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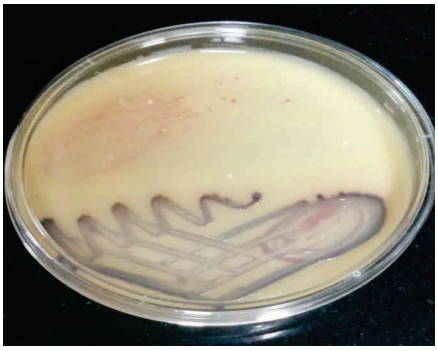

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CONTENT

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From the Editor's Desk

Dear Colleagues,

We are happy to bring out the new issue of Sri Ramachandra Journal of Medicine after a short gap. Thanks to the efforts in the formation of new Editorial Board initiated by our Vice Chancellor made it possible to bring out this edition. We have resolved to take this journal to higher levels of indexing and make it useful journal for all specialties. This will only be possible if the Faculty, Students and Research Scholars continue to contribute good Research materials.

A new transparent system of peer reviewing and editing has been introduced to facilitate easy submission and processing.

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Original Article

STANDALONE ANCHORED SPACER REDUCES DYSPHAGIA RATE IN ANTERIOR CERVICAL DISCECTOMY AND FUSION

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ABSTRACT

Background:

A variable percentage of patients (2% to 67%) have either transient or prolonged post operative dysphagia with Anterior cervical discectomy with fusion using Smith and Robinson's technique. In this study, we have prospectively followed up patients who underwent Anterior Cervical Discectomy and Fusion (ACDF) in single or multiple levels using the Polyetheretherketone (PEEK) Prevail cervical interbody device (Medtronic, Memphis, TN) and its implication in dysphagia.

Materials and Method:

With institutional review board approval, we enrolled 40 patients between May 2014 to May 2016 suffering from single or two level degenerative cervical disc disease from C3-C4 to C7-T1. PEEK prevail device was used in all the 40 patients. Patients were evaluated pre operatively with VAS neck pain and arm pain scores expressed as 0 to 100 and neck pain and disability scores measured as 0 to 100. Clinical improvement was also graded by Odom's criteria at final follow up. Length and Severity of Post operative dysphagia were recorded by Bazaz's criteria at each follow up.

Results:

15 of 37 patients followed up had symptoms of mild dysphagia (40%) at immediate post op period . Out of these 15, only 3(8%) had mild dysphagia at 3 months follow up.

Conclusion:

Rates of dysphagia using stand alone anchored spacer were much less when compared to anterior cervical decompression and fusion with plating and bone grafting/ interbody cages. Hence stand alone anchored spacer is a good alternative for plating and bone grafting/ interbody cages in anterior cervical decompression and fusion.

Keywords: *Anterior cervical discectomy fusion, Cervical disc, Dysphagia, Standalone anchored spacer, VAS score.*

SRJM 2017;10:1-5

INTRODUCTION

Anterior cervical discectomy with fusion using Smith and Robinson's technique with or without plating has been the gold standard treatment in the operative management of cervical disc disease, especially in older patients and in patients where use of disc replacement prosthesis is contraindicated.[1,2] A variable percentage of patients (2% to 67%) have either transient or prolonged post operative dysphagia with this procedure.[3,4] In this study, we have prospectively followed up patients who underwent ACDF in single or multiple levels using the Polyetheretherketone (PEEK) Prevail cervical interbody device (Medtronic, Memphis, TN) and its implication in dysphagia.

PATIENTS AND METHODS

With institutional review board approval, we enrolled 40 patients between May 2014 to May 2016 suffering from single or two level degenerative cervical disc disease from C3-C4 to C7-T1. Inclusion criteriae were skeletally mature patients from 18- 70 years, patients with unilateral or bilateral radicular pain with/ without axial neck pain, MRI confirmed single or two level cervical disc disease from C3-C4 to C7-T1 and had completed at least 6 weeks of conservative treatment without any improvement. The exclusion

Fig 1: Standalone anchored Spacer

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criteriae were previous surgery at the diseased level, congenital or iatrogenic fusion of the adjacent level, patients needing more than 2 levels of surgery, developmental cervical stenosis, systemic or local infection, active rheumatoid arthritis,uncontrolled diabetes and other co morbidities compromising surgical outcome, severe Osteoporosis, known allergy to PEEK or titanium alloy and pregnancy or planning for pregnancy during the study period. 30 patients had single level disease and 10 patients had 2 level disease. All of our patients had radicular arm pain with or without neurological/functional deficits with axial neck pain present in most patients. Associated myelopathy was seen in 20% of patients, mostly older people with multilevel disease. PEEK prevail device (Fig 1) was used in all the 40 patients. Patients were evaluated pre operatively with VAS neck pain and arm pain scores expressed as 0 to 100[5] and neck pain and disability scores measured as 0% to 100%.[6] Pre operative imaging include anteroposterior, lateral and flexion extension radiographs of cervical spine and MR Myelogram of cervical spine.

Post operatively, patients were mobilised under supervision with soft collar support in the first post operative day. Post operatively intravenous antibiotics third generation Cephalosporin were given for 1 day and intravenous paracetamol 1 gm thrice daily were given for two days and converted into oral aceclofenac twice daily for three days. No active physiotherapy of the neck was allowed for 6 weeks. Initial post operative clinical and radiological assessment was done at the time of the discharge and then during follow up during follow up at 6 weeks, 3 months, 6 months and every 6 months thereafter. The severity of dysphagia can vary. When mild, it can mean a feeling of food just taking longer to pass through the oesophagus and it can be painless. Liquids may well cause no problem. When severe, it can mean both solids and liquids do not pass at all down the oesophagus and may cause you to vomit back (regurgitate) food and drink. When moderate, it can be somewhere in between these extremes.

Three patients were lost to follow up at 3 months and were exclude from the study, leaving 37 patients for final analysis. Clinical improvement was also graded by Odom's criteria[7] at final follow up. Length and Severity of Post operative dysphagia were recorded by Bazaz's criteria at each follow up.[3] Implant related and surgery related complications were documented. Pre and post operative radiographic parameters were assessed by two independent investigators Statistical analysis was performed using SPSS software. Student's paired T test was used to assess the significance of difference between means.

Graph 1-Dysphagia rates

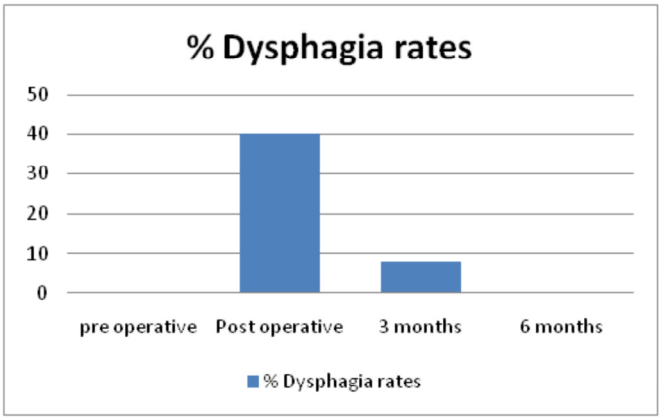

Table 1-Mean pre and post op vas score

Parameters	Pre operative	Post operative	Last follow up	P value (Pre vs post)	P value (Pre vs Last)
VAS arm pain	71.62 ± 6.61 (SEM-1.09)	45.38 ± 8.79 (SEM-1.44)	30.35 ± 3.51 (SEM-0.58)	<0.0001	<0.0001
VAS neck pain	66.43 ± 5.83 (SEM-0.96)	47.59 ± 6.39 (SEM-1.05)	36.95 ± 7.83 (SEM-1.29)	<0.043	<0.001

Table 2-Neck Pain and Disability Score

Parameter	Pre operative	3 months follow up	Last follow up	P value (pre vs 3	P value (pre vs last)
% Neck Disability Index	66.27± 6.18 (SEM-1.02)	38.54± 6.22 (SEM-1.02)	39.32±5.5 (SEM-0.91)	<0.001	<0.001

RESULTS

The mean follow-up of 37 patients continued in the study was 21.5 ± 2.5 months. 15 of 37 patients followed up had symptoms of mild dysphagia (40%) at immediate post op period (VAS throat pain score of 39.25 ± 7.2). Out of these 15, only 3 (8%) had mild dysphagia at 3 months follow up (VAS throat pain score of 32.72 + 6.9). One patient had symptoms that persisted for more than 6 months (Graph 1). The mean VAS arm pain and mean VAS neck pain were tabultaed as per Table-1. The mean NPAD-D score also improved at 3 months compared to pre operative scores(Table-2). According to Odom's criteria, 27 patients (73%) had good outcome (Fig 2, Fig 3), 4 (10%) patients had excellent outcome and 3 (8.5%) had fair outcome and 3 (8.5%) had poor outcome.Only 2

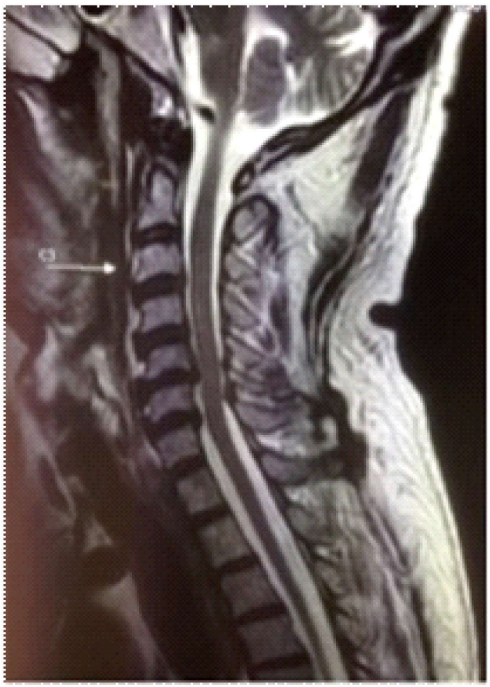

Fig 2: Pre-operative MRI showing cervical disc

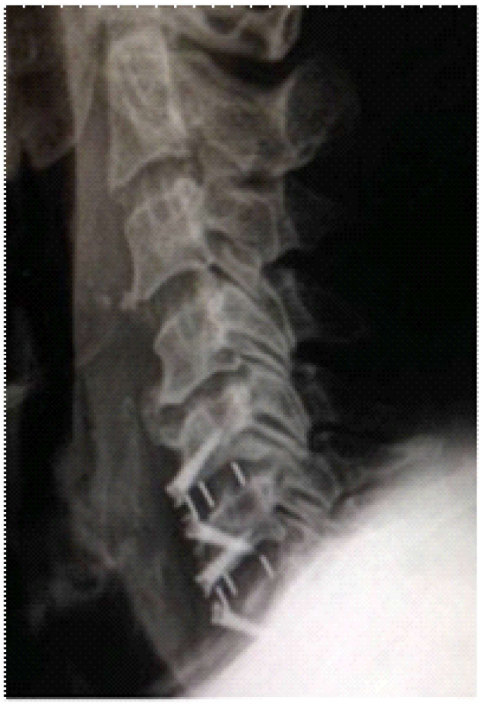

Fig.3: Post-operative x-ray showing standalone anchored spacer

patients had an increase in interspinous distance of more than 2mm in flexion-extension x rays. Three patients (8%) had evidence of non union at 1 year follow up x rays according to Pitzen's criteria.[10] (27%) patients had radiologicallysignificant subsidence.

DISCUSSION

The PEEK PREVAIL Device is an implant used to treat patients who suffer from a degenerative condition that affects the neck (cervical spine). The PEEK PREVAIL Device is designed to provide stability during spinal fusion, which involves joining two bones together, such as adjacent vertebrae. The zero-profile PEEK PREVAIL Device eliminates the need for a plate and attaches to the spine using only two screws. The PEEK PREVAIL Device is to be used with autograft and implanted via an open, anterior approach. Casper et al and Geisler et al in one of the largest studies describing plate fixation for ACDF concluded that addition of plates for ACDF greatly reduce the need for reoperation.[8,9] They also advocated removal of anterior osteophytes near the endplates before the plate placement to prevent hardware prominence and dysphagia. It is an advantage in standalone devices that, they don't need extensive surgical preparation for placement but rather a "focal spodylectomy" along the trajectory of the cage saving surgical time and blood loss.[10] The major concern in standalone devices is whether they provide biomechanical stability enough to achieve fusion. Studies using anchored spacers with 4 screw construct,[11] three screw construct[12] and two screw construct showed comparable biomechanical stability in flexion-extension, lateral bending and axial torsion with standard anterior plating. The "I beam'' shape of the cage and Nitinol locking mechanism increases the stability of screw implant interface. PEEK material used in our implant is radio opaque allowing for better evaluation of fusion and it is more rigid than autograft.[13] Moreover, several studies have shown PEEK to provide 100% fusion rates with good to excellent clinical outcome[14,15] with minimal subsidence maintaining foraminal decompression and sagittal alignment.[16]

Post operative Oro Pharyngeal dysphagia is a major concern in anterior cervical spine surgery.[17,18] Some authors even consider dysphagia as an inevitable result of the surgery rather than a complication.[19] There are a number of objective instruments to measure dysphagia after post operative cervical spine surgery although none is universally accepted.[20] Even though it is widely used and helps us to compare results among studies, Bajaj score for dysphagia grading has various drawbacks as pointed out by skeppholm et al.[21] Patient reported instruments are more effective in identifying swallowing dysfunction, but none of these were used in our study.

Karen et al[20] in their metaanalysis, delineated various risk factors for post operative dysphagia in anterior cervical spinal surgeries. They include age >60 years, female gender, Fusion surgeries with use

of shorter and thicker plates, increased number of levels operated, surgery at cranial levels, increased esophageal retraction pressure with prolonged operative time. Since the thickness of plates correlates with the severity of dysphagia according to Lee et al,[4] mechanical irritation is a major cause of long term dysphagia, although other causes such as esophageal retraction or edema, injury of the esophageal nerve plexus or of the superior laryngeal nerve and prevertebral soft-tissues swelling cannot be ruled out.[22] 40% of our patients had short term dysphagia (< 2 months post operative period) which is comparable with other studies in literature,[3,4] while only 8% of patients had dysphagia persisting more than 2 months which is substantially less than these studies. Higher short time dysphagia rates in our study and in other studies using low profile stand alone cages[23] indicate that early dysphagia is inherent to any anterior cervical spine surgery regardless of the implant used. In our study 87% of patients had excellent to good outcomes and 13% had fair to poor outcomes which is comparable to other studies with ACDF and plating[24,25,26] and stand alone cages.[23]

Hofstetter et al[27] evaluated post operative radiographs for pre vertebral swelling and found that patients operated with plates had significant post operative prevertebral swellings that persisted for more than 6 months compared to patiens who had Zero profile device fixation. Decreased incidence of midterm and late dysphagia in our study and other studies with zero profile devices, clearly support the hypothesis of hardware prominence and scarring associated with plating leading to prolonged dysphagia symptoms More over most our patients had odynophagia rather than true dysphagia, indicated by increased VAS throat pain scores in early post operative period.

CONCLUSION

Dysphasia is a common post operative complication of anterior cervical decompression and fusion with plating and bone grafting/interbody cages. The functional outcomes of stand alone spacer are comparable to plating and grafting/interbody cages. Since the dysphagia rates are low, stand alone anchored spacer is a good alternative for plating and bone grafting/ interbody cages in anterior cervical decompression and fusion.

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A PROSPECTIVE STUDY ON MRSA INFECTION POST-OPERATIVELY AMONG THE PATIENTS UNDERGOING CARDIOTHORACIC SURGERY AND ITS RISK FACTOR ANALYSIS

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ABSTRACT

Introduction: *Emergence of Methicillin Resistant Staphylococcus aureus (MRSA) has been a major concern in health care facilities since 1990 throughout the world. They are known to cause surgical site infection including mediastinitis, in patients undergoing cardiothoracic surgery. Proper screening and treatment of MRSA carriers prior to invasive procedures help in decreasing the infection associated morbidity.*

Aim: *Primary- To determine the rate of MRSA carriage in patients undergoing cardiothoracic surgery unit. Secondary- To determine the rate of post-operative wound infections caused by MRSA.*

Material and Methods: *A prospective observational study was conducted in the Department of Microbiology in collaboration with Cardio Thoracic Vascular Unit. All the patients posted for the cardiothoracic surgery were included in the study. Preoperatively a detailed history of the patient was taken and recorded and for MRSA screening, swabs were taken from nostrils, axilla, umbilicus and groin. Post-operative follow up was done for presence of any wound infection with MRSA.*

Results: *A total of 47 patients (27 male & 20 females) were screened pre-operatively for MRSA and risk factors were analysed. MRSA carriage was observed in 36.1%. Post-operative infection (POI) was observed in 19.1%, of which MRSA constituted 5.8%. Other risk factors contributing to Post-operative infections were increased HbA1c levels, prolonged hospital stay, increased BMI and smoking habits.*

Discussion & Conclusion: *Patients necessitating cardiothoracic surgeries have often several predisposing risk factors like diabetes, hypertension and obesity accentuating the probablity of developing POI with MRSA and several other microbes. Though Nasal carriage of MRSA was high in our study, post operative infections in the patients were low due to the effective antibiotic prophylaxis. Hence pre-operative MRSA screening and decolonisation is a crucial step in the prevention of postoperative infectionsin the patients undergoing cardiothoracic surgeries.*

Key words: *BMI, CABG, Prolonged hospital stay, HbA1C, MRSA Screening, Smoking & Post-operative infections.*

SRJM 2017;10:6-8

INTRODUCTION

Surgical site infections are a known complication for any operative procedures increasing the patients stay in the hospital and indirectly burden the patient financially.[1] Coronary artery bypass graft surgeries have become very common nowadays because of increase in incidence of coronary artery diseases due to diabetes, hypertension, hypercholesterolemia and various other contributing factors. *Staphylococcus aureus* is present in 10 to 35% of healthy individual's nares. It is the most common cause of skin and soft tissue infections (SSTI) and nosocomial infections.[2] Emergence of Methicillin Resistant *Staphylococcus aureus* (MRSA) has been a major concern in health care facilities since 1990 throughout the world. They are associated with both community acquired and health care associated infections and also known to cause post-operative mediastinitis, in patients who have undergone coronary artery bypass graft surgery.[3] Proper screening and decolonisation of MRSA carriers prior to invasive procedures help in decreasing the morbidity and mortality associated with infections caused by them.

