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August 2014: **ISSN: 2072 – 1625** **VOLUME 13, No. 1**

TABLE OF CONTENTS **Page #**

Content page:---------- 1 – 2

ORIGINAL RESEARCH PAPERS

Prostate Cancer in Fiji – Disease Trends and Services Available for Patients: A Retrospective Study: Simione Turaganiwai, Iris Wainiqolo and Jenny M. Wilkinson: Vol. 13, No. 1, August 2014: ---------- 3 – 14

Bone Mineral Density of Children with Cerebral Palsy in the Age Group 7 to 14 Years Aisha Ayyub, Atif Ahmed Khan, and Khalil Ahmed: Vol. 13, No. 1, August 2014: ------ 15 – 20

Advanced Maternal Age at the First Pregnancy and Obstetric Performance: A Retrospective Study: Eugene M. Ikeanyi and Alphonsus N. Onyiriuka: Vol. 13, No. 1, August 2014: ---------- 21 – 31

Assessment of Thyroid Status of Patients in Solomon Islands: A Retrospective Study: Doris Ula Manongi and Victor J. Temple: Vol. 13, No. 1, August 2014: ---------- 32 – 42

Efficacy and Safety of Triple Drug Fixed-Dose Combination of Telmisartan, Amlodipine and Hydrochlorothiazide in the Management of Hypertension: Subrato Bhattacharya and A. A. Faruqui: Vol. 13, No. 1, August 2014: ---------- 43 – 51

CASE REPORTS

Growth in the Ventral Portion of Tongue: Case Report: Eshitha Ebrahim, *Prasanna Kumar Rao, Laxmi kanthChatra, Prashanth Shenai, Veena KM, Rachana V Prabhu, Tashika Kushraj and Prathima Shetty: Vol. 13, No. 1, August 2014: ---------- 52 – 55

Capillary Haemangioma: A Case Report: Nidhin Naroor, Prashanth Shenai, Laxmikanth Chatra, VeenaKM, Prasanna Kumar Rao, Rachana V Prabhu, Tashika Kushraj, Prathima Shetty and Shaul Hameed: Vol. 13, No. 1, August 2014: ---------- 56 – 59

Chronic Arthritis in Juvenile Behcet's Syndrome: A Rare Case: Tapaswini Bagh, Laxmikanth Chatra, Manjunath Shenoy, Prashanth Shenai, K M Veena, Prasanna K. Rao and Rachana V. Prabhu: Vol. 13, No. 1, August 2014: ---------- 60 – 66

Focal Reactive Soft Tissue Lesion of Gingiva: A Diagnostic Dilemma: Usha Chikkaiah, H J Jaikrishna, KB Hemavathy, Gururaju CR, Jyothi PA and Madhu Kiran: Vol. 13, No. 1, August 2014: ---------- 67 - 73

Instructions for Authors: ---------- 74 – 79

PROSTATE CANCER IN FIJI – DISEASE TRENDS AND SERVICES AVAILABLE FOR PATIENTS: A RETROSPECTIVE STUDY

***Simione Turaganiwai, **Iris Wainiqolo and ^Jenny M. Wilkinson**

*Colonial War Memorial Hospital, Pathology Department, Suva, Fiji, **Department of Public Health & Primary Care, Tamavua Campus, Suva, Fiji College of Medicine & Nursing & Health Sciences, Fiji National University and ^School of Biomedical Sciences, Charles Sturt University, Australia

^Correspondence Author: Email: jwilkinson@csu.edu.au

ABSTRACT:
In this retrospective study prostate biopsy data from the three divisional hospitals in Fiji was reviewed to determine the rate of prostate cancer in the period 2001 – 2010. In addition key hospital staff members were interviewed to gain an understanding of the support services available to those diagnosed with cancer. A total of 455 prostate biopsies of patients in the age group 45 to 70+ years were done over the 10 year period. The results of 133 (29%) were positive. No statistically significant increase or decrease in prostate cancer (CaP) positive biopsies was observed over the study period. Although 80% of the samples were from the 60 years age group, the proportion of positive samples in each age group was not significantly different. Of 116 biopsies graded, 59% had a Gleason score of 7 or higher. The interviews with medical staff indicated that support was primarily surgical and clinical care. A number of areas of deficiency were perceived by staff including lack of support groups and counseling services, geographical and financial factors affecting access to clinics and medications and the need for improved staff training. Data obtained in this retrospective study indicated that those diagnosed with prostate cancer in Fiji are typically older, have a poor prognosis and that there is an opportunity for providing improved support services for patients.

Keywords: prostate cancer, social support, Fiji
Submitted: March 2014; Accepted: July 2014

INTRODUCTION:

Prostate cancer (CaP) is the second and third most common cause of death in developed and developing countries respectively [1-4]. In western countries, prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer death among elderly men [5]. Prostate cancer is the most common malignancy in American men and the second leading cause of cancer mortality and is diagnosed among African Americans more often than other ethnic groups [6]. In 2009,

approximately 27,130 African-American men were diagnosed with prostate cancer, and approximately 3,690 African-American men died of prostate cancer [6]. In Asian countries, CaP has become more common in recent years and is associated with a larger aging population and westernized lifestyle [5]. In Germany, prostate cancer is one of the most prevalent male cancers with an estimated annual incidence of 58 000 new cases in Germany and of 678 000 new cases worldwide [7]. In Australia prostate cancer causes 15% of the cancer burden in men with an estimated 16, 800 men in Australia diagnosed in 2010 and 3,300 died of the disease [8].

In many parts of Oceania, including Australia, Fiji, New Caledonia and New Zealand, CaP is the most common male cancer [9]. In addition, it is the most common cause of cancer-related deaths for males in New Caledonia (26%) and the second most common cause-related deaths in Australia (15%), New Zealand (14%), Fiji (12%), and Polynesia (10%) [10]. A study in 2011 reporting data from 2002-2005 revealed that the leading cancers among males were lymphoid and haemopoietic (12.6% of males cases) and followed by prostate (12.5% of cases) from the 2002-2005 data [11, 12].

In addition to the surgical and other treatment needs of those diagnosed with cancer, various support services play an important role in enhancing quality of life and providing resources to assist in the management of cancer or treatment-related symptoms. Research suggests that social support can have an impact on health-related quality of life. Social support has two separate domains; structural and functional. Structural social support is the actual physicality of the support such as frequency of contact with friends or family, voluntary organizations or associations, religious services and other community services. Functional social support includes happiness with such areas as verbal and physical appraisal, tangible help with tasks, communication of helpful information and guidance and social companionship [13]. Little is known about the support services that are available to men diagnosed with CaP in Fiji.

The purpose of this study was to investigate the rate of positive findings in prostate biopsies at the three divisional hospitals in Fiji for the period 2001-2010 and also to assess the types of support services available to patients with CaP.

MATERIALS AND METHODS:

Routinely collected data on prostate biopsies for the years 2001 – 2010 were extracted from the

histopathology registers at the three divisional hospitals in Fiji: Colonial War Memorial (CWM), Lautoka and Labasa hospitals. The variables extracted were: year of biopsy, patient age, ethnicity, Gleason grade and scores and hospital where the biopsy was taken and diagnosed.

Variables for patients below 30 years of age were excluded as the risk of prostate cancer was low amongst this group. Extracted data was entered in a paper-based collection form and subsequently entered into Statistical Package for the Social Sciences (SPSS) version 16.0 for data analysis. The variables were then analysed by year, age group (<49, 50-54, 55-59, 60-64, 65-69, 70-74, 75 years or above and unknown), ethnicity (Fijians, Indo-Fijians and others), hospital (CWM, Lautoka and Labasa) and Gleason score. The Gleason scores 2–4 were classified as well differentiated prostate cancer, 5 and 6 as moderately differentiated, 7 or higher as poorly differentiated [14]. Chi squared analysis was used to compare groups with $p<0.05$ deemed to be statistically significant.

The second part of the study involved carrying out key informant interviews with urology clinic staff. The aim of this data collection was to explore the types of service available for CaP patients and identify gaps in the services. Staff members at the urology clinic were approached, the purpose of the study was explained and each was invited to participate. Permission was sought from the interviewees to record the interviews. Each interviewee was asked a series of questions relating to support services: (1) Can you describe for me the range of services that you offer to patients with prostate cancer? (2) Apart from health services, what other services do you think are important for the care and support of patients with prostate cancer? (3) What are these other services and what "needs" would they address? (4) In your opinion what do you see as weakness in the support services for prostate cancer patients? (5) Do you have any recommendations in relation to the identified weakness? The duration of the interview was between 15 to 30 minutes. Recorded interviews were later transcribed verbatim and analyzed thematically.

This study was approved by the Ministry of Health Ethics committee, the Medical Superintendents at the three divisional hospitals and the Charles Sturt University Ethics in Human Research Committee.

RESULTS:

In the period 2001-2011 a total of 455 specimens were received for CaP testing and diagnosis at the three divisional hospitals, with 133 (29%) of

all samples testing positive (Table 1). The proportion of positive samples from the three ethnic groups was not statistically different with 32% of samples from Fijians testing positive; 22% from Indo-Fijians and 39% from others. Most samples were tested at the CWM hospital (n=307) followed by Lautoka (n=112) and Labasa hospitals (n=36). There were 94 (31%) positive cases in CWM, 27 (24%) in Lautoka and 12 (33%) in Labasa hospitals.

