions and 6 (0.6%) with other chromosomal abnormalities

Conclusion:Cytogenetic analysis is an important investigation in the workup of couples with recurrent miscarriages.

Mental Decline and Proteinuria in T2 DM

There is compelling evidence that people with type 2 diabetes are at increased risk of developing cognitive impairment in comparison with the general population. But until now there was no marker to predict the risk. Now in a study conducted on more than 3000 patients with type 2 diabetes (average age of 62 years), researchers from the Emory School of Medicine, found that those with persistent proteinuria for over four to five years had greater declines in their cognitive abilities than those without proteinuria. The results suggest that persistent proteinuria may be the earliest warning sign of a future mental decline. However, the changes initially are subtle and clinically evident mental impairment requires 10-15 years to manifest. Since diabetics are 50 to 60% more likely develop mental deterioration compared to general population, these findings are considered significant. However, there is no obvious causal relationship. (CJASN CJN.11321112; published ahead of print August 29, 2013, doi:10.2215/CJN.11321112)

- Dr. K. Ramesh Rao

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