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AIM

Primary- To determine the rate of MRSA carriage in patients undergoing cardiothoracic surgery in our unit.

Secondary- To determine the rate of post-operative wound infections caused by MRSA.

MATERIAL AND METHODS

A prospective observational study was conducted during the month of May and June 2015 by the

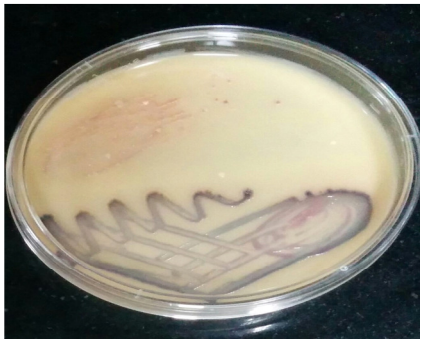

Fig 1: Colonies of Methicillin Resistant Staphylococcus aureus and Methicillin Susceptable Staphylococcus aureus in chrome agar.

Department of Microbiology along with the Cardio Thoracic Vascular Unit (CTVS) at Sri Ramachandra Medical College and Research Institute after obtaining the institutional ethical clearance (Ref No: CSP/15/APR/41/18). All the patients posted for the cardiothoracic surgery were included in the study after obtaining their written consent. Patient who were not willing to give the consent and those with pre-existing wound infections were excluded from the study. Preoperatively, a detailed history of the patient was taken. For MRSA screening, swabs were taken from nostrils, axilla, umbilicus and groin. The swabs were transported to the microbiology laboratory within one hour time. The swabs were inoculated into 5% sheep blood agar and MRSA chrome agar (Fig.1). After 24 to 48 hrs of incubation the plates were observed for the presence of growth. Plates showing growth was further processed to confirm the presence of *Staphylococcus aureus* and their susceptibility to Oxacillin 1μgm and Cefoxitin 30 μgm was determined by Kirby-Bauer disc diffusion method as per CLSI guide lines 2015. All the patients colonised with MRSA were decolonised as per the hospital protocol (Chlorhexidine bath, nasal mupirocin application) and surgical antibiotic prophylaxis was given with Vancomycin or Teicoplanin.

RESULTS

During the study period 47 patients who underwent cardiothoracic surgery were screened pre-operatively for MRSA and their risk factors were analysed. Among the 47 patients, 27 (57.4%) were males and 20 (42.6%) were females. Mean age of the study group was 49.1 and the male female ratio was 1.4:1. Of the 47 patients enrolled, 25.5% (n = 12) were in the age group of more than 60 years. In our study population, 20 of them were diabetes mellitus patients and 12 of them had uncontrolled diabetes with HbA1c level more than 7(60%:n = 20). A total of 14 (29.8%) patients were smokers. Duration of stay was more than 15 day in 26 (55.3%) patients. BMI of the patients enrolled is shown in Fig 2.

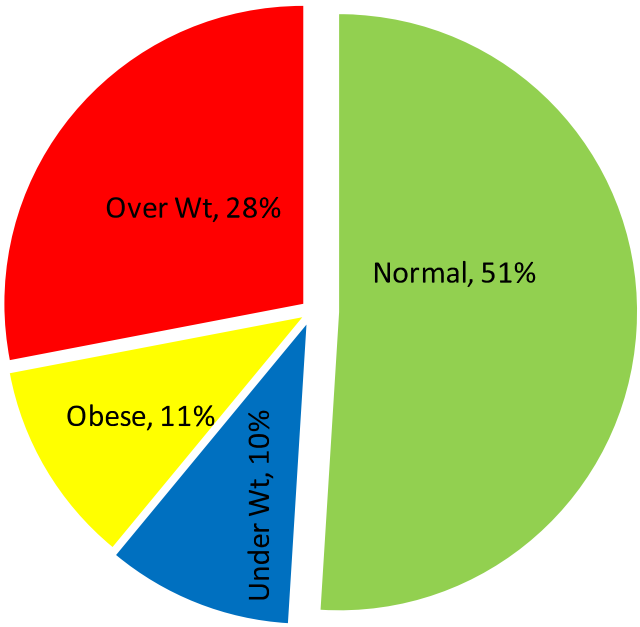

Fig 2: BMI of the study population.

Out of the 47 patients MRSA colonisation was seen in 36.1% 17. Out of the 47 people, Post-Operative Infection (POI) was observed in 19.1% (n = 9). Among the 9 patients who had POI, 6 (66.7%; n = 9) were diabetic and 4 (66.7%; n = 6) had uncontrolled diabetes. Out of the 14 smokers in the study population, 3 (21.4%: n = 14) had POI. Eight (88.9%) of the POI patients had duration of stay more than 15 days. Out of the 17 people who was colonised with MRSA only 1(5.8%) patient had POI with MRSA. Organisms isolated from POI patients are shown in Fig.3.

DISCUSSION

Patients necessitating cardiothoracic surgeries have often several predisposing risk factors like

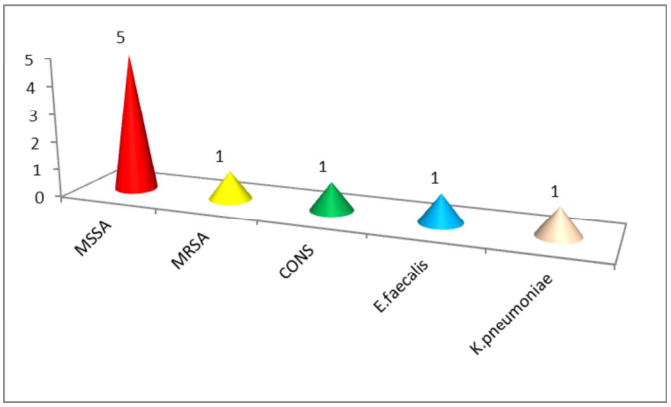

Fig. 3 Organisms isolated POI patients.

diabetes, hypertention and obesity accentuating the probablity of developing POI with MRSA and several other microbes.

In our study which involved 47 patients, the incidence of POI was high in those who were overweight (23.1%) and obese (40%). Though the relationship between obesity and infections have not been established, few studies have shown correlation between severity of infection and obesity. Patients who stayed for more than 2 weeks had higher infection rates (30.8%) when compared to patients who stayed for less than 2 weeks. This finding was consistent with the finding of Bhatia et al., the severity of infection is more when the duration of stay in hospital is longer. Also patients with Diabetes mellitus and those who had HbA1C >7 had greater incidence of POI (30% and 66.7% respectively). Hence, our study had a good correlation of POI with the presence of risk factors like obesity, diabetes mellitus and longer duration of hospital stay.

In our study the screening for MRSA was done in more than one site i.e nose, groin, umbilicus and axilla. The colonisation rate of MRSA was 36.1% in either one of these sites which is comparatively high. The nasal carriage was 23.4% in our study, which is in accordance with Bruce Y Lee et al, 2010. Nasal carriage rates reported from various studies ranges from 0.4% to 20.6%.[4] Many studies have reported nasal colonisation with MRSA as predisposition for POI and poor out come.[5,6,7,8] In most of the tertiary health care centers,the patients undergoing cardiothoracic surgeries are being provided with chlorhexidine bath and prophylactic antibiotics, which help in decolonisation of MRSA. This protocol is strictly followed in our hospital. In the present study, even though the MRSA carriage rate is 36.1% the POI with MRSA is only 2.1%. This underscores the effectiveness of the pre-operative prophylatic measures followed in our hospital. Screening for the colonisation of MRSA in these patients pre-operativevely have a vital role in preventing POI in these patients, thereby decreasing the morbidity, mortality and the financial encumbrance of the patient. Henceforth it is mandatory to follow standardised infection control practices to reduce the occurrence of POI in these patients.

SUMMARY AND CONCLUSION

Nasal carriage of MRSA was high in our study, however post operative infection due to MRSA was low due to effective pre-op decolonisation and antibiotic prophylaxis in these patients. Hence pre-operative MRSA screening and decolonisation remains as a crucial step in the prevention of postoperative infections in patients undergoing cardiothoracic surgeries.

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Review Article

NEUROLOGICAL INFECTIONS CAUSED BY HERPESVIRIDAE: PATHOGENESIS, CURRENT TRENDS IN LABORATORY DIAGNOSIS AND TREATMENT

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ABSTRACT

Members of the family Herpesviridae are capable of producing acute and chronic infections. Acute clinical manifestation is seen during primary infection. In a vast majority of individuals the virus become latent and has the potency to be reactivated and produce severe disease especially in immunosuppressed individuals. Chronic infections with clinical features are also seen in immunosuppressed patients. Acute infections which are life threatening can be seen in immunocompetent individuals as well. The serious disease related to infections with family Herpesviridae affect the central nervous system with manifestations like meningitis, encephalitis, GBS and ADEM. Rapid diagnosis using techniques like real-time PCR have revolutionized the options for early life saving treatment. The antiviral agents against herpes viruses include acyclovir, gancyclovir, foscarnet and valcyclovir. CNS infections are best treated with appropriate IV preparations. Till date there is only one effective vaccine for a prevention strategy of herpesvirus infections i.e. against VZV. Pre-emptive therapy is used in SOT & BMT patients for CMV.

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INTRODUCTION

Herpesviridae are double stranded DNA viruses. Neurological infections by herpes viruses both acute and chronic may lead to morbidity and mortality.[1,2] The neurotropic DNA viruses include Human herpes virus 1 commonly known as Herpes simplex virus 1 (HSV-1), Human herpes virus 2 (Herpes simplex virus 2 -HSV-2), Human herpes virus 3 (Varicella zoster Virus -VZV), Human herpes virus 4 (Epstein-Barr virus-EBV), Human herpes virus 5 (Cytomegalovirus -CMV), Human herpes virus 6 (HHV-6), Human herpes virus 7 (HHV-7) and Human herpes virus 8 (HHV-8). HHV-6 and HHV-7 are not implicated in primary infections of the central nervous system (CNS). This review highlights the neurotropic herpes viruses that infect the CNS and explores the recent methods for diagnosis and treatment.

Neuropathogenesis of *Herpesviridae* infections

During primary infection virus attaches to the surface epithelial or endothelial cells. Further it provokes signaling from the infected cell to surrounding uninfected cells by secreted cytokines which results in infection. Following infection, viruses may be cleared by specific antibodies and T cells. Reactivation of virus from latent state by stress, immunosuppressants and excessive exposure to sunlight and other infections is primarily seen in herpes viruses causing CNS infections.[2,3,4] It should be noted that DNA viruses that show neurotropism establish primary infection in the host with or without symptomatic disease and CNS disease.

During viral dissemination in a patient with impaired cell mediated immunity, both pro-inflammatory and anti-inflammatory cytokines are elevated.[5] Such response in the brain can lead to meningitis, encephalitis, meningoencephalitis or death. In immunosuppressed patients such as patients with tumors on chemotherapy, post transplant recipients and those with human immunodeficiency virus (HIV) infection, herpes viruses can reactivate and cause the disseminated disease.[6] Laboratory diagnostic methods for detection of Herpesviruses include histopathology, serology, culture and detection of viral nucleic acid.

Protective mechanisms of BBB in CNS

Blood Brain Barrier (BBB) consists of endothelial cells, pericytes, astrocytes, and the basement membrane. Pericytes and astrocytes ensheath the capillary wall and regulate the BBB homeostasis. Brain microvascular endothelial cells (BMVECs) are connected by tight junctions. These junctions restrict the entries of microorganisms from blood vessel.[5] A thick extracellular matrix known as basement membrane limits movement of pathogens.

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Virus enters the CNS by two ways either (a). Direct infection of nerve endings in the tissues or (b) Infecting cells in the circulatory system ultimately gets transmitted through the BBB into the CNS.[2,3,4,5]

Direct infection of nerve endings

HSV-1, HSV-2 and VZV can enter the peripheral nervous system (PNS) by binding through neuronal receptor (Nectin-1) on axon termini of sensory and autonomic neurons.[7] Through membrane fusion virus enters to sensory nerve endings and engages the dynein motors for retrograde transport of virus to the neuronal cell body. [8] The viral DNA enters to the host nucleus, presented as either acute or latent infection (dormant).[9] HSV-1 reactivates more efficiently from the trigeminal ganglia whereas HSV-2 reactivates more efficiently from the lumbosacral dorsal root ganglia (DRG).[10,11]

Invasion via the Olfactory Epithelium and Olfactory Neurons.

The olfactory system is a portal of entry to the CNS from the periphery.[5] The bipolar olfactory receptor neurons have dendrites in the olfactory epithelium at the roof of the nasal-pharyngeal cavity. The olfactory epithelium is protected from infections by mucus and the presence of pathogen recognition receptor systems.[12, 10]

Infection of Brain Microvascular Endothelium Cells (BMVECs)

CMV and EBV

Through cellular adhesion molecules in the BMVECs, the virus attaches and subsequently there is an infiltration of immune cells into the brain parenchyma which results in inflammation. Infection often leads to the disruption of BBB integrity and infects the astrocytes in the neurons and activate perivascular macrophages (i.e., microglia) residing between the endothelial cells. This results in the breakdown of endothelial barrier, thus T helper and T cytotoxic cells enter the CNS causing neurological disorders. Both EBV[13] HCMV[14] can infect BMVECs and become latent.[13] Besides BMVECs, astrocytes, pericytes, neurons, microglial cells, and neural stem cells also can be infected by HCMV.[14,15] Primary infection during pregnancy, can result in underdeveloped immune-system of the fetus and may result in fatal CNS abnormalities such as mental retardation and hearing loss.[16] Due to increased inflammatory cytokines in response to HCMV infection, it favours the fetal neuro-development diseases.[5] During virus reactivation increased inflammatory cytokine and chemokine results in the progression of the inflammatory neurological disease such as multiple sclerosis (MS).[13]

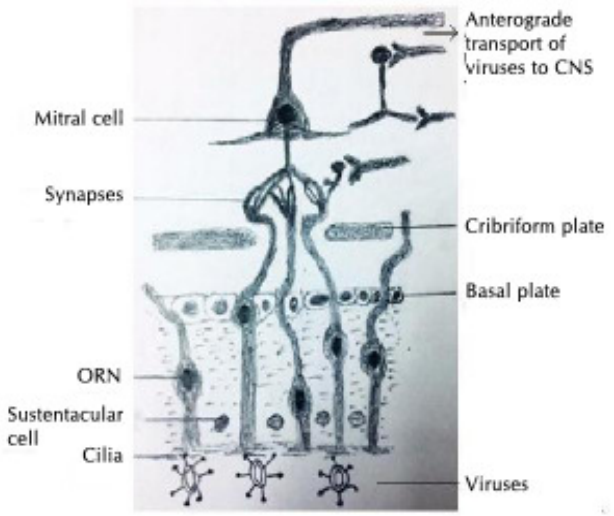

Fig. 1: Schematic representation of HHV6 virus entry into CNS via olfactory system

ORN: Olfactory receptor neurons

HHV6

HHV-6 have been associated with neurodegenerative disorders. Autopsy specimens of the olfactory bulb/tract region and the nasal mucosal samples suggest that the virus enters the CNS through the olfactory pathway.[17]

Olfactory transmission of HHV-6 to CNS has been explained in the Fig.1. The virus attaches to dendritic terminals of olfactory receptor neurons and transmitted to the synapses of the mitral cells (second order neurons) in the olfactory bulb and spreads to the amygdala and hippocampus. This is called anterograde movement of virus (Fig.1). There are two varieties of the virus i.e. HHV-6A and -6B. Under in vitro conditions, human fetal astrocytes are infected by both HHV-6. It is suggested that *in vivo* HHV-6A may have note worthy neurotropism.[18] HHV-6 causes CNS disease in children presenting as rhombencephalitis (primarily infecting the hindbrain (cerebellum and brainstem).[19] Table: 1 shows features of *Herpesviridae* related to invasion of CNS.[20-25]

Neurological manifestations caused by *Herpesviridae* HSV

(a) *Aseptic meningitis*

Viral meningitis is much more common with HSV-2. The predominant symptoms are fever, headache, vomiting, photophobia, and nuchal rigidity. Meningeal symptoms usually start 3 to 12 days after the onset of genital lesions. In immunocompetent individuals, aseptic meningitis is usually benign which resolves without sequelae.[26]

(b) *Autonomic nervous system dysfunction*

Table: 1: Identified features of *Herpesviridae* related to invasion of CNS.[20-25]

Taxonomic name/ Trivial name	Subfamily and characteristics	CNS Manifestations	Virus cell surfacreceptor	CNS entry	Latent replication form	Main site of latency
HHV-1 / HSV-1	α (Alpha), infects somatic cells	Encephalitis seen in older children & adults meningo-encephalitis	Heparin sulphate	sensory nerve endings, ORN	Circular episome	Dorsal root ganglia
HHV-2 / HSV-2	α,infects somatic cells	Encephalitis seen in neonates, meningitis & meningo-encephalitis	Heparin sulphate	sensory nerve endings, ORN	Circular episome	Dorsal root ganglia
HHV-3 / VZV	α, fibroblast,	Aseptic meningitis, encephalitis, transverse myelitis, CNS vasculitis	mannose-6-phosphate or myelin-associated glycoprotein	sensory nerve endings, ORN	Circular episome	Dorsal root ganglia
HHV-4 / EBV	γ (Gamma) grows in lymphocytes	Primary central nervous systemPTLD, GBS, myeloradiculitis	gp350/BLLF1 and gH/BXLF2	BBB; BMVECs	Circular episome	Memory B-cells
HHV-5 / CMV	β (Beta) grows in lymphocytes	GBS, Chronic meningoencephalitis in immunosuppressed patients	EGFR, integrins,	BBB; BMVECs	Circular episome	Myeloid progenitor cells
HHV-6 / Roseolovirus, Herpes lymphotropic virus	β, grows in lymphocytes	Meningitis, encephalitis in immunosuppressed patients	CD46	blood-brain barrier through the olfactory pathway	Probable telomeric integration	Monocytes

ORN: Olfactory Receptor Neuron; PTLD: Post transplant lymphoproliferative disorder;BBB: Blood Brain Barrier; BMVECs: brain microvascular endothelial cells; GBS: Guillain-Barré Syndrome *Today the serology is considered not useful as compared to molecular testing

* HHV-7 and HHV-8 are not generally associated with neurological disease.