There was no statistically significant (p = 0.37) increase or decrease in the percentage of positive samples during this time period, nor was there any trend based on ethnicity over the ten years. Positive biopsies were found in men over a wide age range (Table 1). The prevalence was higher among the over 60 years age group with a total of 87% of positive samples. The highest number of total biopsies (i.e. suspicious of CaP) was also higher in this group with 80% of all biopsies from those in the over 60 years age group. There was no statistically significant difference (p=0.52) in the percentage of positive samples in each age group. The average age when the men were diagnosed with CaP was 68 ± 9 years (mean ± standard deviation). In total of 29 (7%) individuals had more than one biopsy and in all but 8 cases these multiple biopsies were in the same year. Gleason scores were available for 86.5% of positive biopsies (Table 2) with 59% of biopsies having a score of 7 or higher (45% had scores of 8-10). The data also showed that 51% of individuals were both over 60 years and had a Gleason score of 7 or more with 17% aged over 60 and having a Gleason score of 5 or 6; this suggests that the majority (68%) of men in this study were both 60 years or older and had a Gleason score indicting a moderately to highly aggressive cancer.

In response to the first question, the interviewees responded that the only services provided to CaP patients within the hospitals were urology clinics, blood tests, x-ray, surgery, helping CaP patients in the wards for post-operations and medicine for treatment. The interviewees also felt that other medical and psychological supports are important for the care and support for patients.

Responding to the second question, interviewees nominated provision of counseling services, 24-hour access to medical and other support (either in-person or via toll-free phone lines), the important role of church groups and family, and ensuring that pharmaceutical needs were met. Counseling was felt to provide a safe, supportive and confidential environment at a regular time and place where CaP patients can explore their feelings.

TABLE 1: Summary of biopsy data for the 455 specimens collected at three divisional hospitals in the period 2001-2011.

	Positives cases N (%)	**Total (N = 455)**	**P value**
Ethnicity of patient			
Fijian	87 (32)	271	0.05
Indo-Fijian	34 (22)	153	
Other	12 (39)	31	
Hospital			
Colonial War Memorial	94 (31)	307	0.37
Labasa	12 (33)	36	
Lautoka	27 (24)	112	
Age group			
<49	3 (27)	11	0.52
50-54	5 (25)	20	
55-59	6 (16)	38	
60-64	18 (28)	65	
65-69	30 (31)	96	
70-74	29 (29)	100	
75+	38 (36)	105	
Not recorded	4 (20)	20	
Year			
2001	13 (18)	74	0.13
2002	25 (40)	63	
2003	21 (42)	50	
2004	8 (27)	30	
2005	14 (30)	46	
2006	8 (22)	36	
2007	16 (29)	56	
2008	11 (28)	39	
2009	9 (33)	27	
2010	8 (24)	34	

TABLE 2: Gleason scores for positive biopsies

Category	Gleason scores	Number (%)
Well differentiated	2 - 4	26 (22%)
Moderately differentiated	5 - 6	22 (19%)
Poorly differentiated	7 - 10	68 (59%)

For medical support, all interviewees mentioned that service provision was limited by a low national health budget, lack of infrastructure and staffing in Fiji including lack of access to specialist oncology services. They also felt that medications should be readily available at the hospitals pharmacies and that CaP patients, especially low income earners, should not buy their medications at private pharmacies. An interviewee said *"we don't basically offer all the drugs especially with pain killers as pain management is important for those with very last stage or critically ill patients and with that age too they will have a low pain tolerant so they need a lot of these basic pain management"* (interviewee 1).

For those experiencing financial hardship medication may only be bought when money is available and therefore there is potential for delayed treatment. The cost of patient's medication, travel to appointments and phone calls to the hospitals were all mentioned as limiting factors, particularly for patients in geographically remote areas. All those interviewed mentioned strategies that could assist in this area, for example government subsidized travel, toll free help lines. An interviewee point out that the church groups address the spiritual life, an area for source of hope to CaP patients, *"spiritually we need to lift them up as well, if the person is up spiritually then they can think properly I think that's why the church leaders need to come in and advice patients because most of these patients have no hope to give them"* (interviewee 3); providing support by getting the message out about men's health awareness an interviewee said, *"people listen to pastors and sermons and what's delivered in the pulpit … if we are going to try and improve the services they could come in … a prostate cancer message could be relayed down*

from the pulpit it's a wellness issue its about … when the pastors and preachers say something the community listens to these people and so why can't we use this to effectively deliver strong messages across … any message and prostate cancer is included" (interviewee 4).

The interviewees all saw a need for a more integrated and centrally-provisioned support system in Fiji. An interviewee said *"I think that's where we lacking in our department is support services because we don't have the toll free number, we don't have anybody that can go and visit them at home when they can't make it to the hospital. just a touch of hand or a lend of hand for that support"* (interviewee 3). Also highlighted by one interviewee was the need for family support*, "family support is one of the main important part to play in their life since they are sick and they are having cancer what we always do is bring the family and advise them on the disease"* (interviewee 2).

In addition, most patients present with metastatic disease as one interviewee said, *"now interestingly and very sad also is that most of our patients present in its metastatic form, the last stage of prostate cancer, we rarely seen people coming with curable prostate cancer"* (interviewee 4), which is a product of the lack of screening and other early detection activities. The lack of health services was also mentioned by the interviewee stating that *"the weaknesses I would say is on our health services is our oncological services in Fiji is poorly develop, we lack good clinical leadership in oncology, number one we don't have an oncologist … prostate cancer like any cancer falls under oncology. In the oncology, we lack proper availability of medication … any cancers; chemotherapy drugs are not available on time"* (interviewee 4).

The interviewees made several recommendations to improve support for those with prostate cancer including for the government to have special medication provisions to improve cost and availability, subsidized or free bus fares for CaP patients, provision of counseling services should be provided for all types of cancers and not only for some, toll-free phone lines for CaP patients so that they can access the nurse and urologist 24 hours/day especially those who are non-ambulatory and/or geographically isolated. Finally there was a need to increase staff levels and training.

DISCUSSION:

Prostate cancer is a disease that is seen predominantly in older men in Fiji and is accompanied by high Gleason scores; however

there is no evidence of an increase or decrease in the rates of CaP positive biopsies in the period 2001-2010. While the difference in percentage of positive tests based on ethnicity did not reach statistical significance the data suggests that this may be an area for further exploration. Medical/nursing staff felt that there were deficiencies in the current support services and that there were opportunities for improving support by subsidizing bus fares, providing more affordable and accessible medication medical devices (e.g. indwelling catheters (IDC) and urine bags), having toll-free help lines, provision of home visit services, and providing counseling and support groups. There was also felt to be a need for more staff at the clinics and for training to enable nurses to do some of the work such as IDC changes in the community and at clinics.

As this study was based on data from the three divisional hospitals the findings may under-represent the actual number of prostate cancer cases in Fiji as those presenting to other clinics and hospitals or who fail to present for biopsy were not included. This is supported by the interview findings, *"most of our patients present in its metastatic form, the last stage of prostate cancer, we rarely seen people coming with curable prostate cancer".* Carlsson et al. reported that some men did not present for biopsy at all; this maybe due to personal reasons or the presence of co-morbid conditions [15]. In addition the lack of local availability of the single urologist due to work in non-Fijian sites or while attending training may contribute to lower levels of screening and to presentation of men at later stages of the disease compared to sites where a higher level of services are available. The effect of lower levels of screening on presentation at later stages of the disease was reported in a Chinese population [16]. In this study it was reported that prostate specific antigen (PSA) testing was not popular in China in the years preceding the study and hence patients were more likely to be biopsied because they were experiencing other symptoms. They observed higher detection rates of CaP which subsequently dropped thereafter due to widespread use of PSA test.

In the present study the highest prevalence (87%) of CaP was among the over 60 years age group. This is consistent with reports in the literature that the majority of CaP cases are diagnosed in advanced stage in men older than 65 years [17], and approximately 25% of cases are diagnosed in men older than 75 years [18]. Bolenz et al. in their diagnostic (exploratory cohort) study found that many patients remain under-graded and under staged; an initial

transrectal sextant or 10–12-core biopsy might miss tumor areas in up to 30% of patients, leading to false-negative biopsy results [19]. A study to evaluate the diagnostic findings and treatment options chosen in men aged 70 years and older referred for prostate biopsy revealed that autopsy studies show older men are significantly more likely to have higher Gleason scores and more advanced stage cancer than younger men [18, 20].

The participants for the interview were senior staff nurses and urologist who had at least 3 years experience in their divisions. The types of support services which they highlighted as being important were psychological and medical support services; with gaps being in areas of out-of-hospital support, access to facilities and medication and lack of specialist staff. Currently the Fiji Cancer Society is the only non-governmental organisation (NGO) which provides information about cancer, prevention, diagnosis and treatment. It also offers support and hope to cancer patients and their families. This NGO provides the services of a hospital nurse who administers pain relief morphine injections and patient/family counseling. A similar support group, the "hospital in the home" also provides dressings to cancer patients and social activities for patients in their homes. Local religious organizations provide spiritual encouragement and direction to cancer patients.

For psychological support, community based support which revolved around family and church was highlighted as a need. A similar study [21] reveals that patients felt that more emotional, spiritual and other support services would have been beneficial for CaP patients during their cancer journey. Home visit service to the community is needed especially when patients become bed ridden or when they have bus fare problems to improve their quality of life. It is reported that those men who have low levels of social support from friends or family, voluntary organizations or associations, religious services and other community services also have a lower overall health-related quality of life than those men with higher levels of social support [13]. Nursing staff are also seen to have a key role in assisting those with CaP with both clinical and non-clinical support [22]. Furthermore, in this study pastors were seen as an influential persons in both providing support and getting the message out about men's health awareness. Finally, the institutional support group that did exist focused only on breast and cervical and not on CaP.