It is associated with genital HSV infection and presented with hyperesthesia or anesthesia of the perineal, lower back, or sacral regions as well as urinary retention and constipation. It is requently observed in women with genital herpes and men with HSV proctitis.[27,28] Large bladder, decreased sacral sensation, poor rectal and perineal sphincter tone have also been observed. Impotence and absent bulbo-cavernous reflexes have been observed in men.

(c) *Transverse myelitis*

Primary genital HSV infection associated with decreased deep tendon reflexes and muscle strength in the lower extremities.[29,30]

(d) *Herpes simplex virus encephalitis*

HSV-1 is the most common cause of encephalitis in children and young adults.[33] Virus enters the CNS by neurotropic spread from the periphery through the olfactory bulb. However, mucocutaneous spread was reported before the onset of the CNS symptoms. HSV DNA has been demonstrated in brain tissue from healthy adults.[31] Thus, reactivation of latent CNS infection may be another mechanism of the development of encephalitis.

(e) *HSV encephalitis in neonates*

HSV infection in neonates is invariably symptomatic and frequently lethal. Brain infection of HSV occurs in two ways; disseminated infection in neonates (blood-borne route entering the brain and resulting in cortical haemorrhagic necrosis in multiple areas) and retrograde axonal transport of virus to the CNS.[32] Clinical features of the encephalitis include seizures, lethargy, irritability, tremors, poor feeding, temperature instability, bulging fontanelle and pyramidal tract signs.

(f) *HSV encephalitis in older children and adults*

In older children and adults, HSV infection can manifest with fever, altered state of consciousness, bizarre behavior, and focal neurologic findings, referable to the temporal lobe. Fifty percent of the children develop psychomotor retardation, often in association with microcephaly, hydranencephaly, porencephalic cysts, spasticity, blindness, chorioretinitis, or learning disabilities.

Other neurologic syndromes include recurrent aseptic meningitis (Mollaret's meningitis), brainstem encephalitis, ascending myelitis, post infectious encephalomyelitis, movement disorders, atypical pain syndromes, and temporal lobe epilepsy.[33]

VZV

One of the conditions not widely recognized is the role of VZV in fetal atresia with impaired neurological development. This occurs during the first and second trimester.[34] Zoster is characterized by a dermatomal distribution of pain and rash, chronic pain (post herpetic neuralgia or PHN) or meningitis, meningoencephalitis, cerebellitis, isolated cranial nerve palsies that produce ophthalmoplegia or the Ramsay Hunt syndrome, multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy, myelopathy, various inflammatory disorders of the eye and chronic radicular pain without rash (zoster sine herpete). Rarely, the diverse neurological, ocular disorders could be produced by VZV without rash. Features of zoster are characterized by inflammation and hemorrhagic necrosis associated with neuritis, localized leptomeningitis, degeneration of related motor and sensory roots.

(a) *VZV encephalitis*

VZV can be life threatening in adults and can manifest as acute cerebellar ataxia or encephalitis.[35] However in children it is benign and resolution occurs within 2 to 4 weeks. Clinical symptoms include depression in the level of consciousness with progressive headaches, vomiting, altered thought patterns, fever, and frequent seizures. Abnormal findings include ataxia, vomiting, altered speech, fever, vertigo, and tremors.

Among immunocompromised patients, it is severe and rarely fatal. Patients with lymphoproliferative malignancies are at risk for cutaneous dissemination and visceral involvement, including varicella pneumonitis, hepatitis, and meningoencephalitis.[26] Complication includes VZV retinitis, acute retinal necrosis and chronic progressive encephalitis

(b) *Postherpetic neuralgia (PHN)*

Herpes zoster is defined by three phases of disease: acute, subacute, and chronic. The latter two compose post herpetic neuralgia. The most significant clinical manifestations of herpes zoster are associated with acute neuritis and later postherpetic neuralgia. There is a dermatomal distribution of pain (>3 months) and ganglia analysed for diffuse and focal infiltration by chronic inflammatory cells.

(c) *VZV myelopathy*

It is self-limiting, monophasic spastic paraparesis with or without sensory features. It presents as an insidious, progressive and sometimes fatal myelitis which is most common in immunocompromised individuals. VZV myelitis also occurs in the absence of zoster rash. Pathological analyses have revealed frank invasion of VZV in the parenchyma and in some instances, spread of virus to adjacent nerve roots.[36]

(d) *VZV vasculopathy*

Productive VZV infection in cerebral arteries causes vasculopathy and can manifest as ischemic infarction of the brain, spinal cord, subarachnoid, cerebral hemorrhage, carotid dissection and rarely peripheral arterial disease.[37]

CMV

Asymptomatic CMV infected newborns were often found to develop deafness.[38] CMV infection in CNS can manifest with diffuse encephalitis, ventriculo encephalitis, cerebral mass lesions, spinal cord transverse myelitis and polyradiculomyelitis.

(a) *Meningoencephalitis*

Infected individuals have motor and sensory weakness with features of severe headache, photophobia, lethargy and pyramidal tract findings.

(b) *Polyradiculopathy*

It is most common CNS infection in HIV infected individuals with features of ascending weakness in the lower extremities associated with a loss of deep tendon

reflexes, loss of bowel and bladder control.[39] The syndrome frequently begins as low back pain with a radicular or perianal radiation, followed by a progressive flaccid paralysis.

EBV

CNS complications by EBV are rare in immunocompetent adults. Though rare, it has been reported in children and in immunosuppressed individuals. A considerable number of paediatric patients who had hippocampal lesions.[40]

Neurological features can occur with or without typical signs and symptoms of infectious mononucleosis. Neurological manifestations include encephalitis, meningitis, myelitis, seizures, polyradiculitis, cerebellitis and cranial neuritis as well as primary CNS lymphoma.

(a) *Encephalitis*

Encephalitis is commonly manifested as a cerebellitis and the clinical presentation is similar to that of aseptic meningitis.[26]

HHV-6

(a) *Febrile Seizures*

HHV-6 is known to cause of febrile seizures, meningitis and encephalitis in infants.[41]

(b) *Exanthem Subitum (Roseola Infantum; Sixth Disease)*

Exanthem subitum (ES) is an illness in the infants and young children manifested with unremarkable fever, mild upper respiratory symptoms and occasional cervical adenopathy. As the fever decreases classic diffuse macular or maculopapular exanthem emerges and associated with an atypical lymphocytosis and neutropenia. Complications includes febrile seizures, meningitis and encephalitis.[26]

(c) *Encephalitis and Other Neurologic Disorders*

Encephalitis often occurs 4 weeks post transplantation. One third of SOT and one half of BMT can be associated with fever, rash, graft-versus-host disease, delayed bone marrow engraftment, interstitial pneumonitis, hepatitis, encephalitis and invasive fungal infections.[42]

Neurological syndromes caused by *Herpesviridae*

Acute encephalitis/meningoencephalitis – shows symptoms of acute febrile illness with inflammation of meninges and combination of clinical symptoms like convulsions, delirium, confusion, stupor and coma. They can also present as aphasia and mutism. In the event of patients surviving the acute episode, different cognitive deficits may persist after the acute stage and may present as acute necrotizing encephalitis.[43,44]

Acute disseminated encephalomyelitis (ADEM): Uniphasic syndrome is an ADEM which is associated with an immunization or systemic viral infection. Edema and demyelination within the CNS is characterized by focal or multifocal neurological dysfunction.[45] ADEM has an autoimmune component, in which antibodies to the basal ganglia, cytokine changes results in the inflammation and oligodendrocyte death are documented.[46]

Guillain-Barre´ syndrome (GBS) (acute demyelinating polyneuropathy)

GBS is a demyelinating disease which manifests as an acute, symmetrical, lower motor neuron paralysis. The most common clinical signs are asthenia, tingling, prickling sensation and numbness in the affected areas. Weakness of the muscle specifically starts distally in the legs and reaches the arms proximally. Usually GBS is self-limiting and completely recover after remyelination.[47] Several RNA and DNA viral infections are known to associate with GBS.[48] Among the DNA viruses CMV has a strong association with GBS.

Epidemiology of Herpesviridae in tropical countries including India

Seroprevalence of herpes viruses

Few studies have reported the population prevalence of herpes antibodies with age stratification. The median (50%) age of seroconversion to Herpesviridae is 3 to 4 years. In developing Asian countries, the HSV-2 antibody prevalence is lower (10–30%), similar to developed countries.[49, 50] The antibodies to CMV and EBV attain high levels by early adulthood, in contrast to exposure to VZV. In hospital-based population study in South India, prevalence of IgG and IgM to HHV were reported in different age group (0 to 25 years) among 181 individuals. The seroprevalence of CMV and EBV are age specific, which was found to be 90% by the fourth year of life. The median ages for CMV and EBV infections were <1 year and 1.4 years respectively. However anti-VZV and anti-HSV IgG age-specific prevalence found to be gradual rise in the age group of 15 to 25 years old (VZV:72%, HSV:83%).[51] HHV-6A and-6B is highly prevalent in the adult population exceeding 90%. In a study reported from south India the exposure rate of serum IgG was 58% among adults.[52]

Risk factors for herpes virus infection

(a) *Sex*

Male predominance is observed in HSV1 (91.5% , HSV 2 (10% to 50%), CMV (75%) EBV (50%), VZV (46%) and HHV6 (97.5%) infection. Female predominance is often reported in HSV 1 (89.6%) HSV2 (30% to 80%), CMV (86.8%), EBV (42.2%) VZV (54%), HHV 6 (91.6%).[49,50,53,54]

(b) *Other risk factors*

Factors that influence the transmission of HHV infection includes age, geographic location (crowding, poor hygiene) and socioeconomic status. Other risk factors, such as female gender, caucasian ethnicity, diabetes mellitus, psychological stress, mechanical trauma, heavy metal exposure as well as family history have also been responsible for virus reactivation.[55] SOT and BMT recipients and immuno compromised individuals are at a higher risk for developing the reactivation.

HSV-1 infection is more prevalent than HSV-2. HSV-2 prevalence is highly variable and depends on many factors including country and region of residence, population subgroup, sex, age and it is higher among higher risk sexual behaviour groups.[49,50]

Varicella is highly communicable and is a common disease of childhood under 10 years of age. Twenty percent of adults will experience zoster after the age of 50.[56] Cytomegalovirus can also be transmitted by blood transfusion. CMV sero negative recipients are at higher risk, as a seropositive organ transmits the virus in 60–80% of CMV.[55]

Mode of transmission and source of infection

HSV-1 is transmitted from infected to susceptible individuals during close personal contact (oral secretions or lesions). Neonatal HSV infections are caused by HSV-2 which is usually acquired during passage through the infected birth canal of a mother. Infection may also be acquired postnatally from the mother or by nosocomial transmission.[51] Varicella transmitted by airborne droplets and by direct contact. Infection usually occurs during winter or spring in both temperate and most tropical climates.[57]

CMV is often transmitted by close contact from infected secretions such as urine, saliva, respiratory secretions, semen, breast milk and cervical secretions. It can also spread transplacentally or through blood transfusion, organ transplantation and sexual contact.[58] CMV mononucleosis syndrome was observed in post-transplant recipients or individuals who had blood transfusion. This was observed as a major problem in the West in the early days of establishment of organ transplantation among humans.[59] EBV transmitted primarily by contact with oropharyngeal secretions.

Table 2: Important studies reported from India on CNS disease associated with *Herpesviridae*

Clinical condition	Virus	Techniques used
CNS infections in immunocompetent [73]	HSV-1, HSV-2, VZV, CMV and EBV	Conventional PCR. Real-time PCR
CNS infections in immunosuppressed patients [72]	EBV,CMV,VZV, HSV-1,HHV-6	Multiplex real-time PCR
CNS infections in immunosuppressed patients	CMV, HSV 2, EBV-1, VZV	ELISA
Clinically suspected CNS infections [75]	HSV	Culture, imaging, and SES
Adult-AES cases	HSV 1 and 2, VZV	Conventional PCR , RT-PCR ,CSF IgM capture ELISA
Suspected CNS infections. [74]	VZV	Multiplex molecular diagnostic system – SES
PCNSL in immunocompetent individuals [76]	EBV	In-situ hybridization
Viral encephalitis [71]	VZV,HSV	ELISA

AES: Acute Encephatilis Syndrome; SES: Syndrome Evaluation System; PCNSL: Primary Central Nervous System Lymphoma

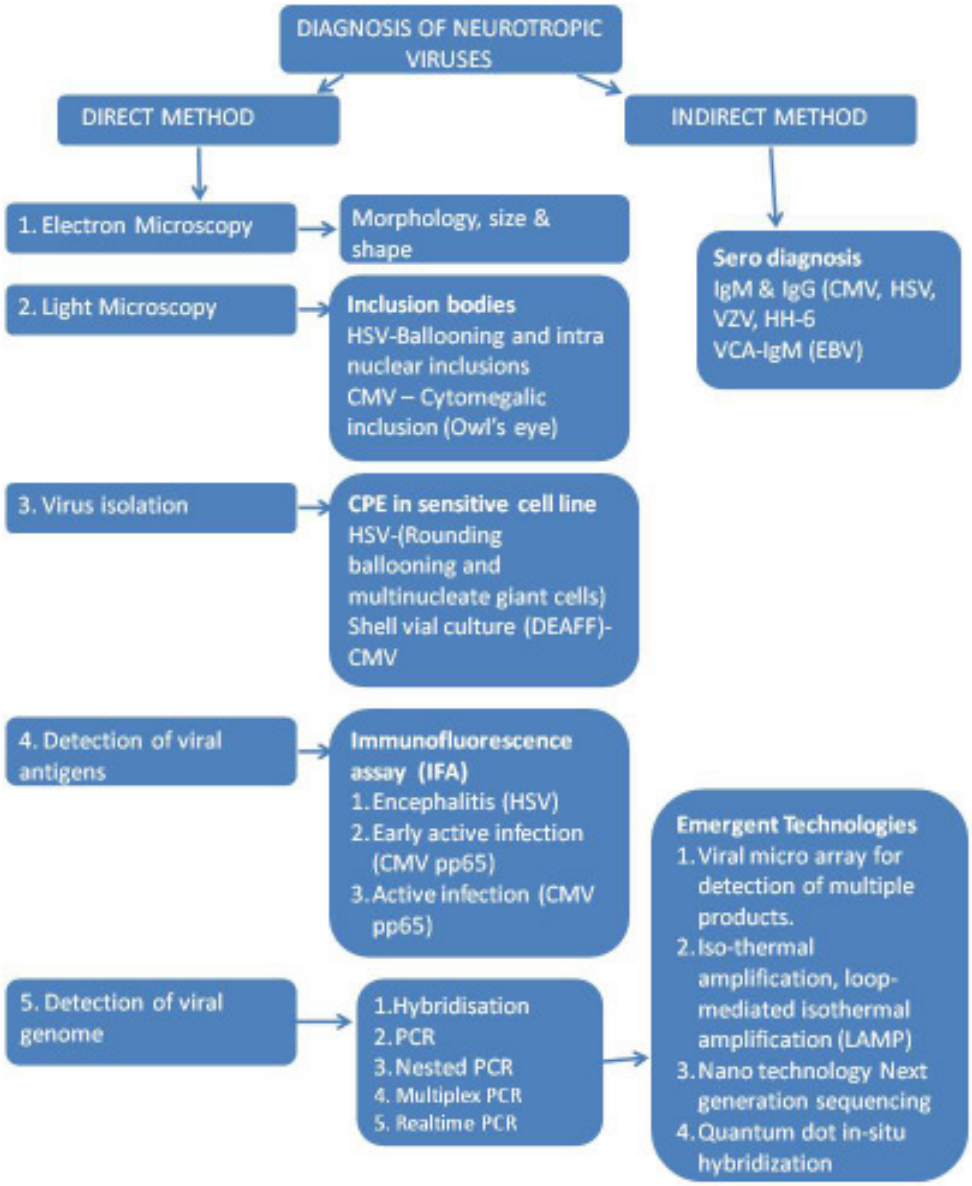

Fig. 2: Diagnostic methods used for detection of neurotropic herpes viruses

HHV-6 infections occur in early childhood via oral secretions. Reactivation appears to be common in hematopoietic stem cell transplantation (HSCT), SOT and during pregnancy.[60]

Opportunistic neurological infections caused by *Herpesviridae*

Post transplant recipients (solid and bone marrow transplant), tumor bearing hosts and people living with HIV are often prone to disseminated and life threatening neurological manifestations by Herpes group of viruses. There are several studies reported from India on the association of *Herpesviridae* members with neurological disease. (Table 2) A study from Spain reported HSV and CMV were associated with fatal encephalitis.[61] In a study from South India, on neurological infections among HIV patients preponderance of EBV has been reported.[62] Subsequently, in HIV patients with CNS disease, CSF revealed presence of multiple viral agents with underlying bacterial and fungal infections have been reported from India, Sub Saharan Africa and China.[63,64]

Methods used in establishing virus etiology/association with neurological disease

A novel approach to CNS infections in terms of etiology determination would be considering it as a clinical syndrome and investigating all possible infecting pathogens leading to acute and chronic infections. Fortunately, today it is technologically feasible, the caveat however, a study could establish etiology in only about 65% of patients with disease.[65]

The efficiency of pathogen detection is about the same using staged molecular testing.[66] A viral etiology of a neurological illness is established in the context of compatible clinicopathological, radiological and relevant clinical findings. This section describes the specific diagnostic methods in virology and broadly classified into two approaches i.e. direct methods and indirect methods. Direct methods include electron microscopy, light microscopy, virus isolation, detection of viral antigen and detection of viral genome. Indirect methods of detection include sero-diagnosis.[4] Diagnostic methods used for detection of neurotropic herpes viruses are shown in Fig. 2.

Direct methods:

Electron microscopy: Morphology of virus particles can be studied using electron microscopy. About 10xE6 virus particles per ml are required for visualization and the magnification normally used is 50,000 to 60,000. Virus may be detected in appropriately processed CSF samples or brain biopsy. Routinely, this method is not applicable except in pathogenesis studies due to expense, prolonged turn-around time and requirement for specialized skill.[4]

Antigen detection: Immunofluorescence has been shown to have application in the diagnosis of HSV encephalitis in CSF. Monoclonal antibodies against CMV phosphoprotein 65 (pp65) antigenemia have been used as a marker of active infection in post transplant recipients. Its application in CNS diseases has not been reported.[67,68]

Virus isolation / antigen detection

Viral etiology of CNS disease can be established by viral isolation through culturing CSF or processed brain biopsy material in a cell culture system.[69] The technique though specific is slow and has low sensitivity. Its sensitivity is similar to virus antigen detection in CSF cell deposit. This requires a laboratory to have multiple cell lines which would allow the virus of interest to grow. The widely used cell lines are Vero, HEp2 and MRC-5. HSV-1, HSV-2, and VZV could be isolated using Vero & HEp2 cell lines.[70] CMV can be isolated by culturing in MRC-5. A positive finding in culture denotes active virus infection. The diagnosis of HSV is rapid as it shows a visible CPE in Vero cells within 24 h of inoculation, whereas in CMV, CPE is delayed and takes an average of 10–30 days in fibroblast cells. Hence, other faster, culturing methods have been developed.[70] Rapid CMV isolation and identification is possible through shell vial system. This technique has enhanced the speed of diagnosis by culture when used in the detection of early antigen fluorescent foci (DEAFF) test format.[60] During the time of inoculation, the vials are centrifuged at low-speed, and after a period of brief incubation (~16-24 h), the cells are stained with a fluorochrome labelled monoclonal antibody to early proteins of CMV.

Role of serology in viral diagnosis

A significant 4-fold rise in the levels of IgG (seroconversion) or IgM positivity in serum indicates an acute infection. IgG- avidity assays are useful in differentiating acute, past CMV infection and reactivation.[71]

Culture of viruses and antigen detection are the methods of choice for detection of acute infections of HSV. EIAs (detection of IgM antibodies to VZV) are primarily useful in diagnosis of acute chickenpox (varicella), shingles (herpes zoster), or obscure eczema with vesicles. EIA from CSF is useful in diagnosis of varicella infection of the nervous system.[72]

Serological assays are often used during suspicion of CMV infection, in pregnancy and transplantation (immunosuppressed patients). Similarly, EBV antibodies (VCA-IgM test- widely used) are observed during suspicion of mononucleosis or sustained fever and lymphadenopathy. [73] IgM based serological assays are useful in diagnosis of HHV-6 infection.

In olden days (pre-PCR) virus isolation and serology was the mainstay in diagnosis of HSV. The morbidity and mortality were very high, due to inability in early diagnosis of HSV encephalitis. The approach then was based on brain biopsy examination and / or serological testing for intrathecal HSV antibodies.

Viral genome detection

In earlier days (Late 70s and early 80s) hybridization with specific nucleic acid probes was used in the detection of viral genome. Now it has been replaced by PCR due to ease, very high sensitivity and specificity. In fact, nested PCR and real-time PCR have gained wide usage especially in viral diagnostic laboratories of developed countries.[4]

PCR has revolutionized molecular biology in the diagnosis of viral infections. PCR possess several advantages over the conventional diagnostic methods which include high sensitivity, rapid turn-around time and its ability to detect non-cultivable agents. Earlier PCR assays were single round PCR and later, the nested PCR was introduced. Nested PCR had a higher sensitivity and specificity.[74] Rowlet et.al 1990, was the earliest report in diagnosis of HSV in CNS from patients with encephalitis. Rowlet and his colleagues

documented HSV DNA in all the four patients with herpes simplex encephalitis which was previously determined by conventional methods.[75]

Multiplex PCR

Multiplex PCRs were developed to detect multiple viruses/pathogens in a cost-effective manner. It employs multiple pairs of primers, and each pair is specific for a target which allows detection of multiple viruses in one reaction tube. Syndrome specific or organ specific screening of multiple viruses can be done by multiplex PCR which significantly reduces consumables and man power. Studies have suggested that with early diagnosis by CNS imaging and CSF testing of viruses by PCR with appropriate antiviral therapy, a majority of patients recover completely from HSE.[76] In case of CNS diseases, multiple etiological agents could be screened by multiplex PCR. However, primer design and optimization are more complex.

Real-time PCR

The demand for quantitation of viral genome led to the development of real-time PCR. The earliest report of kinetic PCR analysis (real-time monitoring of DNA amplification known as real-time PCR) was reported in the year 1993.[77] The accumulation of PCR products is monitored in real-time using various platforms. SYBR green is a cyanine dye that binds to double stranded DNA and reports fluorescence which is observed in real-time. It is widely used due to its cost effectiveness and high sensitivity. Numerous chemistries such as TaqMan probes, molecular beacons, Scorpion primers, fluorescence resonance energy transfer (FRET) probes, primer probe energy transfer etc. are used for real-time PCRs. Real-time PCR offers several advantages over conventional PCRs as it provides quantitative data, reduces the risk of cross contamination, no post-PCR processing, reduced hands-on time, decreased turn-around time and offer high sensitivity and specificity. Real-time PCR in multiplex formats has created phenomenal improvements in molecular diagnosis of

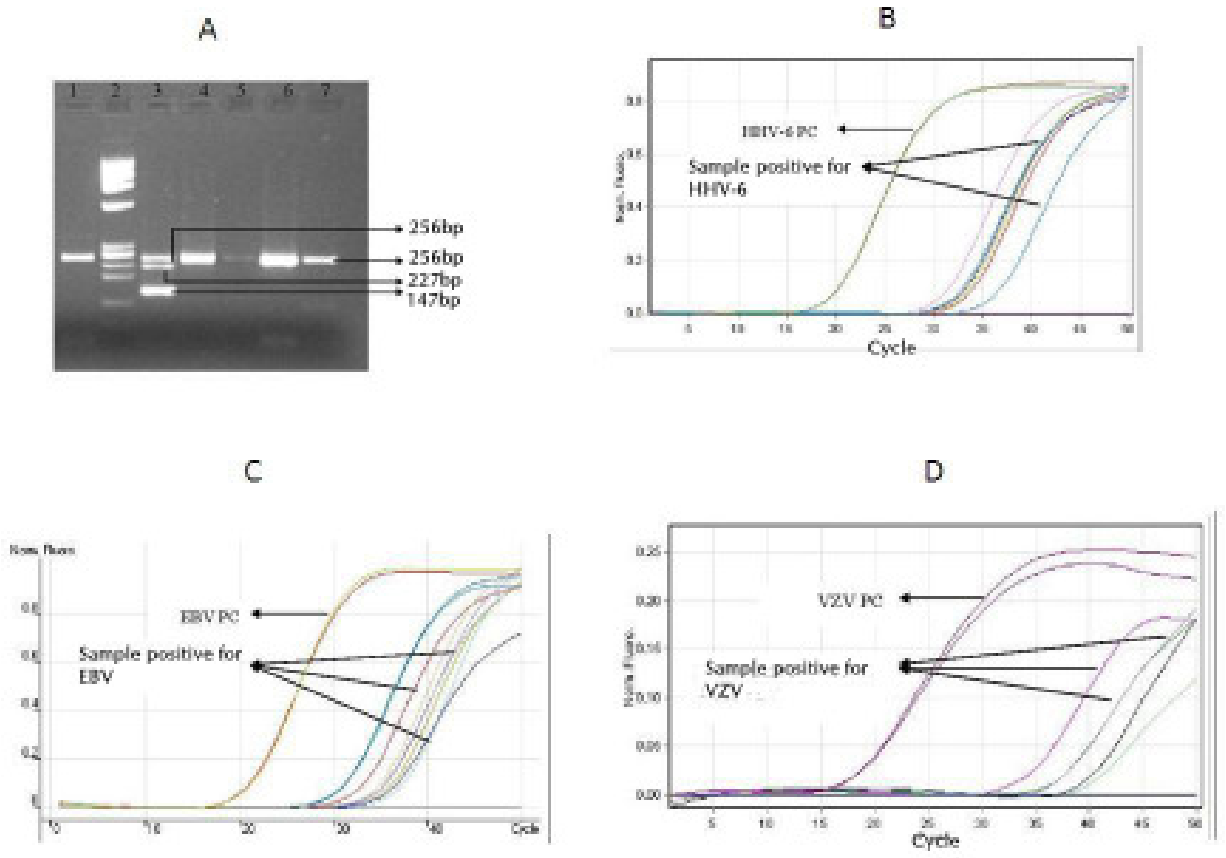

Fig 3: Molecular detection of neurotropic viruses

Panel A: A typical gel picture of Multiplex PCR. Lanes 1,4,5,6 and 7 show samples positive for CMV

Panel B: Amplification curve for HHV-6 positive control and patient sample positive for HHV-6. Probe was FAM-labeled.

Panel C: Amplification curve for EBV positive control and patient sample positive for EBV. Probe was ROX-labeled.

Panel D: Amplification curve for VZV positive control and patient sample positive for VZV. Probe was Cy5-labeled.

viruses. It has significant use for diagnosis of multiple viruses in CNS disease. [78] Real-time PCR (TaqMan) assay results have shown good correlation with CMV pp65 antigenemia assay. Real time PCRs are now being used for detection and quantification of CMV in bone marrow and SOT recipients.

Emergent technologies

The viral microarrays were introduced a few years ago.[79] Now there are numerous microarray methods for many viruses. However, it is based on the PCR assay and visualization of the PCR product with different methods.[80,81,82] Oligonucleotides or longer DNA-fragments are bound to the microarrays platform which aid in detection of viral nucleic acid of interest. The resulting PCR products are attached to oligonucleotides, and the specific hybridization is visualized either by using fluorescence or colorimetric reaction in an enzyme catalyzed substrate precipitation. Microarrays serve as a method for detection of multiple PCR products at one step with better sensitively. Moreover a very small amount of amplicon is sufficient while using microarrays since they have scanners or readers for better visualization of even a minimal fluorescence or color reactions.[80]

Isothermal amplification

Loop-mediated isothermal amplification (LAMP) is a simplified molecular technique and it is increasingly being used. The amplified template can be visualized using agarose gel electrophoresis. Turbidimetric analysis is performed at the end at 400 nm. Turbidimetry is relatively inexpensive compared to fluorometry used in real-time PCR. Other nucleic acid amplification techniques, including signal amplification techniques such as branched DNA, and hybrid capture among others, have limited applications.[74]

Nanotechnology

Nanotechnology for viral diagnostics is based on nanoscale reactions where the interaction of the bioreceptor with the analyte can be detected by a

Table 3: Herpesviruses shown to cause disseminated disease with CNS involvement in immunosuppressed host (HIV infected and post transplant recipients)

Predisposing condition	Neurological conditions and Therapy (intravenous) *					Ref.
	HSV	CMV	EBV	VZV	HHV6	
HIV disease	ACV	GCV valganciclovir	ACV	ACV	GCV, foscarnet	Allen et al. (2013); Meyding-Lamadé U and Strank (2012)
Renal transplant	ACV	GCV, valganciclovir, foscarnet	ACV	GCV, ACV	GCV, foscarnet	Cukuranovic J et al., 2012
Lung transplant	ACV	GCV, valganciclovir, foscarnet, cidofovir, and	ACV	GCV, valacyclovir, ACV	GCV, cidofovir, foscarnet	K Shiley - 2011
Liver transplant	ACV	GCV, valganciclovir, foscarnet, cidofovir, and	ACV	GCV valacyclovir, ACV	GCV, cidofovir, foscarnet	FA Romero and RR Razonable - 2011
Bone marrow transplant**	ACV, foscarnet, valacyclovir	GCV, valganciclovir, foscarnet, cidofovir	ACV GCV,	GCV, foscarnet, ACV	GCV, cidofovir, foscarnet	M Schmidt-Hieber et al. 2016; Solano et al. 2016

ACV- Aciclovir; GCV- Ganciclovir.

*Monotherapy, combination therapy or sequential therapy; **Pre-emptive therapy with acyclovir/valganciclovir

transducer. Bioreceptor plays a significant role in pathogen detection. They are specific as they have selective interaction with the analyte. Transducer converts the biorecognition event into measurable signals. Expertises from various fields like biochemistry and physics have led to the development of biosensors. Biosensors employed in nanotechnology are classified as electrochemical, optical and piezoelectric biosensors.[83] Electrochemical biosensors are used for diagnosis of viruses are sensitive and require simple instrumentation. Multiple nanodevices like carbon nanotubes, nanowire arrays, whispering-gallery mode (WGM) biosensors and quantum dots are under development for virus detection.[84] Molecular detection of neurotropic viruses is shown in Fig.3.

A TaqMan multiplex PCR was developed for identification of seven HHV and the products were hybridized through DNA Microarray for virus specific detection. The assay had a sensitivity of 96.2% and specificity of 99.3%, the technique is rapid, specific and sensitive for simultaneous detection of seven HHV.[85] The authors amplified HHV by multiplex PCR and genotyped by DNA microarray technique. The results were compared with TaqMan PCR kits of common herpes virus. The sensitivity of PCR-microarray technology was 91.7%, the specificity was 100%.[86]

The efficiency of detection of multiple pathogens has been achieved using Mass Tag PCR. In this technique numerous fluorochrome tagged primer and primer dimers pairs are used for amplification, separation of amplified products from unused primers is carried out by bead based technology before spectrophotometric analysis.[87] NGS was evaluated for detection of HHV-6 among encephalitis/ encephalopathy patients. The sensitivity was determined by comparison of NGS determined number of sequences of HHV6 with load measured by real-time PCR. The authors concluded that NGS is useful in detection of encephalitis/encephalopathy among pediatric patients.[88]

A study was carried out to improve EBV detection by using quantum dots in Fluorescent in situ hybridization detection, which was found to be efficient. Such techniques could be evaluated on CSF deposits smears for rapid detection of herpes viruses.

Insights from a few studies on neurological viruses

Multiple herpes viruses in individuals with neurological disease in the absence of HIV infection have been previously reported from South India.[89]

This study compared the real-time PCR and conventional multiplex PCR for detection of neurotropic viruses (CMV, HSV-1, HSV-2, EBV, VZV, and JCV) in CSF samples. Analysis showed that rate of positivity has been higher by using real time PCR [74(58.7%)] comparatively with conventional PCR [5(4%)] in patients with acute and chronic CNS disease.[89] New commercially available multiplex molecular (PCR based) diagnostic system - SES (Syndrome Evaluation System) have been evaluated for diagnosis of CNS infections by viral, bacterial and fungal pathogens. This system had 10 times higher detection rate than conventional tests with clinical specificity of 100% and sensitivity of 57.4%.[90] Primary central nervous system lymphoma (PCNSL) can occur in both immuno suppressed and immuno competent individuals. Retrospective study was done in immunocompetant individuals with PCNSL by immuno histochemistry and in-situ hybridization for EBV LMP-1 and EBV-Early RNA (EBER). This study reported that immuno competent individuals with PCNSL are not associated with EBV infection.[91] VZV was shown to be associated with neurological disease in HIV patients. A representative documentation of such reports is shown in table 3.

Infections with HSV, CMV and VZV viruses cause neurological disease with acute manifestations but CMV disease could be insidious with a tendency to become chronic. EBV infections manifest often as lymphoproliferative disease with prolonged immuno-suppression, often a couple of years after transplantation. The availability of molecular testing has greatly increased the efficiency of early diagnosis and allows for prompt antiviral therapy.

Therapy and Prevention of Herpes virus infections.

Therapy of Herpes virus infections

Several antiviral drugs are nucleoside analogues. These nucleoside analogues are acyclovir for HSV infections and lamivudine for HIV and hepatitis B virus infections.[92]

Ganciclovir is active against both HSV-1 and HSV-2; however, it is more toxic than acyclovir, valacyclovir, and famciclovir. Acyclovir and its antagonist famciclovir and valacyclovir have been used for mucocutaneous infections. Oral antiviral drugs for HSV infections are effective in controlling the infection to prevent recurrences. Acyclovir is now routinely given as prophylaxis for organ transplant recipients. Oral administration of ACV 400 mg three times per day is used as prophylaxis. Intravenous acyclovir (30

mg/kg per day, given as a 10-mg/kg infusion over 1 h at 8-h intervals) is given for 10 days to reduce the rates of death and morbidity. Higher doses of IV acyclovir are used for neonatal HSV infection (60 mg/kg per day in three divided doses). Mutations in the thymidine kinase (TK) gene of HSV are associated with resistance to acyclovir. In post transplant recipients with acyclovir drug resistance, IV- Foscarnet 80–120 mg/kg/day was used for two to three divided doses until healing is complete. A real-time PCR assay has been developed to quantitate the viral load for determination of antiviral susceptibility of HSV- 1.[93]

Prophylactic and pre-emptive treatments are the two principal approaches to prevent CMV infection in SOT patients. Other modalities of management include passive immunization, vaccination, prophylactic use of oral or IV Ganciclovir and oral Valaciclovir. Ganciclovir or valganciclovir therapy for CMV in post transplant recipients and in patients with CMV retinitis and colitis.[90] Therapy consists of a 14- to 21-days induction course (5 mg/kg IV twice daily for ganciclovir or 900 mg twice daily for valganciclovir). In immunosuppressed individuals with CMV infections IV ganciclovir, Foscarnet (60 mg/kg every 8 h for 2 weeks) or a combination of both are given.[94]

In Varicella and Zoster infections, acyclovir, valciclovir or famciclovir are recommended as therapeutic options. Acyclovir therapy (800 mg by orally five times daily for 5–7 days) is recommended for adolescents and adults with chickenpox of 24 h duration. Likewise, acyclovir therapy may be of benefit to children < 12 years of age if initiated early in the disease (< 24 h) at a dose of 20 mg/kg every 6 h.