The interviewees highlighted that very little medical support was available to CaP patients. An example provided by one interviewee was

adequate provision of analgesics by the hospital pharmacy to assist patients to manage pain. When out of hospital patients may hold on to their prescriptions until they have the money to buy their medication which may delay treatment or symptom control. In other countries cancer foundations or agencies may provide and distribute medication [23] for their patients hence it is suggested that this may be a strategy to assist patient support in Fiji. Currently patients need to attend divisional hospitals when IDC and urine bags require changing, which incur extra cost and inconvenience especially for those in geographically isolated areas. It is also recommended that this facility be made available at sub divisional hospitals to provide greater access to services by patients. Awareness campaigns are needed to highlight the need for early diagnosis and management of prostate to minimise the number of men presenting with advanced or metastatic cancer; previous studies have shown that this can reduce the rate of death from prostate cancer by 20% [3].

This study is the first to provide information about the needs to improve support services of men with CaP patients where qualitative interview method of data collection was used and in-depth interviews to effectively capture the unmet health needs that are important to CaP patients in Fiji. There is a need to do research on CaP patients to record their experiences and opinions of the currently available services and how to provide better clinical services support systems for cancer patients. Further as most care is delivered on an outpatient basis, community program planners should consider increasing supportive care services to CaP in their homes.

CONCLUSION:

The results obtained in the present study indicate that prostate cancer is prevalent among older men in Fiji and is accompanied by high Gleason score. There was no statistically significant data to indicate increase or decrease in the rates of CaP positive samples in the period 2001-2010. Urology services are provided monthly at all three divisional hospitals; however improvements in a number of areas could enhance the medical and other support services needed by patients diagnosed with prostate cancer.

Conflict of Interests:

The authors declare that they have no conflict of interests

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Bone Mineral Density of Children with Cerebral Palsy in the Age Group 7 to 14 Years

***Aisha AYYUB & **Atif Ahmed KHAN & **Khalil Ahmed**

*Department of Chemical Pathology, Army Medical College, National University of Science and Technology (NUST), Islamabad, Pakistan. **Department of Physical Medicine and Rehabilitation, Armed Forces Institute of Rehabilitation Medicine (AFIRM), Rawalpindi, Pakistan

Corresponding author: Email: atifafirm@gmail.com

Running Title: Bone Mineral Density in Children with Cerebral Palsy

ABSTRACT:

Cerebral palsy children have increased tendency to develop fractures later in life, for which low bone mineral density might be one of the factors. The aim of this study was to evaluate the bone mineral density in children with cerebral palsy and factors affecting it. A total of 82 diagnosed children with cerebral palsy were sampled by non-probability purposive sampling from the outpatient department of Armed Forces Institute of Rehabilitation Medicine. Bone mineral density (BMD), z-score was measured at lumbar spine with Dual Energy X Ray Absorptiometry (DEXA) at L1- L4 lumbar vertebra. Analysis was done using SPSS (Version 20). Statistical comparisons were made using independent sample t-test. Of the 82 children 37 (45.1%) were males and 45 (54.9%) females. The mean age for all the children was 5.6 + 2.34 years and mean BMDz- score was -2.12 + 0.67. There were statistically significant differences in BMDz score with respect to age groups, pattern of involvement and ambulation status ($p<0.05$) but there were no statistically significant differences in gender, physical therapy programme and nutritional status ($p>0.05$). The BMDz-scores were lower, especially in the quadriplegic and non-ambulant children. BMD if identified early and managed timely can prevent future fragility fracture risk and avoid delay in rehabilitation process.

Keywords: Cerebral Palsy, Bone Density, Absorptiometry, Photon

Submitted: June 2014, Accepted: July 2014

INTRODUCTION:

Cerebral palsy (CP) is the most common causes of motor disability in childhood [1]. In Asian population the prevalence of cerebral palsy is 1/1000. In Pakistan spastic CP comprises 90.2% of all cases which includes quadriplegic, diplegic and hemiplegic types [2]. These children also frequently experience health problems such as epilepsy, recurrent pulmonary infections, gastro-esophageal reflux, constipation and low bone mineral density [3].

Children with CP can have low bone mineral density (BMD) because of different factors like mobility, skeletal maturity, nutritional status, use of anticonvulsants and vitamin D levels [4]. The incidence of low BMD increases with age [5]. Low BMD can result in an increase risk of fractures which in turn can have significant impact on quality of life and delay in rehabilitation of patients [6]. The incidence of fracture in patients with CP is 15.7% [7]. Comprehensive management can reduce the risk of fracture because timely start of nutritional adjustment, medication, mobility and rehabilitation can improve the bone mineral density.

Dual-energy X-Ray Absorptiometry (DXA) of spine and hip is the gold standard for monitoring BMD. The measurement of bone mineral density z-score (BMDz-score) by DXA is used as an index of bone strength and fracture risk [7].

To our knowledge, the information about BMD and factors influencing it are lacking for CP population in Pakistan. The aim of this study is to emphasize the importance of BMD measurement in CP children as low BMD can predispose the children to fractures later in the life.

SUBJECTS AND METHODS:

A total of 82 children with CP were selected from June 2012 to June 2013 from the CP clinic of Armed Forces Institute of Rehabilitation Medicine (AFIRM) through non-probability consecutive sampling. Eligibility criteria for the study was children of 3-14 Year of age with CP. Excluded from the study were children who were athetiod or ataxic CP, children with metal implants or fixators at the lumbar spine, children with history of long term steroid use and children with family history of any bone disease. Parents/guardians were explained the procedure of the study and informed consent was obtained. Study was also approved by local ethical committee.

Detail medical history and complete examination were carried out on all the selected children. The height (Ht) and weight (wt), were measured. Body wt was measured in bare minimum clothes with the help of standard hospital digital scale; portable standiometer was used to measure height. Basal Metabolic

Index (BMI), daily calcium and caloric intake were determined. The appropriate parameters were used to assess the growth and nutritional status, on the basis of which children were classified as having either poor or good nutritional status. On the basis of pattern of involvement, children were divided into quadriplegic CP and non-quadriplegic CP.

Children who were undergoing physiotherapy session for the last six months were enrolled as "regular" while physiotherapy session less than six months was labeled as "not undergoing physiotherapy". Children who were able to walk more than 100 feet without support, with or without assistive devices were labeled as "ambulators" while other were labeled as " non-ambulators" for this study. BMD at lumbar Spine (BMD-LS) was measured by an experienced radiographer using dual energy x-ray absorptiometry (DXA) machine (Hologic Discovery A, QDR series). Anterioposterior Scan of Lumbar1 to Lumbar 4 (L1-L4) vertebrae was taken for dexa imaging [8]. The system on its inbuilt database converts the BMD values into sex and age normalize z-score. A z-score of less than -2.0 was taken as low BMD [2].

STATISTICAL ANALYSIS:

Data was analyzed with the help of statistical program SPSS version 20.0. Descriptive statistics were calculated for both qualitative and quantitative variables. Frequency and percentages were calculated for qualitative variables like gender and pattern of CP. Mean and standard deviations were calculated for quantitative variable like age and BMDz-score. Independent sample t-test was use to see the statistical significance. P-value <0.05 was used as level of significance.

RESULTS:

The demographic characteristics of the children with CP are presented in Table 1. Out of total 82 cerebral palsied children included in the study, 37 (45.1%) were males and 45 (54.9%) were females. The mean age for all the children was 5.6 ± 2.34 years and mean BMDz-score was -2.12 ± 0.67. When the children's BMD values were assessed with respect to their age group, gender, pattern of involvement, ambulation, nutritional status and physical therapy programme as shown in Table 1, there were statistically significant differences between the children in the 3 to 7 years age group compared to those in the 7 - 14 years age group, between the quadriplegic and the non quadriplegic, and children who were ambulant versus non- ambulant ($p < 0.05$).

There were no statistically significant differences between the males and females, those who had and had not taken regular physical therapy programme and those who had good nutritional status versus poor nutritional status ($p>0.05$).

Table 1: Demographic characteristics of cerebral palsy children and comparison of their bone mineral density (BMD) z-scores

.

Characteristics		N (%)	BMDz-score	p-value*
Age groups	3 to 7 years	56 (68.3)	-1.94 ± 0.58	
	7 - 14 years	26 (31.7)	-2.50 ± 0.68	<0.05
Gender	Male	37 (45.1)	-2.11 ± 0.63	
	Female	45 (54.9)	-2.12 ± 0.70	>0.05
Pattern of involvement	Non-quadriplegic	57 (69.5)	1.82 ± 0.51	
	Quadriplegic	25 (30.5)	-2.80 ± 0.42	<0.05
Ambulation status	Ambulant	37 (45.1)	-1.82 ± 0.48	
	Non-ambulant	45 (54.9)	-2.36 ± 0.69	<0.05
Nutritional Status	Poor	14 (17.1)	-1.91 ± 0.45	
	Good	68 (82.9)	-2.16 ± 0.69	>0.05
Physical Therapy	Regular	44 (53.7)	-1.99 ± 0.57	
	Not at all	38 (46.3)	-2.26 ± 0.74	>0.05

*p-value of <0.05 is significant

DISCUSSION:

Children with CP are a diverse group of population, and there are multiple factors affecting their skeletal growth and maturation. Evaluating the factors that can delay bone development, augment bone loss, distort bone status and hence increasing fracture incidence, and then rectifying that factor to reducing fracture incidence is critical to ensuring optimal quality of life for these young people [6]. As predilection to develop pathological fractures is high amongst children with CP [9], we aimed to evaluate the bone mineral density (BMD) in these patients with cerebral palsy and to highlight factors that may affect the BMD. Factors may include immobilization, poor nutritional status, type of involvement and anticonvulsant use [10]. Studies have shown that children with CP had significantly low BMD [11-13]. In our study BMD at lumber spine was also low. Different studies have shown that the values of BMD in ambulant CP children are significantly higher then nonambulatory CP children [14]. One other study also showed increase values of BMD with ambulation [15]. Results from another study revealed that ambulation status has no significant effect on the BMD [13]. In our study there was significant difference in BMD depending on the ambulatory status with mean BMD of ambulatory CP children was -1.82 ± 0.48 as compared to non ambulatory CP children having BMD of -2.36 ± 0.69 ($p<0.05$).

Regular Physiotherapy (PT) has no significant effect on the BMD of children with CP [12]. In our study there was also no significant effect of regular physiotherapy on the

BMD of children with CP. Nutritional status can also influences growth and bone maturation in these children [16]. In our study nutrition has no significant affect on BMD. Henderson et al. in their study reported low value of BMD in quadriplegic as compared to hemiplegic and diplegic [11]. One other study has also found significantly low BMD in quadriplegic as compared to non quadriplegic children [13]. We in our study also found significantly low BMD values of -2.80 ± 0.42 in quadriplegic CP children as compared to BMDz-score value of -1.82 ± 0.51 in nonquadriplegic CP children ($p<0.05$).

Our results demonstrate that CP children have lower BMDz-score. Furthermore, factors like the pattern of involvement & ambulation status had significant effect on BMD value in Children with CP where as Gender, nutritional status and Physiotherapy program had no significant effect on BMD value in children with CP.

Conflict of Interest: Nil

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ADVANCED MATERNAL AGE AT THE FIRST PREGNANCY AND OBSTETRIC PERFORMANCE: A RETROSPECTIVE STUDY

***Eugene M. Ikeanyi & **Alphonsus N. Onyiriuka**

*Department of Obstetrics and Gynecology, College of Health Sciences, Niger Delta University, Wilberforce Island Bayelsa State, Nigeria. **Department of Child Health, University of Benin Teaching Hospital, Benin City, Nigeria

***Corresponding Author**: abuchikeanyi@yahoo.com

Running Title: Evaluation of the influence of age and parity on female reproductive capacity.

ABSTRACT:
Maternal Age of 35 years or more at first pregnancy and childbirth is considered advanced reproductive age and a high pregnancy risk associated with increased adverse maternal and perinatal outcomes. The industrialized and developing countries are replete with supporting scientific literatures but only a few data on nulliparous women in our setting hence our interest to appraise the correlates of advanced maternal age at first childbirth and obstetric performance in Nigerian women. The objectives were to determine the influence of advanced maternal age at first pregnancy on the obstetric and perinatal outcomes. To compare the obstetric performance of women advanced in maternal age at first delivery with their younger counterparts and to determine the trend of identifiable adverse outcomes with increasing maternal age at first delivery. This was a retrospective comparative study of 1684 nulliparous women that had their childbirth between 2009 and 2013 at a mission Hospital. Those aged 35 years and above were the study subjects while those aged 20 - 34 years the control. Relevant database was raised from the case files. The prevalence of elderly nullipara in this study was 1.6%. They were statistically significant different in primary level of education (OR = 4.1, P = 0.02), prenatal care lack (OR = 2.6, P = 0.02), caesarean section (OR = 2.5, P = 0.0006), incidental myomectomy (OR = 19.1, P < 0.0001), prolonged pregnancy (OR = 0.6, P = 0.04) and episiotomy at vaginal delivery (OR = 0.5, P = 0.01). They were also insignificantly worse in ante partum hemorrhage (APH), induction of labor, perineal tear, HIV infection, postpartum hemorrhage (PPH), preterm birth, Low birth weight (LBW), Intrauterine growth restriction (IUGR), stillbirth ,neonatal birth asphyxia and Perinatal mortality. Caesarean section rate, caesarean myomectomy, APH, induction of labor, stillbirth rate, LBW and Perinatal mortality each maintained a statistical significant linear tendency (P < 0.05) with maternal age. First pregnancy at advanced maternal age is fraught with increased maternal morbidity, perinatal morbidity and mortality. We proffer early education, marriage or and childbearing, quality prenatal care and skilled attendance at delivery for safe motherhood.

Keywords: Advanced maternal age, elderly nullipara, obstetric performance, trend.
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INTRODUCTION:

Maternal age and parity have been considered among the key determinants in obstetric performance and pregnancy outcomes [1 - 5]. The extremes of reproductive life and parity have been respectively widely associated with increased adverse obstetric outcomes. Pregnancy in women aged 35 years or above are termed advanced maternal age and for the first time mother elderly nullipara. The International Federation of Gynecology and Obstetrics (FIGO) in 1958 defined 'Advanced maternal age' as 35 years and older and recommended that a nullipara aged ≥ 35 years should be accepted as the international standard for elderly nullipara [3, 6 - 8]. They are high risk pregnancies because available scientific data suggest that they are prone to poor obstetric outcomes which tend to accelerate from age of 35 years and steeper from 40 years of age [1]. A woman's fertility and potential to have a conception end in a live birth within a year peak in her early to mid twenties [9] . The highest natural monthly fecundity of only 20 - 25% occurs in women under 30 years of age and drops to less than 10% at 35 years and above [10,11]. The yearly rate declines from a peak of about 90% in women in their 20s to 65% at 35 years, 40% at 40year and 10% at 45years [4-5], [9-12]. This is due to the decline in quality and quantity of the ovarian capital with increasing women age. Again at advanced maternal age there is increase in chronic medical disorders and the conception at increased risk of congenital disorder mostly of chromosomal origin leading to various degrees of birth defects [4, 12, 13]. This indicates an increased need for preconception care for safe motherhood especially in these high risk pregnancies. The results of analysis showed that age at first pregnancy depends on geopolitical zone, location of residence, level of educational attainment, marital status, religion and the age of first sexual initiation [14]. Work from Asia showed only increased incidence of Intrauterine growth restriction (IUGR) and Caesarean Section rate with advanced maternal age [15]. There is plethora of other scholarly scientific literatures on this but only a few of them from our setting. This study therefore sets out to appraise the correlates of advanced maternal age at first pregnancy and delivery in Nigerian.

SUBJECTS AND METHODS:

One thousand six hundred and eighty four (1684) women of the 1726 that had their first delivery between June 2009 and Dec 2013 in St Philomena Catholic Hospital (SPCH) Benin City Edo state Nigeria were retrospectively studied. All the adolescent mothers and those whose pregnancy ended in abortion were excluded. Data on the socio-demographic characteristics, prenatal and delivery details, maternal and perinatal outcomes were

extracted from the case files into the computer. The main outcome measures were maternal and perinatal complications. The women were stratified into two clinically important age groups for comparative analysis. The study groups were those aged ≥35 years (elderly nulliparae) and those aged 20-34 years served as the control group. The control group was further subdivided into three groups for intra-group analysis for trend testing where necessary. For the purpose of this study a nullipara or nulliparous woman is defined as a woman who has never carried any pregnancy to viability and delivered irrespective of the number of early pregnancy losses (abortions, ectopic gestations or gestational trophoblastic disease) she has had previously and or the gestational age of the pregnancy she is currently carrying. Viable gestational age by World Health Organization (WHO) is 24 completed weeks or greater. Those women aged 35 years or more are termed advanced or elderly nullipara while those aged 20 - 34 years are termed normal aged or young nullipara (FIGO). Preterm birth is childbirth at earlier than 37 completed weeks of gestation while prolonged pregnancy is that beyond 40 weeks of gestation from the day of onset of the last normal menstrual period (LNMP). Low birth weight newborn weighed less than 2500 grams while macrosomic newborn weighed 4000grams or more each at birth. SPCH is a secondary tier mission hospital with fairly well equipped and staffed maternity department. It has over a thousand deliveries annually. The medical record unit was fairly satisfactory. The facility has adequate obstetric and pediatrics coverage. The study was approved by the hospital ethics and research committee. Analysis was done with EPI-INFO version 3. 5. 1 and INSTAT statistical software where appropriate. Chi-square (X^2), Fisher's Exact test and Student t-test statistical packages were used as appropriate setting the Statistical significance at p-value < 0.05.

RESULTS:

Total deliveries at the center during our study was 3976, the first deliveries were 1726 out of which 1684 (42.4%) met the study criteria and were included for this study. The women aged 35 years and above at their first delivery constituted 1.6% of all the deliveries at the centre during this study and 3.8% of the nulliparae. The mean age of the study group was 36.5 ± 1.4years and modal age 35 years while the values for the control counterparts were 26.9 ± 1.7 and 27 years respectively. There was statistically significant difference in their mean age (t = 44.9, P < 0.0001). The study group was significantly more of primary (7.1% v 1.8% OR = 4.1, P = 0.02), but similar in secondary (23.2% v 26.8% OR = 0.8, P = 0.6) and tertiary (69.7% vs. 71.1%, OR = 0.9, P = 0.8)) levels of education respectively (Table 1). All the study group were married while 11 (0.7%) of the control group were unmarried at the time of their first childbirths (OR 1.1, P =

1.0). Eight (12.3%) of the study group and 82 (5.1%) of the control group had no prenatal care (OR = 2.6, P = 0.02). This was statistically significant but did not maintain a statistical significant linear trend (X^2 = 0.4859, P = 0.5). The study group though not statistically significant, was twice as likely as the control counterparts to be unemployed at the time of their child birth. In Table 2, among those who had prenatal care at the center the study group comparatively had reduced risk of anemia (5.3% vs. 9.8%, OR = 0.5, P = 0.4) at their first visit though the difference was not statistically significant. They more than twice tested positive to human immunodeficiency virus infection (HIV) screening than the control group (6.2% vs.3.0%, OR = 2.1,P = 0.1) but this failed to maintain a significant linear trend (X^2 = 2.851, P = 0.09). The study group were more prone to ante partum hemorrhage (OR = 2.5, P = 0.6) relative to the control group and there was statistical significant linear trend (X^2 = 7.481, P = 0.01).There was a slight increase risk of premature rupture of membranes at advanced maternal age at first delivery when compared with the control group (9.7% vs. 8.4%, OR = 1.1, P = 0.8). There was a non-significant increase of induction of labor among the study group (28.0% vs. 22.3, OR = 1.4, P = 0.4) with a significant linear trend (X^2 = 5.128, P = 0.02). The two groups were similar in augmentation rate (26.0% vs. 26.3, OR = 1.0, P = 1.0). The study group were less likely to have assisted vaginal delivery (0. 0% vs. 0.95, OR = 0.8, P = 1.0). Caesarean section rate was more than twice increased among the study group (43.1% vs. 23.45, OR = 2.5, P = 0.0006) relative to the control group. The difference was statistically significant and followed a statistically significant linear trend (X^2 = 12.669, P = 0.0004). The mothers in the study group were significantly at increased risk of incidental caesarean myomectomy (7.7% vs. 0.4% OR = 19.1, P < 0.0001) and this also maintained a statistically significant linear trend (X^2 = 17.431, P < 0.0001).