Passive immunization like VZV immunoglobulin prevents varicella infection. As of date it is possible to prevent varicella infections and its complications by vaccination of children and adults especially those at considerable risk. Immunization is given to children, adults and close contacts prior to SOT. In EBV and HHV-6, antiviral like Ganciclovir, valciclovir, famciclovir and cidofovir acts in vitro which accounts for the clinical success in the treatment against these viral infections. It has been observed that there are similarities in the antiviral susceptibilities of HHV-6 and CMV.[95]

In the last fifteen years transplant surgeons and hematologists have started using pre-emptive therapy which to a substantial extent protects against reactivation of latent herpes viruses and disease production. In some cases, due to failure of prophylactic antivirals some breakthrough infections are detected which are quickly treated with second line of drugs. Such breakthrough infections are detectable only by close monitoring of patients using molecular testing for these viruses in appropriate samples. Clinicians often use virus load to know the disease progression. This is now the current practice in management of infections in post-transplant patients.

Prevention of Herpes virus infections

Majority of herpes virus infections occur in early childhood. These infections are mostly asymptomatic but prime the immune system thereby it is possible to demonstrate both antibodies and specific cellular immunity.[51]

Advances in molecular techniques have minimized the need for invasive procedures such as brain biopsy, and with effective antiviral therapies, have improved overall outcomes.

Most genital herpes is caused by HSV-2, although HSV-1 accounts for most of new cases in developed countries. Most genital HSV-2 infections are unrecognized and undiagnosed; infected individuals shed HSV and can infect sexual partners. Antiviral treatment of the infected partners is necessary. Condoms usage reduces the risk of sexual transmission of HSV-2.

In SOT and BMT recipients, CMV are opportunistic viral infection and this is associated with high morbidity and mortality rate. Blood from seronegative donors have been greatly decreases the rate of transfusion-associated transmission. Matching of organ or bone marrow transplants by CMV serology and organs from seronegative donors to seronegative recipients reduces rates of primary infection.

CMV Towne strain vaccine has by itself not proven efficacy to prevent CMV infection in previously unexposed individuals, so may not be useful even in pre-transplant patients. [148] In contrast, the live attenuated (Oka strain) VZV vaccine is efficacious against primary chickenpox and hence, could be considered as a prophylactic vaccination in children, adults and immunosuppressed patients to prevent neurological illness. The vaccine is contraindicated in highly immunosuppressed individuals.[96,97] Presently, there is a newly approved glycoprotein E based vaccine in a special adjuvant (AS01B) administered as two doses for VZV.[98]

CONCLUSION

Hospitalized patients with CNS disorder have high mortality and morbidity rate due to several viral

etiologies added on with other acute and chronic conditions. In India, CNS diseases like meningitis, aseptic meningitis, meningoencephalitis, ADEM, GBS and motor neuron disease cases are seen throughout the year. Neurologists in India routinely diagnose encephalitis due to HSV, based on clinical and laboratory findings and successfully treat with antivirals. The role of other viruses is not routinely investigated. In most hospitals in India, other than some national institutes or corporate hospitals, it is difficult to establish documentary evidence of viral infections. Molecular testing is restricted to a small percentage of specialized hospitals. Real-time PCR is one of the rapid, specific and sensitive to lower limit detection of virus. In post-transplant patients it plays a significant role in viral load detection, drug resistance and progress of the disease. The commonly used antiviral drugs for Herpesviridae infections include: acyclovir, gancyclovir, valcyclovir and foscarnet. In CNS infections intravenous preparations of the drug are preferred. To date it is possible to prevent VZV infections through vaccinations.

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MALIGNANCY IN A THYROGLOSSAL CYST- A RARITY

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ABSTRACT

Introduction: *Thyroglossal cyst is a cystic swelling that develops from remnant of thyroglossal tract.It is usually located in the midline of the neck. Carcinoma in thyroglossal cyst is extremely rare.*

Case *:We report a case of a 45 year old man diagnosed with papillary carcinoma in a thyroglossal cyst, that was successfully managed.*

Results: *Patient underwent excision of the thyroglossal cyst in toto and recovered completely.*

Key Words*: Papillary carcinoma of thyroid, Thyroglossal cyst, Thyroglossal tract.*

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INTRODUCTION

The thyroid gland develops from the thyroglossal tract that descends from Foramen Caecum in the tongue to its location below the thyroid cartilage superficial to the cervical trachea. Usually, thyroglossal tract disappears during the 5th-10th gestational weeks. Incomplete atrophy of thyroglossal tract or retained epithelial nests leads to the formation of thyroglossal cyst.[1]

Thyroglossal cyst is the most common congenital anomaly in development of thyroid gland. Carcinomas in thyroglossal cyst have been reported only in 1% of cases of thyroglossal cyst.[1] The median age of presentation is 40 years and most patients are asymptomatic.

CASE REPORT

A 45 year old male patient from West Bengal presented with complaints of swelling on the anterior aspect of the neck of one year duration. It was insidious in onset, progressively increasing in size. He did not have any complaints of pain or difficulty in swallowing.

Examination of neck showed a swelling measuring 1.5cm x 1.5cm in the midline which was mobile on deglutition and fixity on protrusion of tongue. Thyroid function tests were found to be normal. Ultrasound scan of neck showed well defined thin walled cyst in the midline below the larynx about 2.5x 2.5 cm and cysts in both lobes of thyroid measuring 2x1.3 cm in right lobe and 2.1x1.2 cm in left lobe of thyroid (Fig 1). Patient was counselled to undergo surgical excision of thyroglossal cyst under general anesthesia.

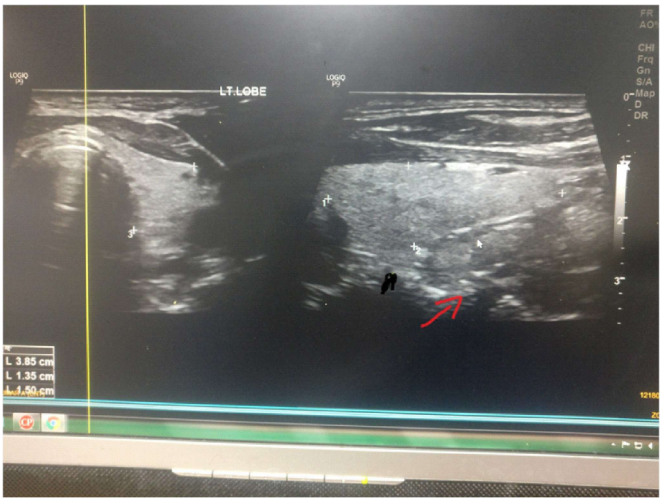

Fig 1: Arrow shows ultrasound picture of the cyst and the left lobe of thyroid.

SURGICAL PROCEDURE (SISTRUNK'S OPERATION)

Under General Anaesthesia, horizontal skin incision about 4 cm was made, over the swelling Strap muscles were dissected and retracted. The cyst was found underneath the strap muscles adherent to left sternohyoid muscle. The cyst was dissected from the surrounding muscle and tissue, 2x2 cm cyst was found adherent to the lower border of thyroid and cricoid cartilage. Perichondrium of cricoid was excised along with the cyst in toto (Fig 2).

Postoperative period was uneventful. Histo-pathological examination of excised specimen was

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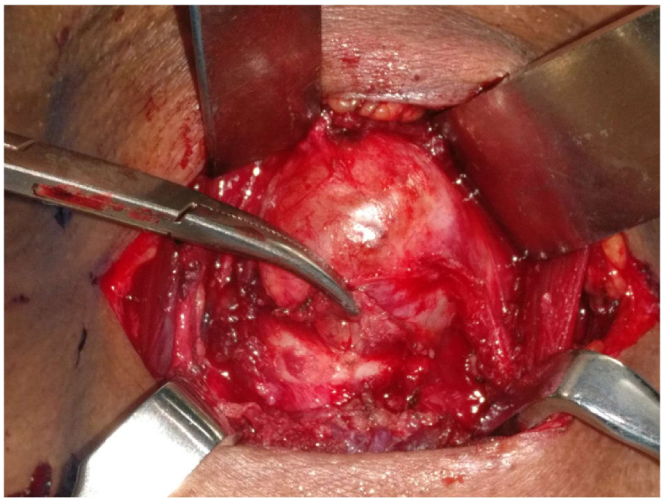

Fig 2: Intraoperative picture of cyst in midline of neck attached to perichondrium of cricoid cartilage.

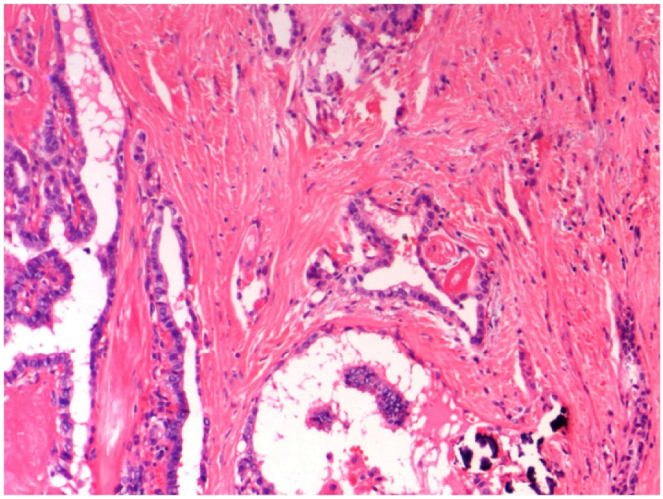

Fig 3: H&EX 100; Sections show tumour with papillary structures and calcification.

reported as papillary carcinoma of thyroid, within the thyroglossal cyst (Fig.3 & Fig.4).

DISCUSSION

Malignancy in thyroglossal cyst occurs only in 1% of patients diagnosed with thyroglossal cyst. It commonly occurs in younger adults with a median age of 13-15 years.

It is reported that Papillary carcinomas are commoner among the malignancies in thyroglossal cyst.[1,2,3] Diagnosis is usually made by histopathological examination postoperatively. Papillary carcinomas generally originate as either primary cancers in small remnants of ectopic thyroid or as metastases from primary cancers in thyroid gland.[2] Surgical excision is the treatment of choice. Opinion is divided about extent of surgical excision. There is no definite consensus on optimal treatment

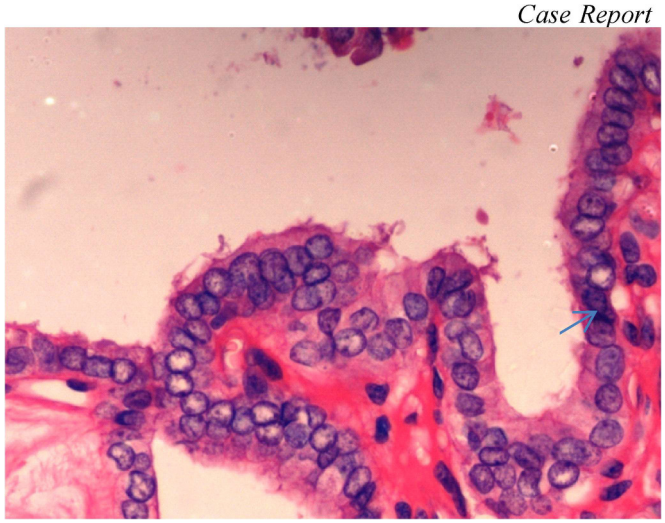

Fig 4: H&EX 400;Nuclear enlargement, overlapping empty looking nucleus (Orphan Annie Nucleus) and nucleus grooving in a papillae.

of papillary carcinomas in thyroglossal cyst between total thyroidectomy and long term follow up.[4,5]

Lymph node metastases in primary thyroglossal cyst cancers range from 7.7% to 12% which is lower when compared to papillary carcinoma of thyroid.[6] Thyroidectomy is preferred when the thyroid gland is nodular with cold nodule in the thyroid scan or when enlarged lymph nodes are present or when history of neck irradiation exists.[7]

CONCLUSION

Thyroglossal cyst in adult population should be initially evaluated by USG guided FNAC. When a diagnosis of thyroglossal papillary carcinoma is made, an evaluation of thyroid gland must be done during surgery. Long term follow up (up to 10 years) is recommended in order to detect early recurrences in thyroid gland or cervical lymph nodes.

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POST REHABILITATION CHANGES IN AN IRRADIATED MAXILLOFACIAL TUMOR DEFECT - A CASE REPORT

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ABSTRACT

Rehabilitation of irradiated maxillofacial patient requires meticulous care and constant follow up. The case becomes challenging once the effect of irradiation begins its implications within the oral cavity. This case report with a four year follow up shows series of changes observed in a patient who underwent subtotal maxillectomy and radiotherapy for tumor management.

Keywords: *Irradition induced caries, maxillectory, Xerostomia,*

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INTRODUCTION

Maxillofacial defects could be a consequence of congenital abnormalities, trauma or surgical resection of tumors. The principal goal of rehabilitation is to reduce the ailment and to enhance the quality of life for the patients.[1] The rehabilitation of defect should include restoration of function, speech and also esthetics to some extent. Prosthetic rehabilitation with an obturator prosthesis is a predictable intervention to reconstruct an anatomical barrier between the oral and nasal cavities.[2] Prosthetic interventions should start from the time of surgical resection and will be essential for the rest of the patient's life.[3,4] Rehabilitation of maxillofacial defects are challenging, as the factors that influence the predictable and definitive outcomes are many. The weight, gravity and extent of the defects determines the retention of the maxillary denture and also the prognosis of the abutments bearing the clasps. Moreover, the patients undergoing radiotherapy are predisposed to higher caries risk due to reduced salivary flow and hypoplasia of the tooth. This article shows the series of intraoral changes observed in a patient treated by subtotal maxillectomy and radiotherapy.

CASE REPORT

A 49 year old female patient was referred from Department of Oral Maxillofacial surgery, for fabrication of an obturator following subtotal maxillectomy of right maxilla. The surgical history stated that the patient was diagnosed for squamous cell carcinoma of the right maxillary region and treated by subtotal maxillectomy procedure followed by radiotherapy sparing salivary gland for a total period of 2 months. After completion of 2 weeks from the day of surgical procedure, the patient had reported for the fabrication of an interim obturator. On clinical examination, oro-nasal defect measuring 3cm x 2.5cm

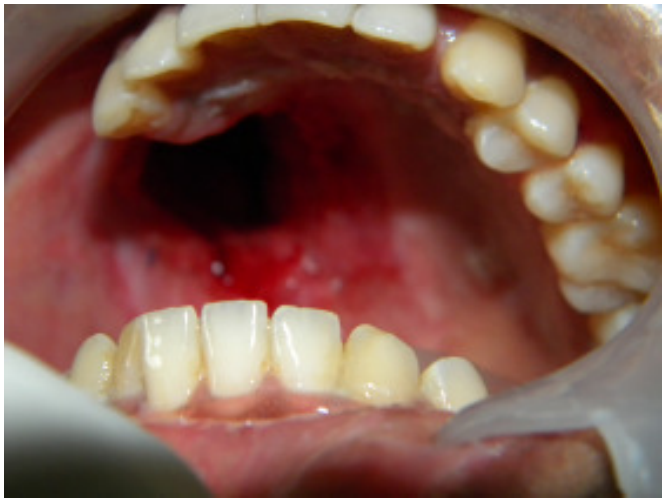

Fig.1: Post operative view of the oro-nasal defect of 3 cmx2.5 cm dimension at the second week of surgery.

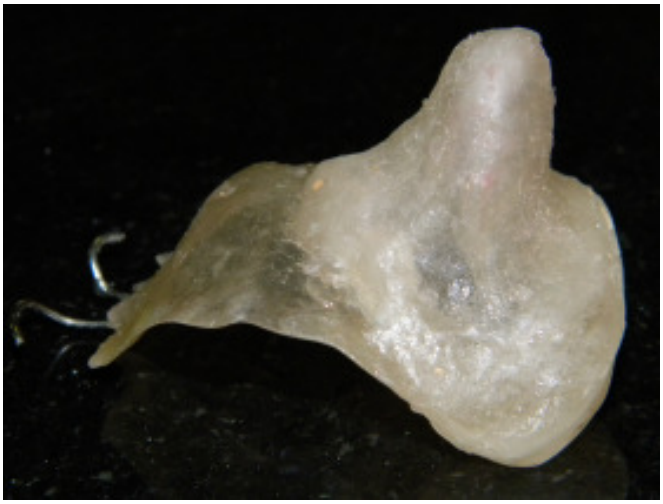

Fig 2a- Interim obturator with closed hollow bulb fabrication.

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(Fig.1) was noted. An interim obturator was fabricated to restore the defect and improve the quality of speech and mastication (Fig. 2a, 2b). Periodic follow up was done and the patient had a predictable healing. During a recall visit, six months following the surgical procedure, the oronasal defect had reduced to a dimension of 2.5cm x 1.5cm (Fig.3). The patient presented with signs of decreased salivary flow and hypoplastic changes in cervical aspects of the teeth. Patient was advised artificial salivary substitute to be

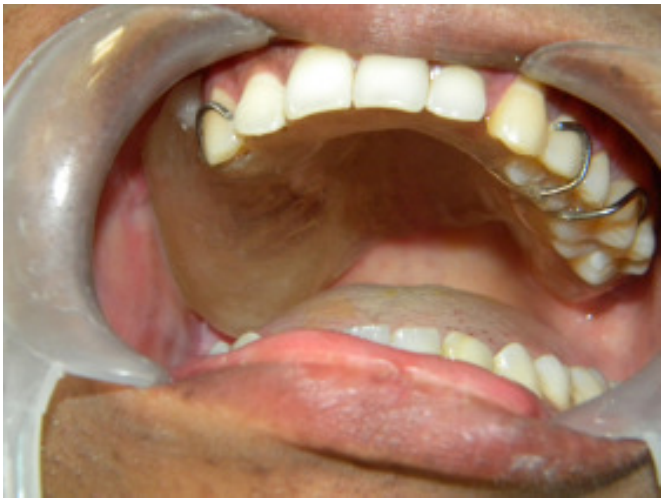

Fig.2b : Interim obturator placed intraorally in the maxillary arch

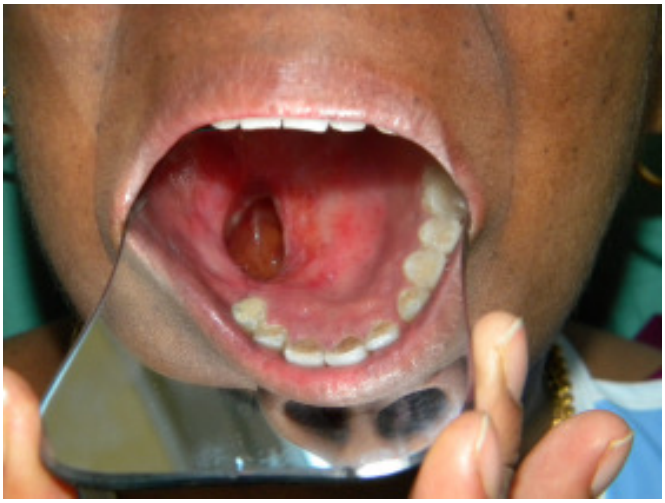

Fig.3 : Post operative view at the six month of surgery depicting oronasal defect reduced to a dimension of 2.5cm x 1.5cm.

sipped at regular intervals of time and rehabilitation plan was developed. Mouth preparation was done for a definitive obturator with rest seat prepared in 13,23,24,25,26 for receiving a conventional cast partial retained definitive obturator. Impressions were made for construction of the definitive obturator. The final prosthesis was delivered (Fig.4) and the patient was reviewed after 24 hrs, 1 week, 1 month, 3 months and

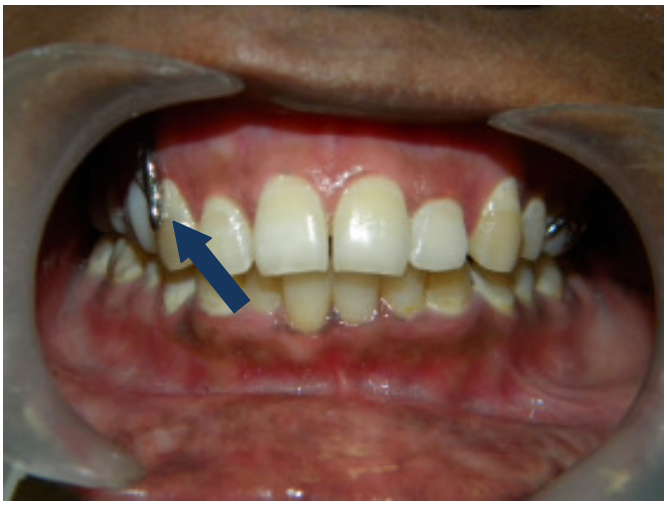

Fig.4: Definitive obturator inserted, signs of hypoplasia in cervical region of teeth

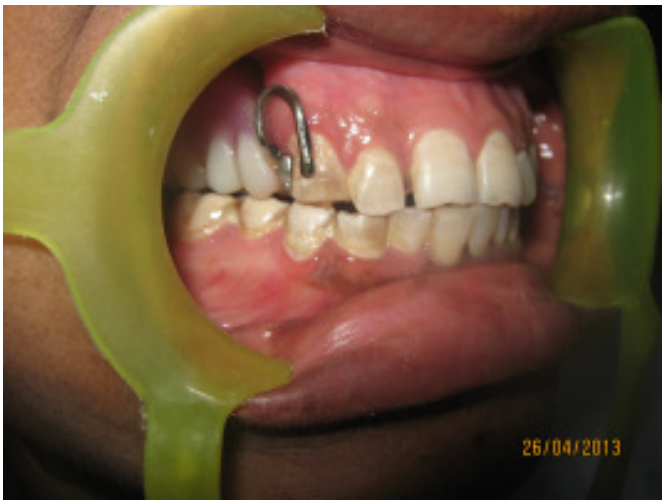

Fig 5 : Post operative view at the fourth year of surgery depicting generalized hypoplasia and wearing of tooth

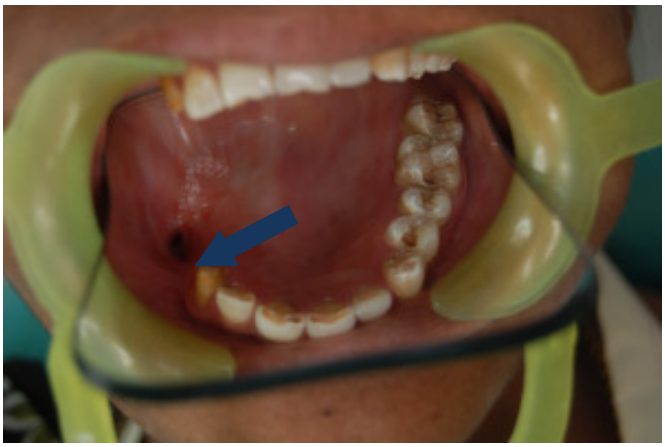

Fig 6 : Intra oral view of oronasal defect reduced to a dimension of 0.7cm x0.3cm

6 months from the day of the insertion of the final prosthesis. During the 24 hrs review, patient had pain in the oronasal defect region, for which the extensions of the prosthesis were adjusted. Patient was advised

to continue salivary substitute and was scheduled for regular recall visits. With an increase in the ease of using the prosthesis, the frequency of patient recall was reduced. After four years the patient reported with pain in the right maxillary canine and mentioned about the non-usage of the salivary substitute. On intraoral examination, patient had generalized hypoplasia of the teeth and wearing of tooth structures was evident especially on the cervical and incisal regions (Fig.5). Right maxillary canine was discolored with significant loss of tooth structure. Pulp vitality test revealed the non-vital state of 13. In addition, the oronasal defect had reduced to a dimension of 0.7cm x0.3cm (Fig.6). Patient was advised endodontic management of 13, followed by a full crown restoration. The patient was advised to stop using the obturator. Fluoride therapy was initiated with 1% neutral sodium gel applied daily in a mouth guard. Artificial salivary substitute was restarted. Patient was reinforced about the importance of periodic dental check-up with fluoride therapy and salivary substitute.

DISCUSSION

Management of maxillofacial defects of a patient is a multidisciplinary task and requires special attention. Irradiated patients are at amplified risk for the progression of widespread carious lesions owing to the reduced salivary flow.[5] The present case report showed the typical dental changes in an irradiated patient. There was a significant reduction of oronasal defect in 2 year follow-up. Radiation effect normally shows 30-70% decrease in tumor size.[6] In this present case, the defect was consolidated from 3 cm to 0.7cm at its greatest dimension. The constriction of the defect can be attributed to the radiation given at the early stage of the tumor management or due to the scaring of the oral tissues following irradiation. The patient was comfortable even without an obturator as there was no regurgitation problem.

Radiation caries was observed in our patient which is a late complication affecting the cervical and incisal edges of teeth, progress rapidly to involve the pulp if left untreated.[7] Initial lack of fluoride therapy had developed the present situation. Application of a 1% neutral sodium fluoride gel applied daily in custom trays was the promising solution to significantly reduce caries in irradiated patients [8] and the same was followed for our patient. Meticulous treatment plan and proper oral hygiene would ensure a much more predictable rehabilitation of a patient with maxillofacial defect following radiotherapy. Reinforcing the importance of periodic checkup has an indispensable and integral role in the improved quality of life of patients with maxillofacial defects.

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INCOMPLETE KAWASAKI DISEASE INDUCED BY MEASLES IN A 9-MONTH-OLD MALE INFANT -A CASE REPORT

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ABSTRACT

Kawasaki disease (KD) is an acute systemic vasculitis occurring mainly in early childhood. This disease presents as persistent fever, bilateral nonexudative conjunctivitis, polymorphous rash, oral mucosal changes, cervical lymphadenopathy, erythematous induration of the extremities, and even coronary artery aneurysms. Although the etiology of Kawasaki Disease remains unknown, it is currently believed that one or more as yet unidentified infectious agents induce an intense inflammatory hostresponse in genetically susceptible individuals. Approximately 20 to 25% of untreated children develop coronary artery abnormalities , whereas < 5% of children treated with Intra Venous Immunoglobulin develop Coronary artery aneurysm. In this case report, we present a 9-month old male infant who had incomplete Kawasaki Disease with measles.

***Key words**: Aspirin, coronary artery aneurysm, criteria,, infectious agent, Kawasaki disease, measles.*

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INTRODUCTION

Kawasaki Disease, formerly known as mucocutaneous lymphnode syndrome and infantile poly arteritis nodosa, is an acute febrile illness of childhood seen worldwide with the highest incidence occurring in Asian children. Kawasaki Disease is a medium vessel vasculitis with a predilection for coronary arteries. The cause of Kawasaki Disease remains unknown, but certain epidemiologic and clinical features support an infectious origin. These features include the young age group affected, epidemics with wave - like geographic spread of illness, the self - limited nature of the acute febrile illness, and the clinical features of fever, rash, enanthem, conjunctival injection and cervical lymphadenopathy. Further evidence of an infectious trigger includes the infrequent occurrence of the illness in infants younger than 3 months , likely the result of maternal antibodies, and the rarity of cases in adults. Approximately 20 to 25% of untreated children develop coronary artery abnormalities, whereas < 5% of children treated with Intravenous Immunoglobulin[2] develop Coronary artery aneurysm.[1] The clinical and laboratory criteria for Kawasaki Disease aids in early diagnosis, which is the key to successful treatment and reduction in morbidity and mortality.

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CASE REPORT

A 9 month old male child presented with the complaints of fever with rash for 3 days, vomiting and loose stools for 2 days. Fever was high grade, not associated with chills and rigor. There were no aggravating factors and the fever was relieved with oral antipyretics. Initially rashes started on forehead, progressed to all parts of body in a span of 3 days. There was a history of cough and cold with watering of eyes since 2 days. There was history of loose stools since 2 days, watery, non mucoid and not blood stained. Urine output was adequate. Child was not vaccinated for measles. On admission, his vitals were stable, axillary temperature was 101°F. Physical examination revealed Exanthematous rash on day 2 of admission initially on forehead, later generalised all over the body. Systemic examination was normal. Laboratory studies exhibited elevated total count with polymorphonuclear predominance. Platelet count was normal and ESR was high. In view of suspected measles, child was managed with oral Vitamin A for 4 days [2,00,000 IU]. As fever was persistent for more than 5 days, counts were repeated and cultures were sent, started on intravenous Ceftriaxone. ECHO was done to determine cardiac involvement as Kawasaki disease was suspected. ECHO done showed dilated left main coronary artery and left anterior descending artery which was suggestive of Kawasaki Disease. In view of strong clinical suspicion of Kawasaki Disease, child was given Intravascular Immunoglobulin (2g/kg) and started on high dose (80 to 100mg/kg) of aspirin. High dose of aspirin was continued till fever subsided and later changed to low dose (5mg/kg). Lab

investigations for other causes of fever with rash were negative.

Loose stools was managed conservatively. As both blood and urine cultures were sterile, antibiotics were stopped. Measles IgM was positive and child was managed conservatively. As child was afebrile for more than 72 hours, he was discharged . During follow up child was continued on low dose aspirin and repeat ECHO done showed persistent dilatation of left main coronary artery.

DISCUSSION

The 2004 American Heart Association criteria are the most commonly used guidelines for the diagnosis of Kawasaki Disease, which include fever for at least 5 days and four or more of the following five major clinical features: conjunctival injection, cervical lymphadeno-pathy, oral mucosal changes, polymorphous eruption, and swelling or redness of the extremities.[3] Incomplete Kawasaki Disease refers to patients who have some but not all of the clinical features of Kawasaki Disease. It is more common in children younger than 1 year and indicates a paradoxically higher hazard of coronary abnormalities. Diagnosis of incomplete Kawasaki Disease depends on a high level of suspicion in children presenting with some of the Kawasaki Disease features, evidence of systemic inflammation, and echocardiographic findings of coronary artery abnormalities.

In the present report, we encountered a 9-month-old male infant who had persistent fever with high white blood cell count and erythrocyte sedimentation rate. More importantly, echocardiography showed mild dilatation in the left coronary arteries.Therefore, the diagnosis of incomplete Kawasaki Disease in our patient was made. Although the etiology of Kawasaki Disease remains obscure, an infectious agent is strongly suspected based on clinical and epidemiologic features.[2] Host immune responses such as immune complex-mediated injury, cytotoxic T-cell-mediated immune responses, and autoimmune reactions are speculated to play a crucial role in the onset of Kawasaki Disease in our patient with measles infection. Similarly, an earlier report mentioned a measles virus isolated from a child with Kawasaki Disease a few weeks after measles vaccination.[4] A selective prolonged T-cell unresponsiveness to activation via the T-cell antigen receptor CD3 has been observed in patients with Kawasaki Disease which may lead to an incomplete responsiveness to measles vaccination.[5] Intravenous Immunoglobulin combined with high-dose aspirin is the first choice for suppressing ongoing systemic inflammation in the acute stage of Kawasaki Disease. However, initial Intravenous Immunoglobulin resistance occurs in up to 20% of cases.[6]

The incidence of Kawasaki disease is greatest in children who live in Asia. Kawasaki Disease is particularly difficult to diagnose in areas where measles is still prevalent since the presentation is similar.

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UNICORN FINDING IN OVARIAN TERATOMA

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ABSTRACT

Unilateral ovarian benign mature cystic teratoma is very common lesion but the classical histological finding of a granulomatous inflammation within a teratoma is very rare. To our knowledge, this finding is unicorn among the cases of mature cystic teratoma. A 24 year old female was admitted with bilateral flank pain and abdominal distension. All baseline investigations were done. All biochemical markers were normal except for CA125 which was found to be 233.5. Mantoux test was done and found to be positive. A right salpingo-oophorectomy with frozen section was done, which revealed mature cystic teratoma with granulomatous inflammation and Langhans giant cells. Post operatively patient was started on anti tubercular therapy and the patient is doing well.

Key words: *Granuloma, ovarian, teratoma, tuberculosis.*

SRJM 2017;10:34-37

INTRODUCTION

Ovarian teratomas,being the most common germ cell neoplasm, is composed of different histologic components, derived from all germ cell layers. The origin of teratomas is primordial germ cell. They are divided into three main groups: immature teratoma, mature teratoma, and monodermal specialized teratoma. Unilateral ovarian benign cystic teratoma is very common but a classical histological finding of a tuberculous granulomatous inflammation within a teratoma is very rare. Tuberculosis, caused by Mycobacterium tuberculosis, with its characteristic granulomas are rarely seen in ovarian teratomas.

CASE DESCRIPTION

A 24 year old,married woman presented with complaints of bilateral flank pain since pregnancy, not relieved by medications and abdominal distension for the last one month. History of loss of appetite and loss of weight were noted. Her menstrual cycles were normal. CECT abdomen done showed mass in right adnexa, gross ascites, retroperitoneal lymph nodes enlarged, mild bilateral pleural effusion and partial right Pelviureteric junction obstruction.

On systemic examination, her vitals were normal. There was a lower abdominal distension with a mass corresponding to 20 weeks. Mantoux test was positive with skin induration of 1.8 cm.Biochemical investigation showed increased levels of CA125 and CA19.9. Cytology of ascitic fluid was negative for malignancy. Ultrasound thorax revealed bilateral minimal pleural effusion, right more than left. Ultrasound abdomen showed features suggestive of immature malignant teratoma right ovary. There was free fluid in hepatorenal and splenorenal pelvis, uterus measured 7.6x3.9x4.2 cm, endometrial thickness was 6.2 mm and adnexal mass measured 4.6x4.1 cm, Heterogenous mass lesion with solid and cystic components showing calcifications and hyperechoic foci seen in right adnexa with mild hepatosplenomegaly (Fig.1) Right mild hydroureteronephrosis and moderate ascites was also noted. Laparotomy with right salpingo-oophorectomy was done and right ovarian mass was submitted for frozen and routine histopathological examination. Gross examination of the right tubo ovarian mass measured 7x3x6cm and weighed 220 grams. External surface of the ovary was smooth. However cut surface of the ovary exuded pultaceous material, tuft of hair was

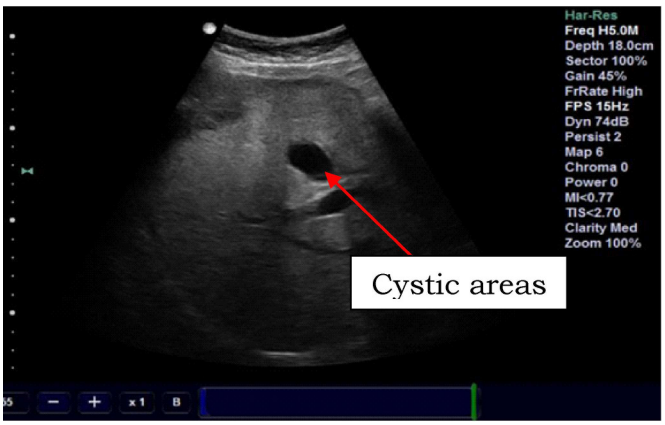

Fig.1: Ultrasound abdomen showing cystic ovary

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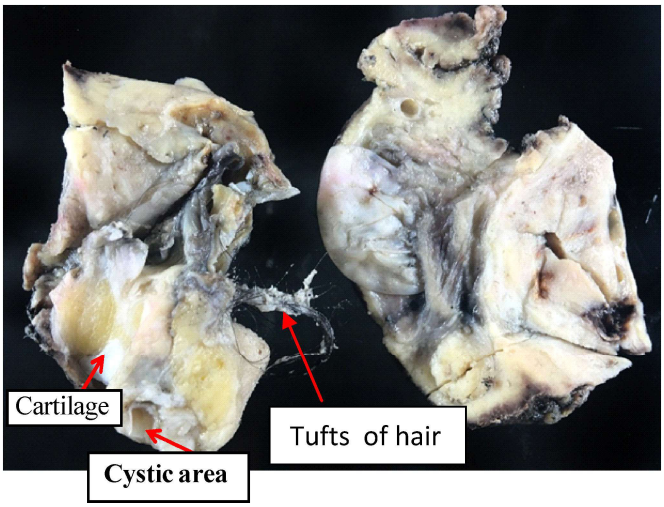

Fig.2: Gross appearance of the ovary showing pultaceous material and tufts of hair.