Compared with the control group, the study group were significantly less likely to require episiotomy at delivery (27.7% vs. 45.1%, OR = 0.5, P = 0.01) but there was no significant linear trend. However the results also indicate that though insignificant, there was an increased risk of perineal tear among study group (15.9% vs. 11.9% OR = 1.5, P = 0.2). The elderly mothers were more prone to postpartum hemorrhage (4.6% vs. 2.8%, OR = 1.7, P = 0.4) though none received blood transfusion unlike the younger group (0% vs. 1.6%, OR = 0.5, P = 0.6). There was no difference in the risk of gestational hypertension (16.9% vs. 16.7%, OR = 1.0, p = 1.0) and twining (P = 0.6) between the two groups. As can be seen in Table 3 there was an increased rate of preterm delivery among the elderly nulliparae (OR = 1.5, P = 0.4). They were significantly 40% less likely to have prolonged pregnancy than the control group (28.1% vs. 40.9%, OR = 0.6, P = 0.04) but

there was no significant linear tendency (X^2 = 0.3164, P = 0.6). Again relative to the newborns of the control group, those of the elderly mothers were twice (OR = 2.1, P = 0.2) more prone to having Apgar score of less than 7 at 5 minute.

TABLE 1: Maternal Characteristics

Variables		**AGE GROUPS IN YEARS (N = 1684)**					
	Age groups	20-24yrs	25-29yrs	30-34yrs	≥35yrs	≥35yrs vs. 20-34yrs	
	N (%)	383 (22.7)	876 (52.0)	360 (21.4)	65 (3.9)	OR	P-value
Education Attainment	Primary	7(2.0)	13(1.6)	8(2.4)	4(7.1)	4.1	0.02 *
	Secondary	150(41.9)	185(22.3)	72(21.7)	13(23.2)	0.8	0.6
	Tertiary	201(56.1)	628(75.9)	251(75.6)	39(69.7)	0.9	0.8
	Nil	0(0.0)	2(0.2)	1(0.3)	0(0.0)	3.5	1.0
Marital Status	Married	376(98.2)	867(99.8)	352(99.4)	62(100.0)	0.9	1.0
	Unmarried	7(1.8)	2(0.2)	2(0.6)	0(0.0)	1.1	1.0
Mean height (cm)	At booking	162.0 ± 7.4	161.3± 9.2	161.3.±11.6	159.7±7.5	t=1.2	0.2
Mean weight (kg)	At booking	66.3±11.4	70.1±13.3	73.3±14.3	73.8±12.1	t=2.2	0.03*
	At last prenatal visit	74.9±11.6	78.4±12.4	81.0±14.4	78.6±12.0	t=0.2	0.8
Booking status	Booked	357(93.2)	841(96.0)	339(94.2)	57(87.7)	0.4	0.02*
	Un-booked	26(6.8)	35(4.0)	21(5.8)	8(12.3)	2.6	0.02 *
Employment status	Unemployed	22(5.7)	33(3.8)	22(6.1)	6(9.2)	2.0	0.1
	Employed	361(94.3)	843(96.2)	338(93.9)	59(90.8)	0.5	0.1

*** = significant**, (All values in brackets are percentages)

TABLE 2: Maternal Outcome Variables

Variables	Age groups in years (N = 1684)					
Age groups	20-24yrs	25-29yrs	30-34yrs	≥35yrs	≥35yrs vs. 20-34yrs	
N (%)	383(22.7)	876(52.0)	360(21.4)	65(3.9)	OR	P-value
Positive HIV test	13(3.4)	18(2.1)	18(5.1)	4(6.2)	2.1	0.1
Twining	7(1.8)	10(1.1)	11(3.1)	0(0.0)	0.4	0.6
Anaemia (at booking)	53(15.0)	70(8.2)	28(8.4)	3(5.3)	0.5	0.4
Induction of labour	57(16.4)	189(23.7)	80(25.1)	14(28.0)	1.4	0.4
Augmentation of labour	104(30.0)	208(26.1)	73(22.9)	13(26.0)	1.0	1.0
Caesarean section	69(18.0)	209(23,8)	101(28.0)	28(43.1)	2.5	0.0006 *
Incidental caesarean myomectomy	0(0.0)	5(0.6)	2(0.6)	5(7.7)	19.1	<0.0001*
Perineal tear	49(12.8)	105(12.0)	39(10.8)	11(16.9)	1.5	0.2
Episiotomy	187(48.8)	387(44.2)	156(43.8)	18(27.7)	0.5	0.007 *
Postpartum hemorrhage	8(2.1)	23(2.6)	14(3.9)	3(4.6)	1.7	0.4
Pregnancy induced hypertension/preeclampsia	64(16.9)	140(16.0)	66(18.3)	11(16.9)	1.0	1.0
Antepartum hemorrhage	2(0.5)	19(2.2)	13(3.6)	2(3.1	1.5	0.6
Malpresentation	14(3.7)	29(3.3)	7(1.9)	2(3.1)	1.0	1.0
Premature rupture of membranes	20(5.3)	74(8.4)	42(4.6)	6(9.2	1.1	0.8
Blood transfusion	3(0.8)	17(1.9)	6(1.7)	0(0.0)	0.5	0.6

***=significant**, (All values in brackets are percentages)

TABLE 3: Perinatal Outcome Variables

Variables	Age groups in years (N = 1684)					
Age groups	20-24yrs	25-29yrs	30-34yrs	≥35yrs	≥35yrs vs. 20-34yrs	
N (%)	383(22.7)	876(52.0)	360(21.4)	65(3.9)	OR	P-value
Intrauterine growth restriction	11(2.9)	30(3.4)	17(4.8)	3(4.6)	1.3	0.5
Preterm birth	29(7.6)	84(9.6)	26(7.2)	8(12.3)	1.5	0.4
Apgar score at 5 min <7	14(3.7)	43(4.9)	21(5.8)	6(9.2)	2.1	0.2
Mean birth weight (g)	3215.3±518.6	3247.0±549.5	3201.1±594.4	3166.2±645.5	t=0.5	0.6
Prolonged pregnancy	152(39.7)	364(41.5)	146(40.6)	18(28.1)	0.6	0.04 *
Stillbirth	5(1.3)	21(2.4)	15(4.2)	3(4.6)	1.9	0.2
Early neonatal death	1(0.3)	1(0.1)	1(0.3)	0(0.0)	3.5	1.0
Perinatal mortality rate	6(15.7)	22(25.1)	15(41.7)	3(46.2)	1.8	0.4
SCBU Admission	5(1.3)	6(0.7)	5(1.4)	0(0.0)	0.7	1.0
Low birth weight	16(4.2)	55(6.3)	33(9.1)	7(10.8)	1.8	0.2
Macrosomia	21(5.5)	65(7.4)	29(6.9)	5(7.7)	1.1	0.8

***=significant**, (All values in brackets are percentages)

The mean birth weight of their neonates was similar (t = 0.5, P = 0.6) despite about double the risk of LBW (OR = 1.8, P = 0.2) and 30% more likelihood of intrauterine growth restriction (IUGR) among the older group. The former followed a significant linear trend (X^2 = 8.136, P = 0.004) unlike the latter (X^2 = 1.840, P = 0.2).There was a slight increase of rate of fetal macrosomia (7.7% vs. 7.1%, OR = 1.1, P = 0.8) among the study group. The study group had more stillbirths relative to the control group (OR = 1.9, P = 0.2).This followed a significant linear trend (X^2 = 5.748, P = 0.02). The Perinatal mortality was about twice increased among the elderly mothers (4.6% vs. 2.7%, OR = 1.8, P = 0.4). This was not statistically

significant but it maintained a statistically significant linear tendency (X^2 = 5.197, P = 0.02).The other maternal and Perinatal outcome variables did not maintain significant linear relationship. Among all the subjects, there was no maternal death or hysterectomy at the center within the period of this study.

DISCUSSION:

The prevalence of elderly nullipara in this study was 1.6 % which compares with previous reports of 1.4-2.0% in other centers in this south –south geopolitical region [6],[16] but lower than an earlier finding of 4.4% in this setting over a decade ago [17] and other reports from other regions [18-19]. The average age at first childbirth is on increase globally [19-20]. This is mainly due to educational, social and most importantly economic reasons. Pursuit of higher educational attainment as a key for stable job, a higher salary and increasing career prospects is common globally not only among the males but the females alike especially in countries like ours with high level of gender inequality ,limited job and high employment insecurity. This quest for increase earning power of career women increases their labor force participation at the expense of early marriage and childbearing.

The decline in prevalence in this setting over the previous decade as observed in this study can be because the earlier study [17] was in a tertiary hospital while this took place in a secondary mission hospital in the same setting. Both studies were however, hospital based and may not be the true representative of the zone. Increasing the level of awareness of the consequences of delay in childbearing and the benefits of early completion of family size among the people might reduce the incidence of elderly nulliparity. A low incidence of elderly nulliparity of 0.42% was reported from the northern part of the country [21]. This may be explained by cultural and religious variations that encourage a high prevalence of early marriage and childbearing in the north. This is supported by the national demographic and health survey report [20].