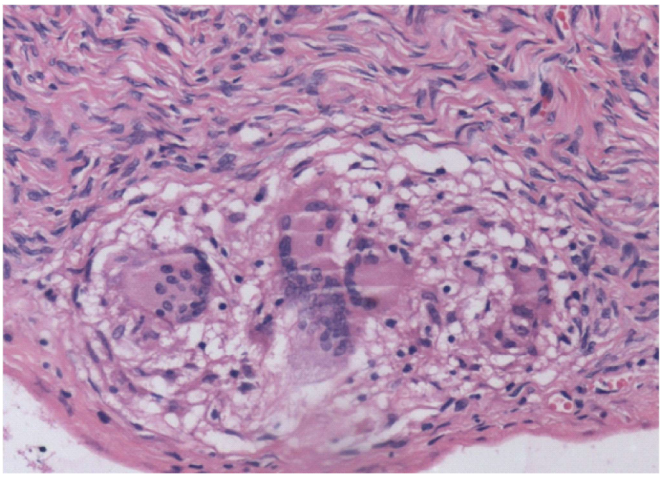

Fig.3: Epithelioid granuloma with Langhans type of giant cells in ovarian stroma.(Hematoxylin and eosin staining X100).

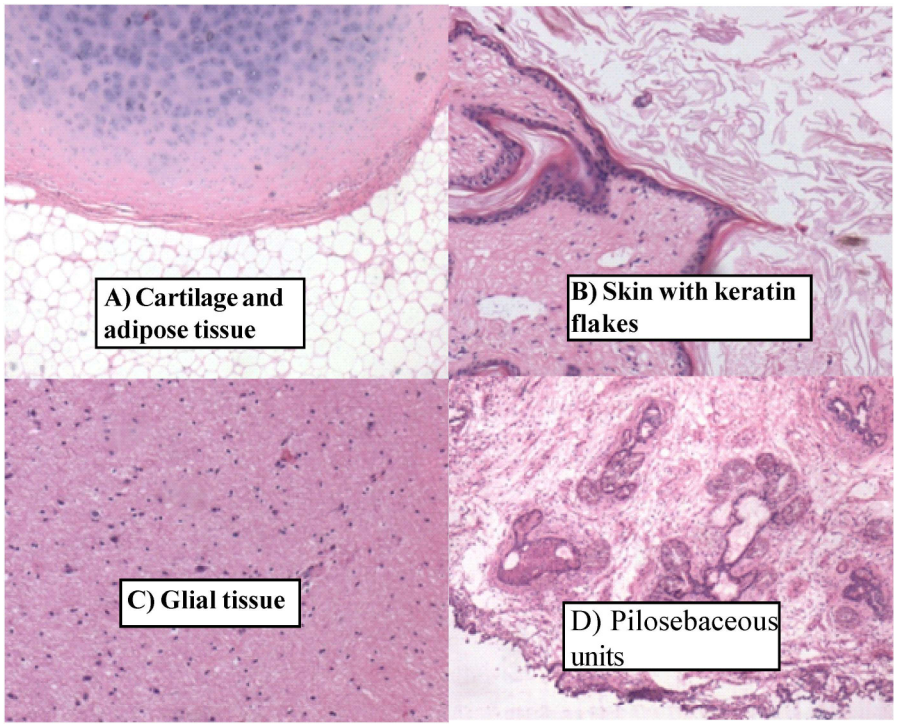

Fig. 4: Components of a mature cystic teratoma
A) Cartilage and adipose tissue H& E X100
B) Skin with keratin flakes H & E X100
C) Glial tissue H & E X100
D) Pilosebaceous unit H&E X100 (H & E: Hematoxylin & Eosin)

present along with a tooth (Fig.2). Focal gray white gritty areas were also noted. Frozen sections and routine histopathology revealed a mature cystic teratoma and granulomatous inflammation and Langhans type of giant cells (Fig.3). Ovarian tissue showed mature squamous epithelium, keratin flakes, cartilage and mature glial tissue (Fig.4). Ovary and tubes also showed multiple necrotizing epithelioid granulomas with Langhans type of giant cells. Special stain for AFB was negative.

DISCUSSION

"Teratoma" is derived from Greek word "teraton" meaning monster and the term "dermoid cyst" was coined by Leblanc in 1831.[1,2] Teratomas are often composed of multiple embryological layers and are classified as either mature or immature types.[3] Mature

cystic teratoma are the most common type, accounting for approximately 10-20% of the total cases of ovarian tumors.[4]

Ultrasonography and tumor markers, such as CA125, CA19-9 and alpha-fetoprotein, are common tools used for the early detection and characterization of ovarian masses, such as mature or immature teratomas. Among the above mentioned tumor markers, serum CA19-9 is the most reliable biomarker of ovarian mature cystic teratomas, higher levels of serum CA19-9 correlates with larger tumor size.[5] However the diagnostic values of CA19-9 in patients with mature cystic tumors is low when used alone.

Serum CA125 is still used to distinguish between benign and malignant pelvic masses but it can also be seen elevated in many benign conditions such as pelvic inflammatory disease, and indeed tuberculosis and decreasing levels of CA-125 correlates with the resolution of the disease on antituberculous treatment. Serial measurements should be used to determine treatment efficacy.[5]

Genito-urinary tuberculosis is the second most frequent location for extra-pulmonary tuberculosis, most common being the lymphatic system. The ovaries were involved in 62.5% of cases in one study.[6]

In our case, the tissue combination of mature cystic teratoma with a ovarian tuberculosis is less common, so histological examination of granulomas with Langhan's type giant cell, in which nuclei of the macrophages are arranged in the periphery in the form of horseshoe or ring at two poles of the giant cell should be differentiated from foreign body giant cells which contains numerous nuclei (up to 100) of macrophages scattered throughout the cytoplasm in frozen sections is of great importance to conclusively establish the diagnosis and to prevent performing more extensive surgery with the misleaded information regarding laboratory titre. Imaging has low specificity, with both an ovarian malignancy and tuberculous abscess having similar appearance on ultrasound, computerized tomography, and magnetic resonance imaging.[7] Ascites and lymphadenopathy are both frequently present, further confusing the diagnosis. Laparoscopy is very useful as it allows the diagnosis of tuberculosis in more than 97% of cases thus avoiding laparotomy.[8] Nevertheless, in cases with high suspicion of malignancy, laparotomy is often the first choice to avoid tumor seeding along port tracts. However, even at open operation, it may be difficult to distinguish between the two diagnoses, as the macroscopic appearance of pelvic tuberculosis can be similar to the carcinomatosis of extraovarian carcinoma.[9] Pre-operative tests which may aid the diagnosis include a positive Mantoux (tuberculin) test, and staining for acid-fast bacilli in either ascitic or pleural fluid. However, these can be negative despite extensive disease. Treatment for genital TB is mostly medical with multi drug therapy with adequate doses and duration.[10] The national programme of TB control recommends a regime of eight months treatment, with quadruple therapy (rifampicin, isoniazid, ethambutol, pyrazinamide) for the first two months, followed by 6 months of isoniazid and thiacetazone.[11] But in case of female genital tuberculosis short course chemotherapy for 6-9 months is effective.Other treatment options are surgery and improved BCG vaccines.

CONCLUSION

This case has been reported for its vivid presentation Ovarian tuberculosis can mimic that of an ovarian malignancy so familiarity and correlation of various laboratory, imaging and histopathological findings, are crucial for the accurate diagnosis and appropriate treatment

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AN UNUSUAL PRESENTATION OF AN OCCULT MYXOPAPILLARY EPENDYMOMA - A CASE REPORT

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ABSTRACT

The following case study focuses on a 33-year-old man afflicted with a myxopapillary ependymoma, a slow growing glial cell tumor. The patient had an uncommon presentation of the tumour involving a burning sensation and weakness of lower extremities hence requiring radiological diagnosis. A lesion was identified at the level of S4 to L2 and was subsequently removed via a laminectomy. Despite initial diagnostic challenges, the final diagnosis of myxopapillary ependymoma among many other differentials was discerned through the use of immunohistochemistry. Further management was plotted accordingly and the patient made a prompt recovery.

Keywords: *Myxopapillary Ependymoma, Laminectomy, Immunohistochemistry*

SRJM 2017;10:38-41

INTRODUCTION

Ependymomas are a broad category of glial tumours that originate from the ependymal cells within the CNS. Spinal ependymomas are a variant of the aforementioned. Myxopapillary ependymomas are a biologically and morphologically distinct form of spinal ependymoma and it predominantly manifests in the region of the cauda equina.[1] They are slow growing tumours of the WHO grade 1 category and are usually benign in nature.[2] However, despite the deceivingly harmless nature of the tumor they can be responsible for a progressive neurological deficit thus acting as a source of significant comorbidity in patients.

Myxopapillary ependymomas are an exceedingly rare group of tumors that commonly presents itself as pain in the back or the rectal area. They are often diagnosed during the third decade of life and have a predisposition to affect men belonging to younger age groups.[2]

The following is a case of a middle-aged male patient with a burning pain in his right leg caused by myxopapillary ependymoma. This case report aims to reiterate the symptomatology, diagnosis and management of this disease.

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CASE HISTORY

A 33-year-old male presented himself at the OPD with complaints of a burning sensation over the posterior aspect of the right thigh and right lower leg for over 6 months. The patient had earlier been diagnosed by a private practitioner as a case of meralgia paresthetica for which he was treated with analgesics, however he experienced no relief in symptoms, prompting him to seek further medical attention. On physical examination the patient was found to have right lower limb wasting and the spine showed exaggerated lordosis at the lumbar level. No

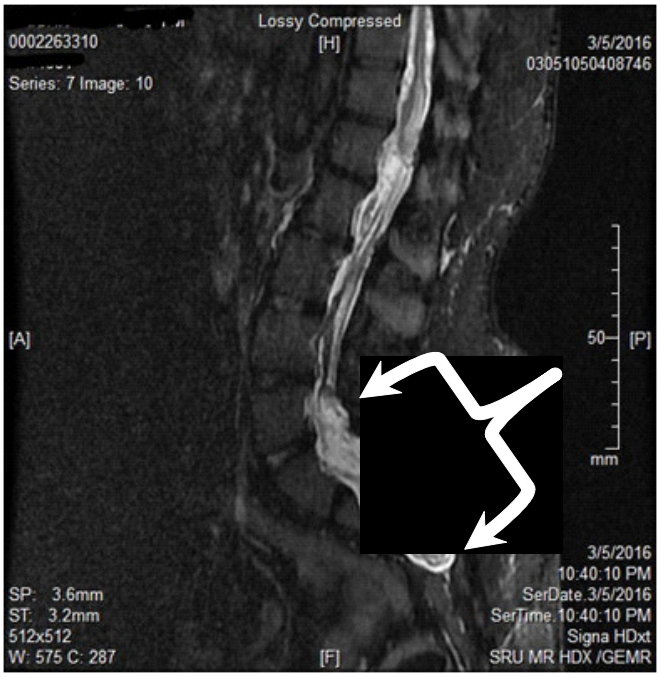

Fig. 1: MRI revealing intradural lesion at level of S4 to L2

obvious signs pertaining to any specific disease were elicited, thus inducing the need for further of investigations.

Radiological Examination

On radiological investigation, the MRI of the lumbosacral spine revealed a well defined heterogeneously enhancing mass lesion of size 2.3 x 9.9 x 3.5 cm extending from L4 to S1-S2 occupying the cauda equina (Fig. 1). S1 and S2 regions were almost completely replaced.

Intervention and Management

Partial surgical excision and decompression of the intradural lesion was done under general anesthesia. The excised lesion was sent for histopathological examination.

The patient was clinically stable post-surgery and he continued to rapidly improve and recuperate with the help of adjuvant physiotherapy. He was advised to repeat an MRI scan every 6 months to check for recurring growth.

Pathological Findings

Grossly multiple soft tissue bits aggregating to 3x2x0.8 cm in size were received.

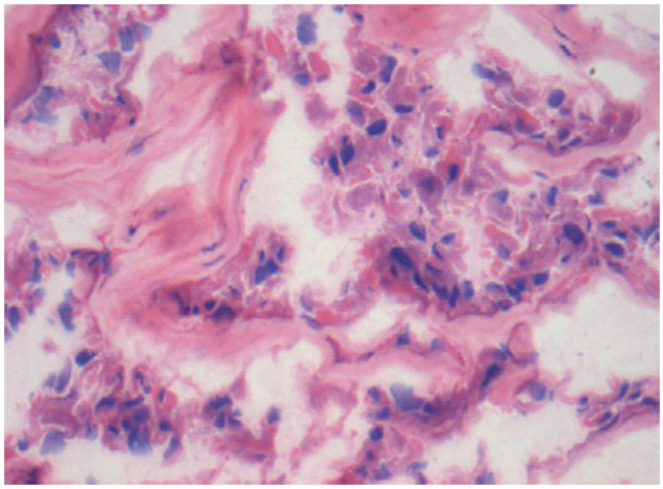

Fig. 2: Histopathological section-Cords of monotonous cells in a myxoid matrix;400x

Frozen report opinion was deferred with different diagnostic possibilities suggesting metastasis, myxopapillary ependymoma and chordoma. Immunohistochemistry was advised for further categorization.

Histopathological examination of permanent section revealed cords and nests of polygonal tumour cells with focal areas showing spindling of cells . The cells show moderate cytoplasm and mild nuclear atypia. Intervening areas surrounding the tumour cells contain amorphous loose filaments and myxoid material. There was no evidence of necrosis or mitosis seen in the sections examined. Typical papillary architecture was absent in the present case (Fig.2).

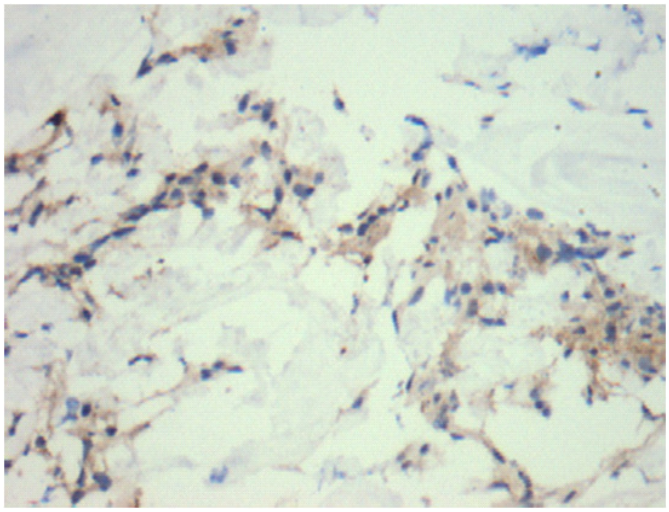

Fig. 3: Immunohistochemistry S100- Tumour cells show cytoplasmic positivity;400x

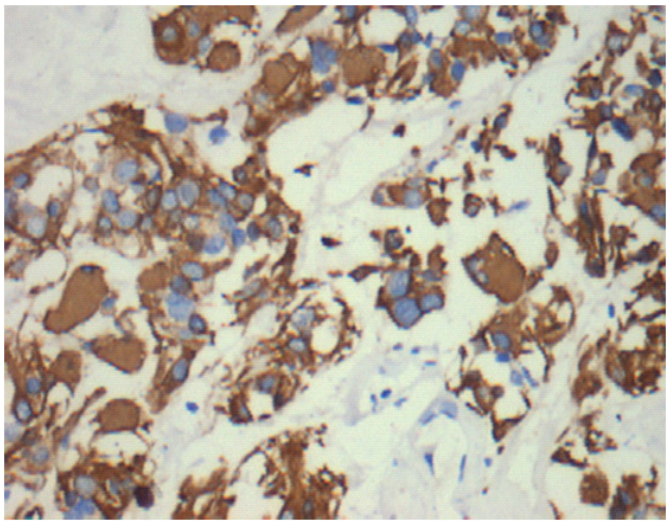

Fig. 4: Immunohistochemistry GFAP- Tumour cells show cytoplasmic positivity for GFAP;400x

By IHC the tumor cells were positive for Glial fibrillary acidic protein (GFAP) (Fig.4) and S100 (focal) (Fig.3). Epithelial Membrane Antigen (EMA) was negative hence ruling out chordoma and the remote possibility of a metastatic lesion. Ki-67 LI was $<1\%$ indicating the low proliferation rate in the tumour cells (Fig.C).

Final Diagnosis

The lesion was hence confirmed as myxopapillary ependymoma.

DISCUSSION

Ependymomas are slow growing glial tumors that grow along the fluid filled spaces within the ventricles

of the brain and the centre of the spinal cord. The myxopapillary variant of the same is characterized by the arrangement of the glial cells in a papillary pattern around vascularized myxoid cores. However some examples show little or no papillary structuring and consist largely of confluent, polygonal tumor cells or fascicles of spindled cells, as seen in the present case. Incidence of myxopapillary ependymoma is very rare and constitute only 1.9% of all primary CNS tumors. The extreme rarity and paucity of research on the same makes it difficult to establish any major predispositions to the tumor. Although, it has been evidenced that there is a small predisposition towards males in the second or third decade of their lives.[3] In addition, the rarity of the disease makes it difficult to associate any characteristic clinical presentation with it. As a result, the pressing complaints of the lesion appear innocuous and can easily be neglected by both the patient and the medical practitioner 4 — as substantiated by the earlier misdiagnosis and delay in the treatment of the case. The most obvious and common complaint presented in a case of a myxopapillary ependymoma is lower back pain.[4] Other symptoms include numbness of lower extremities, bladder abnormalities and impotence. However, in this case, the patient only complained of a burning sensation and weakness in his lower extremities hence proving that the disease does not have any hallmark set of clinical features. Clinical examination may sometimes reveal sensory changes, motor deficits and muscle atrophy of the limbs.[5] Although, these findings are relatively uncommon. A formal diagnosis can never be made on the basis of history taking and examination alone, thus necessitating the need for radiological diagnosis, histopathological examination and immunohistochemistry. MRI is the most efficient radiologic diagnostic modality for myxopapillary ependymomas and typically demonstrates an intradural mass. The role of immunohistochemistry is also indispensable in the case of a myxopapillary ependymoma as it is crucial in confirming the final diagnosis by ruling out its many differentials which include metastasis, chordoid meningiomas, chondromas and chordomas- each of which have similar presenting features but varying treatment modalities and outcomes.[6] The treatment for myxopapillary ependymoma usually just involves surgical resection and may sometimes also include adjuvant radiotherapy. However, the role of radiotherapy in myxopapillary ependymoma is controversial considering its adverse effects as well as the lack of empirical evidence proving any of its supposed benefits.[3] Postoperative outcomes are generally favourable with a good ten year survival rate and minimal incidents of recurrence.[7] However, few incidents of damage to the surrounding tissues during the process of tumor resection take place and this can cause neurological deterioration in the patient.