Evidently, greater proportion of mothers in each category in this study attained tertiary level of education though double the older ones were unemployed at the time of their first child birth. It has been shown that median age at first birth increases with the level of education and socioeconomic status [20].

In all, seven out of the 15 maternal outcomes measured and 8 out of 10 perinatal complications in this study were unfavorable in the study group relative to the control counterparts. Among maternal outcome variables, Caesarean section and incidental caesarean myomectomy were statistically significant different. Others were induction of labor, ante partum hemorrhage, postpartum hemorrhage, and premature rupture of membranes, perineal tear and HIV infection. These compared with these reports [16, 22-25] and at variant with others [6].

Our results were not different in gestational hypertension but compared to other findings [23] but were different from other reports of increased occurrence among the elderly nulliparae [21, 24, 25]. The study group appeared more prone to perineal tears and will require more episiotomy at delivery compared to the control group.

The study group was comparatively significantly more delivered abdominally confirming reports by other workers [17, 23-28]. A significant number of the study group had incidental myomectomy. Advancing age without childbirth has been associated with increased occurrence of uterine fibroids this is supported by other findings [25]. At booking for antenatal care the study group were less prone to anemia because the older mothers have more reserves and less likely to develop anemia as presented in Table 2. This compares with previous reports [28].

The increased likelihood of the older nullipara to have interventional delivery therefore obstetric hemorrhage were not unconnected to their high rate of co-existing uterine fibroids, malpresentation, rigid perineum and ante partum hemorrhage. This confirms another report of increased likelihood of primary postpartum hemorrhage with advanced maternal age [29].

Perinatal adverse outcomes were relatively higher among the older mothers though none was to a statistically significant level. These were preterm birth, low birth weight, early neonatal death, perinatal mortality and stillbirth similar to other findings [24, 25, 30]. Report from southwestern Nigeria revealed no adverse perinatal outcome in advanced maternal age pregnancy [14]. This was not on first time pregnancies and their findings are therefore not strictly comparable with our present study.

Congenital malformation was higher in younger mothers similar to findings by other authors [23]. This may be due to the small sample size of the study group. Congenital anomaly tends to increase with advancing maternal age [12-13]. This work also confirmed the significant increase of prolonged pregnancy among the younger group as earlier reported [21]. There is the need for increased campaign against excessively widened bio-social gap to forestall delay in commencement of childbearing.

Our data indicate that the maternal and perinatal morbidities tend to increase with increasing maternal age.

One of the limitations in our study is that it is retrospective and hospital based therefore it may not be a true representative of the geopolitical region. A multicenter study would have a better spread and representation. A randomized prospective study with statistically appropriate sample size is hereby suggested for further study.

It is evident from this study that early and regular prenatal care in a well equipped health facility for proper screening, regular evaluation, and health education especially on nutrition in

pregnancy, pregnancy and childbirth, continuous counseling and psychological support through the gestational period and childbirth is essential for safe motherhood and healthy neonates among this group. The need for skilled attendance at their delivery need not be overemphasized.

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ASSESSMENT OF THYROID STATUS OF PATIENTS IN SOLOMON ISLANDS: A RETROSPECTIVE STUDY

***^Doris Ula Manongi and **Victor J. Temple**

*Principle Medical Technologist, Serology Section, Medical laboratory, National Referral Hospital MHMS, Honiara, Solomon Islands.

**Micronutrient Research Laboratory, School of Medicine and Health Sciences, Division of Basic Medical Sciences, University of Papua New Guinea, National Capital District, Papua New Guinea

^Correspondence Author: ulamanongi@gmail.com

ABSTRACT:
Thyroid Function Tests are used for assessing the thyroid status of an individual. In the Solomon Islands blood samples for thyroid function tests are collected and sent to the Royal Brisbane Hospital Laboratory in Australia on a weekly basis. The major objective of this study was to use the thyroid function tests results obtained over the period 2008 to 2012 to retrospectively assess the prevalence of thyroid dysfunction in the Solomon Islands. This study used convenience sampling that included all the 2070 requests for thyroid function tests from 2008 to 2012 recorded in the registry books in the Clinical Biochemistry Department in the National Medical Laboratory Pathology Division in the National Referral Hospital in Honiara Solomon Islands.
The data collected were analyzed using Microsoft excel for Windows 8 and the Statistical Packages for Social Sciences version 20 for Windows. Ethical clearance and permission were obtained from the appropriate authorities. A total of 1485 (71.7%) recorded results were used for data analysis. Thyroid disorders were prevalent in 51.5% of the patients in 2008, 43.9% of the patients in 2009, 54.8% of the patients in 2010, 52.6% of the patients in 2011 and 51.8% of the patients in 2012. The prevailing thyroid disorder in each of the five years was primary hyperthyroidism, 36.4% in 2008, 25.8% in 2009, 31.5% in 2010, 28.7% in 2011 and 28.2% in 2012. The number of thyroid function tests requests for females was about twice that of males in all the various years. Prevalence of primary and subclinical hyperthyroidism was significantly higher among the female patients compared to the male patients in all the various years.

Keywords: Thyroid function tests, Solomon Islands, hyperthyroidism,
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INTRODUCTION:

The Thyroid glands synthesize and release the thyroid hormones, Thyroxine (T4) and Triiodothyronine (T3). This process is regulated by Thyroid Stimulating Hormone (TSH) produced in the anterior lobe of the pituitary gland, which is regulated by Thyrotropin Releasing Hormone (TRH) produced in the Hypothalamus [1 – 3]. The regulation occurs via the Hypothalamic-Pituitary-Thyroid axis (HPT axis) [1 – 3]. The thyroid gland releases mainly T4, which is de-iodinated to T3 in target tissues containing the Deiodinase with Seleno-Cysteine [3]. The thyroid hormones are transported in blood mainly bound to Thyroxine-Binding Globulin (TBG). The actions of thyroid hormones are carried out by the very limited unbound fractions (FT4 and FT3) in blood plasma [1 – 3]. FT3 is the biologically active form of the thyroid hormones, because it binds to receptors and triggers end-organ effects [1 – 3]. The level of TSH in blood is inversely related to the levels of FT4 and FT3 in blood, a process regulated via the negative feedback control of the HPT axis, which is essential for maintenance of normal thyroid function [1 – 3]. Thyroid Function Tests (TFT) is the recommended biochemical tests for assessing the thyroid status of an individual [1 – 5]. The TFT involve assessing the serum or plasma levels of TSH, FT4 and FT3. The request for TFT can be for serum or plasma TSH alone, a combination of TSH and FT4, or for TFT [1 – 5]. In most circumstances the clinicians select the type of TFT that is most appropriate to diagnose or exclude thyroid dysfunction [2, 5]. The assay of serum TSH level is considered as the most sensitive, specific and reliable first step for assessing the thyroid status in both overt and subclinical thyroid dysfunction [2, 4 – 6]. However, the TSH test alone is not absolute in diagnostic accuracy, which can be enhanced by careful selection of the combination of TFT [4, 5]. Thus, for reliable diagnoses to be made the complete TFT should be requested at least once for an individual with thyroid dysfunction, or a strong clinical suspicion of thyroid dysfunction [4, 5].

According to Dayan [4] six different combinations or panels of TFT results can occur in clinical practice. The six panels are [4]: Low TSH, Raised FT4 or FT3: indicative of Primary Hyperthyroidism; Low TSH, Normal FT4 or FT3: indicative of subclinical Hyperthyroidism; Raised TSH, Low FT4 or FT3: indicative of Primary Hypothyroidism; Raised TSH, Normal FT4 or FT3: indicative of Subclinical Hypothyroidism; Low or Normal TSH, Low FT4 or FT3: indicative of non-thyroidal illness (Euthyroid sick syndrome); Normal or Raised TSH, Raised FT4 or FT3: indicates discordant result.

TFT results can be classified as concordant or discordant [4]. Concordant is indicated when the TSH, FT4 or FT3 results indicate the same

findings or they agree as in Euthyroid, Hyperthyroid or Hypothyroid. Discordant is indicated when the TSH, FT4 or FT3 results are contradictory, because they do not indicate the same findings [4].

In most developed countries TFT are routinely used for screening, diagnosis and monitoring treatment of patients with suspected or overt thyroid dysfunction [2, 5, 7]. In some resource limited countries TFT are used in very limited clinical settings, mainly for the diagnosis of patients with suspected thyroid dysfunction. The blood samples are collected from the patients, the serum or plasma samples obtained are then sent to laboratories outside the country for the assay of TFT. In these resources limited countries it is important to regularly assess the TFT results in order to determine the prevalence and trend of thyroid dysfunction among the population.

The Solomon Islands is one of the resource limited countries in which TFT are done outside the country. Blood samples are collected and serum samples are prepared and sent to the Royal Brisbane Hospital Laboratory in Australia on weekly basis. Although this process has been in place for several years, there are no published data on the prevalence of thyroid dysfunction among the population in the Solomon Islands.

Results obtained in a recent study on the status of iodine nutrition among school-age children in Honiara, Solomon Islands indicated successful implementation of the universal salt iodization (USI) strategy [8]. The report further indicated that iodine deficiency was not a public health problem among schoolchildren, age 6 – 12yrs, in Honiara, Solomon Islands. The reported median urinary iodine concentration (UIC) for all the children was 328.0ug/L and the Inter-quartile range was 210.4 – 437.0ug/L. In addition, a total of 257 (55.6%) children had UIC over 300.0ug/L, which indicates risk of developing adverse health consequences. The authors also reported that 170 (36.8%) children had UIC in the 300.0 to 500.0ug/L range and 87 (18.8%) had UIC greater than 500.0ug/L, which indicates Iodine Induced Hyperthyroidism (IIH). The data reported in this study strongly indicates the need to assess the thyroid status of the population.

The major objective of the present study was to use the TFT results obtained over the period 2008 to 2012 to retrospectively assess the prevalence of thyroid dysfunction in the Solomon Islands.

SUBJECTS AND METHODS:

The Solomon Islands have six main islands and nine provinces. Seven of these nine provinces have one public hospital each. There are three private hospitals, one in the Western province, one each in Malaita and Choiseul provinces [9 – 11]. The major general hospital that also serves as the National Referral Hospital (NRH) for all the nine provinces is located in Guadalcanal, which is the biggest province in the Solomon Islands [9 – 11].

Honiara the capital city and main administrative centre in the Solomon Islands is also located in Guadalcanal.

The specific site for this retrospective hospital based study was the Clinical Biochemistry Department (CBD) in the National Medical Laboratory Pathology Division (NMLPD) in the NRH, Honiara, Solomon Islands. All samples for TFT from the public and private hospitals in Solomon Islands are sent to the CBD in the NMLPD NRH for registration and shipment to the Royal Brisbane Hospital Laboratory (RBHL) in Australia on a weekly basis. The TFT results are sent back to the CBD NMLPD NRH, where the results are recorded before they are released to the appropriate clinicians in the various hospitals.

This study used convenience sampling that included all the TFT recorded in the registry books in the CBD in NMLPD NRH from 2008 to 2012. The information collected from the registry books included, laboratory identification number (ID) and name of each patient, age, gender, tests requested, date the sample was received, date the sample was sent to RBHL in Australia, date the results were received from RBHL and the TFT results obtained. In the books the age for most of the patients was registered as adult. The laboratory ID and names were use to identify patients with more than one tests per year. The recorded reference ranges were those used in the RBHL; they are TSH: 0.3 to 4.5mU/L, FT4: 7.0 to 17.0pmol/L and FT3: 3.5 to 6.0pmol/L.

The data collected were analyzed using Microsoft excel for Windows 8 and the Statistical Packages for Social Sciences (SPSS) version 20 for Windows.

Ethical clearance and permission for this study were obtained from the Ministry of Health and Medical Services (MHMS), Honiara, Solomon Island and the ethics and research grant committee in the School of Medicine and Health Science (SMHS) in the University of Papua New Guinea (UPNG).

RESULTS:

A total of 2070 TFT requests were recorded in the registry books in the CBD NMLPD NRH during the period 2008 to 2012. All the 2070 plasma samples were collected and sent to RBHL in Australia for analyses. According to the records, of the 2070 samples a total of 1485 (71.7%) were completed and results recorded. The results for 120 (5.8%) samples were received but not recorded, results for 403 (19.5%) samples were not returned and 62 (3.0%) samples were recorded as insufficient. Further analysis of the 2070 requests indicated that 296 (14.3%) were repeated cases or follow ups of patients and 1774 (85.7%) were new patients. All repeated and follow up results were excluded from further analysis of the data; furthermore, most of the repeated and follow up results were among those not recorded and those not returned. In the present study the mean age, age range and age groups of the patients in the various years were not

determined because "adult" was entered in the age column for over 75% of the patients in the various years.

Table 1 shows the distribution of the 2070 TFT requested and sent for analysis in the various years. From 2008 to 2011 a gradual increase was recorded in the number of TFT requested and sent for analysis. The lowest request (342) was made in 2008 and the highest (483) was made in 2011. In 2012 the number (378) of TFT requested and sent for analysis was 21.7% lower than the 2011 requests. The total number (%) of TFT completed and results received in the various years are also presented in Table 1. The combination of TFT requested and completed in the various years is presented in Table 2. Plasma [TSH] and [FT4] was the major combination of tests requested, which is standard procedure for TFT. The TFT combination that included plasma [FT3] was requested in fewer occasions in the various years, with the highest is 2011. Classification of the TFT results received in the various years is presented in Table 3. The percent distribution of the concordant results was higher in all the various years compared to the discordant results. The highest percentage (20.1%) of discordant results was obtained in 2010, followed by 19.3% in 2011, with the lowest (14.0%) in 2008. The unclassified results were mainly normal plasma [FT4] but with no corresponding results for plasma [TSH] or [FT3].

The concordant and discordant TFT results obtained in the various years are summarized in Table 4. Euthyroid status was the highest reported cases throughout the various years. Primary Hyperthyroidism was the most prevalent thyroid dysfunction results reported throughout the various years. This was followed by subclinical hyperthyroidism. Prevalence of primary hypothyroidism and subclinical hypothyroidism were each slightly above 5.0% in each of the various years. Non-thyroidal illness and other thyroid disorders were also slightly above 5.0% in each of the various years.

Table 1: Number of Thyroid Function Tests (TFT) requested and sent for analysis and TFT results received and recorded in the various years

TFT	2008	2009	2010	2011	2012
Requested	342	394	473	483	378
Results recorded	207 (60.5%)	248 (62.9%)	393 (83.1%)	379(78.5%)	258 (68.3%)

Table 2: Number of thyroid function tests combination completed and results received in various years

TFT requested	2008	2009	2010	2011	2012
Plasma [TSH]	207	248	393	379	258
Plasma [FT4]	207	248	393	379	258
Plasma [FT3]	60	93	182	262	156

Table 3: Classification of TFT results received in the various years

	2008 (n = 207)	**2009 (n = 248)**	**2010 (n = 393)**	**2011 (n = 379)**	**2012 (n = 258)**
Concordant	177 (85.5%)	205 (82.7%)	308 (78.4%)	300 (79.1%)	211 (81.8%)
Discordant	29 (14.0%)	39 (15.7%)	79 (20.1%)	73 (19.3%)	44 (17.0%)
Unclassified	1 (0.5%)	4 (1.6%)	6 (1.5%)	6 (1.6%)	3 (1.2%)

Table 4: Summary of concordant and discordant TFT results obtained in the various years

	Euthyroid	Primary Hyperthyroidism	Primary Hypothyroidism	Subclinical Hyperthyroidism	Subclinical Hypothyroidism	Non-thyroidal illness
2008 (n = 206)	100 (48.5%)	75 (36.4%)	2 (1.0%)	17 (8.3%)	2 (1.0%)	10 (4.9%)
2009 (n = 244)	137 (56.1%)	63 (25.8%)	5 (2.1%)	17 (7.0%)	12 (4.9%)	10 (4.1%)
2010 (n = 387)	175 (45.2%)	122 (31.5%)	11 (2.8%)	46 (11.9%)	13 (3.4%)	20 (5.2%)
2011 (n = 373)	177 (47.4%)	107 (28.7%)	16 (4.3%)	35 (9.4%)	22 (5.9%)	16 (4.3%)
2012 (n = 255)	123 (48.2%)	72 (28.2%)	16 (6.3%)	25 (9.8%)	9 (3.5%)	10 (3.9%)

For further analysis the TFT results were separated according to gender. Table 5 shows the gender distribution of the TFT requested and sent for analysis in the various years. The total number of female patients was more than twice the number of male patients in all the years. Gender distribution of the TFT results received in the various years is presented in Table 6. Although more female TFT results were received the percent frequency of the results received for both male and female patients were similar. Thus, no significant differences were observed in the proportions of TFT results received for both males and females patients in the various years. No specific reasons can be given to explain the similarity in the proportionality of the results received. The TFT results received for both males and females in the various years were classified into concordant and discordant results. There were no significant differences in the percent distribution of the concordant results among the males in the various years and also among the females in the various years. However, the percent distribution of the concordant results of the females was significantly ($p < 0.05$) higher than those of the males in the various years. Similar findings were obtained for the discordant results among the males and among the females, and also between the males and females in the various years. These results are summarized in Table 7. Euthyroid status was high among the male and female patients throughout the various years.

Primary hyperthyroidism and subclinical hyperthyroidism were the prevailing thyroid disorders among the male and female patients. However, these disorders were significantly higher among the females compared to the males in the various years. The prevalence of Primary Hypothyroidism and subclinical hypothyroidism were each below 5.0% in the male and female patients in the various years. However, it was slightly higher among the female patients compared to the male patients in some of the years. Non-thyroidal illness and other results were more prevalent among the female patients in some of the years.

Table 5: Distribution according to gender of TFT requested and sent for analysis in various years

	2008 (n = 342)	**2009 (n = 394)**	**2010 (n = 473)**	**2011 (n = 483)**	**2012 (n = 378)**
Males	106 (31.0%)	124 (31.5%)	137 (29.0%)	142 (29.4%)	116 (30.7%)
Females	236 (69.0%)	270 (68.5%)	336 (71.0%)	341 (70.6%)	262 (69.3%)

Table 6: Gender distribution of TFT results for males and females received and recorded in various years

	TFT	2008	2009	2010	2011	2012
Males	Sent	N = 106	N = 124	N = 137	N = 142	N = 116
	Received recorded	64 (60.4%)	72 (58.1%)	117 (85.4%)	117 (82.4%)	72 (62.1%)
Females	Sent	N = 236	N = 270	N = 336	N = 341	N = 262
	Received recorded	143 (60.6%)	176 (65.2%)	276 (82.1%)	262 (76.8%)	186 (61.0%)

Table 7: Summary of concordant and discordant TFT results for males and females obtained in the various years