CONCLUSION

Myxopapillary ependymoma- despite its rarity- is indeed a substantial possibility. The symptoms associated with the disease such as the back pain and radicular pain ought to be monitored as signs stemming from a progressive neurological deficit however rare a diagnosis of myxopapillary ependymoma may be. This case emphasizes on the importance of thorough neurological examinations accompanied by concise radiological and histopathological diagnosis along with immuno-histochemistry.

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DNET- A CURABLE SEIZURE-A CASE REPORT

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ABSTRACT

Dysembryoplastic Neuroepithelial Tumors (DNET) are a group of uncommon slow growing benign tumor of the brain accounting to 0.6% of diagnosed CNS tumors. These tumors comprise of the glial and neural cells and arise from either the cortical or deep grey matter. DNETs are mainly characterized by recurrent episodes of chronic seizures, usually in childhood. Grossly, multinodular cortical lesion is observed, which is soft and gelatinous. Hallmarks of this lesion are glioneuronal cells with intervening floating neurons. Anaplastic transformation is rare.

A 17-year-old female presented with recurrent history of chronic seizures going six months back. Radiological examination showed a bubbly nodular lesion in the right temporal part of the cerebrum which was pseudo cystic in appearance. There was no edema. Right frontotemporal craniotomy was done to excise the tumor.

*Gross pathology examination showed multiple grey white soft tissue bits which were about 3*2*1 cm in aggregate. Microscopically, oligodendroglioma-like cells in a mucin-rich background were observed with scattered astrocytes. There was no mitosis or necrosis present.*

Differential diagnosis includes ganglioglioma, oligodendroglioma, pilocytic astrocytoma, rosette forming glioneuronal tumor. The patient was recovering well with no further episodes of seizures. The patient was advised for follow up every six months.

Keywords: *DNET, chronic seizures, benign tumors.*

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INTRODUCTION

A good history taking and a reasonable degree of clinical suspicion are the basis of a good doctor. This was put to test when a young patient came with complaints which led to a diagnosis, atypical to the normal history of the disease.

Dysembryoplastic Neuroepithelial tumor (DNET), is an uncommon slow growing benign tumor (WHO Grade 1) of the brain accounting to 0.6% of diagnosed CNS tumors.[1-3] These tumors comprise of the glial and neuronal cells and arise from either the cortical or deep grey matter.[3] Multiple episodes of seizures are the chief characteristic features of DNETs, which are usually childhood in occurrence.[2, 3] Surgical removal of these tumors can prevent further episodes of seizures.[1-2, 4-5] While the clinical features may seem aggressive, anaplastic transformation is rare.[6]

CASE HISTORY

A 17-year-old female was cleaning her house when she suddenly developed tonic posturing in her upper limbs and was subsequently admitted to the hospital by her father. During investigation, it was found that she had similar complaints which were milder in nature, dating six months back. Tests were then done to find the cause of the seizures.

Radiological examination showed a bubbly nodular lesion in the right temporal part of the cerebrum which was pseudo cystic in appearance. There was no peritumoral edema. (Fig.1 & 2)

Surgical excision: Right frontotemporal craniotomy was done, and the tumor was completely excised.

Gross pathology showed multiple grey white soft tissue bits which were about 3x2x1 cm in aggregate. Microscopically, oligodendrocyte-like cells aligned in columnar fashion along bundled axons and separated by a myxoid matrix background in which were observed scattered astrocytes. (Fig.3 & 4) There was no evidence of mitosis, necrosis or complex microvascular proliferation.

Differential diagnosis considered includes ganglioglioma, oligodendroglioma, pilocytic astrocytoma, rosette forming glioneuronal tumor.

By immunohistochemistry, tumor cells are positive forchromogranin (Fig.5 & 6); negative for Vimentin, GFAP, Synaptophysin and EMA. Ki67 labelling index was $<1\%$.

Final diagnosis: After careful evaluation, a diagnosis of Dysembryoplastic Neuroepithelial tumor was made.

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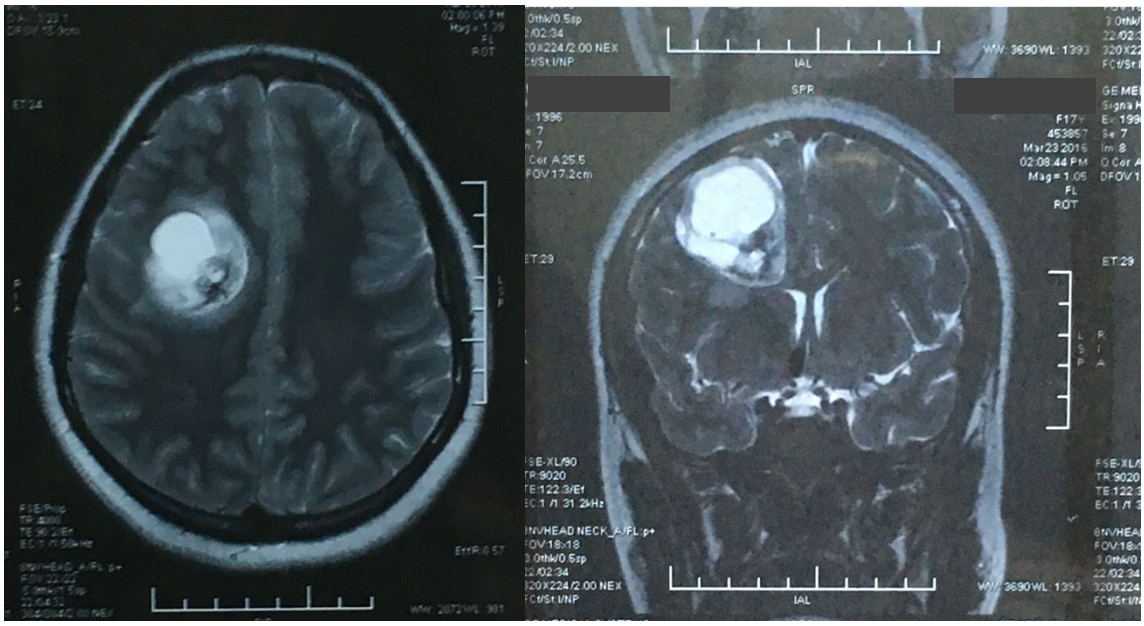

Fig. (1 & 2): MRI, pseudo cystic mass seen in the right temporal part of the cerebrum. No peritumoral edema present.

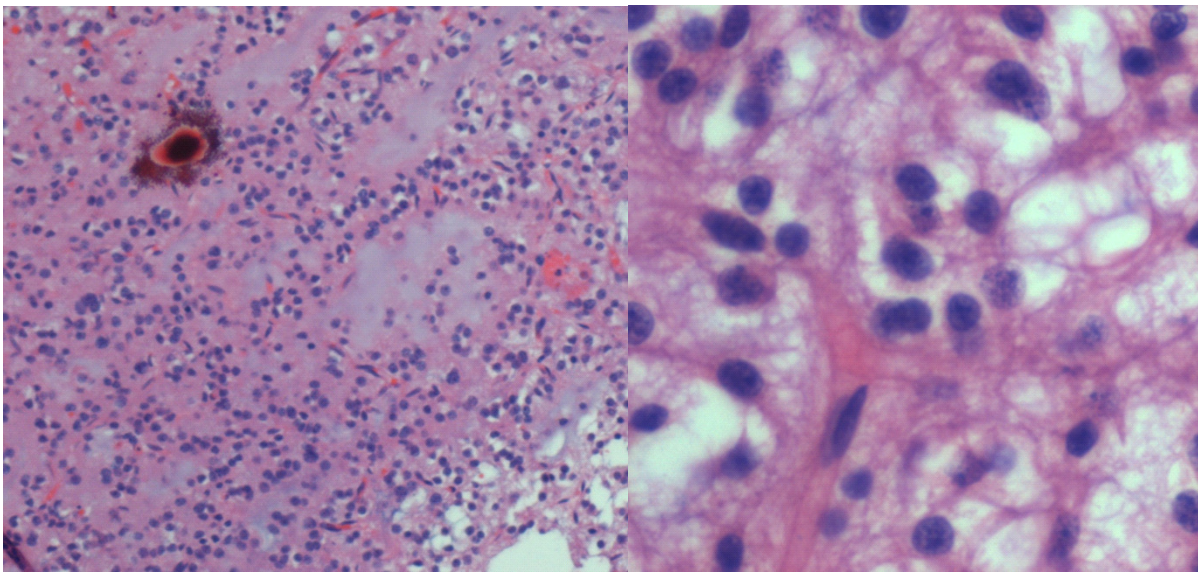

Fig. (3 & 4): H&E - (c)100x, oligodendrocyte-like cells in streaming array separated by myxoid matrix. (d) 400x, round monomorphous oligodendrocyte-like cells.

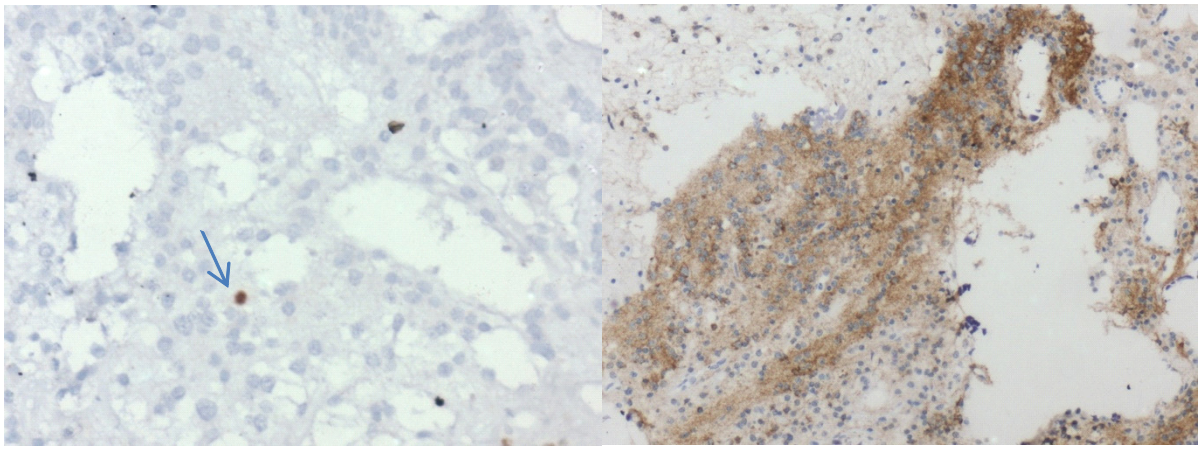

Fig. (5 & 6) : Immunohistochemistry: (e) MIB1Ki 67 LI < 1%. (f) Chromogranin- positive.

The patient was reviewed after six months and recovering well with no further episodes of seizures.

DISCUSSION

DNET is an uncommon clinicopathological entity originally described by Daumas-Duport and colleagues is currently classified as a WHO grade I glioneuronal neoplasm.[1,2] Most of them have protracted history of partial seizures with onset before 20 years of age and without focal neurological deficits.[1] Detection of these tumors before the onset of seizures is therefore extremely rare.[1,3] DNET tumors are typically discovered in the second or third decade, with the majority of them being localized to cerebral cortex, with a predilection for the temporal lobe.[1,2]

In the present scenario our patient gave a short history of seizures, dating a month back. However, on careful evaluation, she gave a history of mild trivial contractures. This finding in the first instance was not corroborating with the classical presentation of DNET. MRI brain revealed a bubbly nodular SOL which on T2-weighted images showed bright signals compared with adjacent brain. However, there was no edema and mass effect except for thinning of the adjacent calvarium. Tissue sent for histopathological examination was diagnosed as DNET, which was further confirmed by immuno-histochemistry. Oligodendroglioma need to be ruled out in this instance which too have a monomorphous cell population. The presence of IDH mutation and 1p/19q codeletion excludes DNET, however caution need to be exercised in pediatric cases where even oligodendroglioma lack these alterations.[1] Also, if the neuronal component shows pronounced dysmorphism or inflammatory infiltrates, one should consider the possibility of a ganglioglioma.

The histogenesis of DNET is uncertain, but an origin from secondary germinal layers has been suggested.[1] Gross total resection of these lesion usually controls seizure and achieves cures.[4] Recurrence if any usually arise from its glial component.[4] Noonan Syndrome is associated with an 8.1-fold increased risk of cancer.[7] Malignant transformation of DNET is rare.[6] The presence of features typically associated with aggressive behavior, such as high mitosis, complex microvascular proliferation and necrosis have not been shown to impact postoperative outcome.[1] Our patient was advised to follow up every six months after her discharge. At the first follow-up after six months, she reported that she was seizure free, and was leading a normal life. The low Ki-67 LI is likely to confer a good prognosis.

CONCLUSION

This case has been presented due to its rarity and because of its atypical presentation. DNET classically presents with chronic seizures, however atypical presentations and incomplete history may divert our attention to other conditions. A high degree of suspicion and a meticulous history and clinical examination, adjunct with MRI and histopathological examination remains indispensable in clinching the diagnosis.

The diagnosis should be made upon careful observation, especially when the architecture is distorted due to inadvertent surgical aspiration. Proper and early diagnosis is of paramount importance as once identified, the need for more aggressive treatment methods such as radiotherapy and chemotherapy can be avoided. Follow up is essential, particularly patients who are older at presentation and those with longer duration of seizures, as they stand a higher chance of recurrence.

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UNDERSTANDING BIBLIOMETRICS

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INTRODUCTION

Measuring the impact of research output is considered as one of the most important quality indicator in higher education. The objective way of measuring the research impact is -Bibliometrics. As transparent, objective and cost effective bibliometrics is used by the individual researchers, departments and faculties of the Institutes, administrators and decision makers of the organizations and by the society. The objective of this editorial is to provide an overview of the bibliometrics used in higher education and to discuss the major bibliometrics tools.

What is Bibliometrics?

Range of Quantitative measures used to assess the research impact. Qualitative indicators such as peer review, grants received and patents generated are considered as complements. Bibliometrics indicates the impact of the publication/research output in academia.

Why Bibliometrics?

Bibliometrics are useful to

* Showcase the research impact of individual researchers, Faculty and Higher education institutions
* Identify the emerging areas of research
* Establish research collaborations
* Succeed in research grants applications
* Bench mark the research outputs (Promotions, grant awards)
* Grade the impact of Higher Education Institutes (World rankings)

COMMONLY USED MEASURES:

Publication counts:

Number of research publications produced by any individual, unit, department and institutions. This is the most basic measurement used to assess the research productivity.

Citation counts:

Number of times each research paper is cited by the other researchers. Citation count is a measure of impact or influence of a published paper. Citation counts can be found through Scopus, Web of Science and Google Scholar. This metric identifies the influence of the research output; however in some cases the impact may be negative. Hence citation counts may not be used a positive reputation of a researchers or institute. Citation counts vary across the fields and should be compared with caution between the fields. It is understood that it takes time for any published paper to accumulate the citation counts.

H-index:

H -index measures the author's productivity and impact. It is calculated from the count of citations to an author's, or group of authors, publications. H- Index is available in web of science, Scopus and Google scholar. For instance if an individual's H-index is 4, which means four (4) of the authors paper cited at least 4 times each. H-index of an individual should be compared with an individual of same specialty, similar academic stage and similar institutes. H-index will not differentiate the active and passive researchers.

Journal impact Factor:

It is the average number of citations per published paper in a particular journal during a specified time period. This metric is useful measuring the impact of a journal in a specialty area; however JIF will not show the impact of the individual article. JIF is available at Journal Citation Reports by Clarivate Analytics.

Altmetrics:

"Altmetrics is the creation and study of new metrics based on the Social Web for analyzing, and informing scholarship" (www.almetrics.org). This metric provides analyse the impacts created by an article at societal level through social media.

CITATION ANALYSIS TOOLS:

Web of Science:

Most widely known citation index, maintained by Clarivate analytics (Thomas Reuters previously.

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COMPARISON OF CITATION ANALYSIS TOOLS:

Citation analysis tool	Advantages	Disadvantages
Web of Science	* Broad coverage of subjects in science and Health science * Advanced analysis features * Data available since 1900	* Subscription required * Dissertations are not covered
Scopus	* Advanced analysis features * 31 % of Health science titles	* Subscription required * Dissertations are not covered * Conference proceedings are limited
Google Scholar	* Free access * Wide coverage * Includes dissertations	* Quality of data * Non scholarly materials

Access to this database requires subscription, contains three citation indexes namely, arts and humanities, science citation index expanded and social sciences citation index.

Scopus:

Produced by Elsevier, Scopus database indexes more than 21,500 titles of various disciplines. Out of all the titles Health Sciences contributes 31%.

Google Scholar:

Provides free access to citation data of wide scope; this covers all type of articles indexed with Google Scholar. The quality of data may be not as good as other two, since it is generated automatically by the computer.

LIMITATIONS

* Direct comparisons cannot be made as the citation pattern across the discipline varies
* Established researcher's work gets more citations compared to the early career researchers of the same field
* Multi authored publications may alter the citation rates
* The highly cited work may not be of higher quality

SUMMARY

Understanding Bibliometrics is important for the researcher as it will enable them to identify the correct journal to publish their research work and to track the impact of the research output. Though the existing measures have their limitations, it provides quantitative metrics to measure the research impact.

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Collaborative Institutional Training Initiative at the University of Miami

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A decade long 'Smile Train' program of USA offers care for Cleft Lip & Palate children in India

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