	Gender	Euthyroid	Primary Hyperthyroidism	Primary Hypothyroidism	Subclinical Hyperthyroidism	Subclinical Hypothyroidism	Non-thyroidal illness
2008 (n = 206)	Males	25 (12.1%)	25 (12.1%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	5 (2.4%)
	Females	75 (36.4%)	50 (24.3%)	0	15 (7.3%)	0	5 (2.4%)
2009 (n = 244)	**Males**	39 (16.0%)	16 (6.6%)	2 (0.8%)	3 (1.2%)	8 (3.3%)	3 (1.2%)
	Females	98 (40.2%)	47 (19.3%)	3 (1.2%)	14 (5.7%)	4 (1.6%)	7 (2.9%)
2010 (n = 387)	**Males**	44 (11.4%)	41 (10.6%)	5 (1.3%)	13 (3.4%)	5 (1.3%)	5 (1.3%)
	Females	131 (33.8%)	81 (20.9%)	6 (1.6%)	33 (8.5%)	8 (2.1%)	15 (3.9%)
2011 (n = 373)	**Males**	52 (13.9%)	42 (11.3%)	4 (1.1%)	8 (2.1%)	8 (2.1%)	2 (0.5%)
	Females	125 (33.5%)	65 (17.4%)	12 (3.2%)	27 (7.2%)	14 (3.8%)	14 (3.8%)
2012 (n = 255)	**Males**	33 (12.9%)	22 (8.6%)	5 (2.0%)	2 (0.8%)	6 (2.4%)	4 (1.6%)
	Females	90 (35.3%)	50 (19.6%)	11 (4.3%)	23 (9.0%)	3 (1.2%)	6 (2.4%)

DISCUSSION:

The results obtained in the current study indicated that thyroid disorders were present in most of the patients for which TFT were requested and the results received and recorded. Thyroid disorders were prevalent in 51.5% of the patients in 2008, 43.9% of the patients in 2009, 54.8% of the patients in 2010,

52.6% of the patients in 2011 and 51.8% of the patients in 2012. These prevalence values obtained for each of the five years (2008 to 2012) were higher than the prevalence values reported for similar hospital based studies in Western part of Nepal (33.66%), Eastern part of Nepal (30.0%) and Kavre Nepal (25.0%) [12,13].

In our study the prevailing thyroid disorder in each of the five years was primary hyperthyroidism, 36.4% in 2008, 25.8% in 2009, 31.5% in 2010, 28.7% in 2011 and 28.25 in 2012. This was followed by subclinical hyperthyroidism. The total prevalence of primary and subclinical hyperthyroidism obtained in each of the five years (Table 4) were higher than the 24.8% reported among patients in Western part of Nepal, 9.0% in Kavre and 1.8% in Pondicherry India [12, 14], but lower than the 58.2% reported by Gomez et al. [15]. Some authors have reported high prevalence of hyperthyroidism among females compared to males in iodine-replete areas [16, 17]. The prevalence of primary and subclinical hyperthyroidism was higher among the female patients compared to the male patients. The high prevalence of primary and subclinical hyperthyroidism among female patients in our study was higher than the prevalence reported for both Western and Eastern parts of Nepal and for Kavre Nepal [12, 13].

Some possible reasons for the high prevalence of hyperthyroidism obtained in the present study include selection bias of a hospital-based study; it may also be due to continuous high consumption of iodized salt. A recent report indicated that iodine deficiency was not a public health problem among school children in Honiara Solomon Island, because of successful implementation of USI strategy, which included availability and use of adequately iodized salt [8]. It is however important to ensure effective monitoring of the USI strategy. One of the consequences in the failure of effective monitoring is the excessive intake of iodine. This may have a complex disruptive effect on thyroid metabolism, which may result in increased risk of thyroid cancer and either hypothyroidism or hyperthyroidism in susceptible individuals [19 – 21].

The prevalence of primary and subclinical hypothyroidism obtained in our present study in each of the five years (Table 4) was lower than the 8.9% prevalence reported for Western part of Nepal [12] and the 9.4% report by Usha et al in India [17], but within the 4.0% and 5.4% prevalence reported for similar studies in Pakistan [18].

The recent report [8] indicating high median UIC (328.0ug/L) among schoolchildren in Honiara, with 55.6% having UIC over 300ug/L and that 18.8% had UIC over 500.0ug/L strongly indicates the need to effectively monitor the implementation of the universal salt iodization (USI) strategy for the control of iodine deficiency in the Solomon Islands. This

report together with the results obtained in the present retrospective assessment of the Thyroid status of patients strongly supports the need for screening of women of childbearing age as a way of monitoring their iodine and thyroid status. Early detection of abnormalities can be corrected or treated so as to prevent the negative effects of thyroid dysfunction.

In conclusion, a search of the literature indicated that no previous study that evaluated the thyroid status of the population in Solomon Islands has been published. This retrospective study clearly indicates prevalence of both primary and subclinical hyperthyroidism in the Solomon Islands with high prevalence among female patients compared to male patients.

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EFFICACY AND SAFETY OF TRIPLE DRUG FIXED-DOSE COMBINATION OF TELMISARTAN, AMLODIPINE AND HYDROCHLOROTHIAZIDE IN THE MANAGEMENT OF HYPERTENSION

Subrato Bhattacharya and *A. A. Faruqui

Consultant Physician & Diabetologist, Bankura, Kolkata;

*Clinical Pharmacologist, Andheri East, Mumbai

***Correspondence Author**: drfaruqui@gmail.com

Running Title: Efficacy and Safety of Triple Drug Fixed-Dose Combination in hypertension

ABSTRACT:

Hypertension is a major health problem in India. Different clinical studies have reported that reducing the blood pressure can substantially decrease cardiovascular risk and all cause mortality. This study was conducted to evaluate the efficacy and safety of triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorthiazide 12.5mg. 41 hypertensive patients having systolic blood pressure ≥ 160 mmHg and diastolic blood pressure ≥100 mmHg who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan-Hydrochlorothiazide combinations were enrolled in this study. The treatment period was of 120 days and patients were administered once daily fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorthiazide 12.5mg. Patients were evaluated on 15th, 30th, 60th and 120th days of treatment. There was statistically significant ($p<0.0001$) decrease in systolic and diastolic blood pressure from baseline to 15th, 30th, 60th and 120th days of treatment. At the end of the study period of 120 days 95.6% & 94.4% patients of age group >60 years and <60 years achieved the JNC VIII recommended target goal respectively. This triple drug fixed dose combination of Telmisartan, Amlodipine and hydrochlorothiazide was found to be effective and safe option for the optimal management of hypertension without any safety concern.

Keywords: Diastolic pressure, Systolic pressure, Hypertension, combination, Telmisartan, Amlodipine, Hydrochlorothiazide

Submitted: July 2014; Accepted: August 2014

INTRODUCTION:

Hypertension is a major health problem in India. It is a major risk factor for cardiovascular disease and contributes significantly to cardiovascular morbidity and mortality. Different clinical studies have reported that reducing BP (blood pressure) can substantially decrease cardiovascular risk and all cause mortality [1]. Clinical studies have shown that every 20 mmHg increase in systolic blood pressure (SBP), or 10 mmHg increase in diastolic blood pressure (DBP), doubles the risk of cardiovascular disease (CVD). It has been observed in meta-analysis that every 20mmHg reduction in SBP can result in 40–45% reduction in cardiovascular disease [2]. Thus for the optimal management of hypertension and for the prevention of cardiovascular morbidity and mortality the goal of therapy is directed to reduce BP effectively. Ample evidences are available from the different clinical studies that multiple antihypertensive therapies are often required for effective control of BP. Although monotherapy is effective in some patients, over 50% of patients may require combination therapy for appropriate control of BP [3]. Based on cumulative data from different clinical trials, it has been estimated that at least 25% of patients require triple combination therapy to achieve BP control [4].

Multiple pills are the most important reason of poor adherence and posses the big challenge in achieving the target BP goal set by JNC VIII (Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Fixed-dose single-pill combination therapies have been associated with better patient adherence and compliance [5]. This approach may facilitate better clinical outcomes, compared with traditional and time-consuming stepped care and add on algorithms in the management of hypertension.

This study was conducted to find out the efficacy and tolerability of fixed dose combination of Telmisartan, Amlodipine and Hydrochlorothiazide in the management of Stage 2 hypertension.

SUBJECTS AND METHODS:

This was a post marketing, non-randomized, open, non-comparative study which was conducted in Kolkata. The triple drug fixed dose combination of Telmisartan 40 mg, Amlodipine 5 mg and Hydrochlorothiazide 12.5 mg was administered to hypertensive patients once daily for 4 months (120 days) who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan-Hydrochlorothiazide combinations. Informed consent was obtained from the patients and the post marketing surveillance (PMS) was in accordance with the principles in declaration of Helsinki and Good Clinical Practice (GCP).

Inclusion Criteria:

Both male and female hypertensive patients who were uncontrolled on dual drug therapy with Telmisartan-Amlodipine or Telmisartan-Hydrochlorothiazide combinations, aged ≥ 45 years old with mean seated cuff SBP (systolic blood pressure) ≥160 mmHg and DBP (diastolic blood pressure) ≥100 mmHg and who were willing to give informed consent were included in this study

Exclusion Criteria:

Patients with any condition which in the opinion of the investigator makes the patient unsuitable for inclusion like; known or suspected secondary hypertension, history of asthma or angina, female patient who was pregnant or willing to get pregnant, and patients with known hypersensitivity to any of the ingredient of the fixed dose combination were excluded from the study. Patient with kidney and liver failure were also excluded from the study.

Patient Distribution:

A total of 41 patients of age range 45-75 years old were included in this study. Out of 41 patients 26 (63.4%) were male and 15 (36.6%) were female patients (Table 1).

Efficacy and Safety Evaluations:

There were two outcome variables to evaluate the Efficacy: Primary outcome and Secondary outcome.

Primary outcome Measures: SBP and DBP were included in primary outcome, which were evaluated at 15th, 30th, 60th and 120th day of treatment.

Secondary Outcome Measures: Global assessment of efficacy and safety included in this outcome. Investigator assessed the efficacy by using a three point scale as poor, good and excellent. Poor was for those patients, whose BP slightly changed from baseline and in the range of 0-5%, good when BP changed by 15% from the baseline and excellent for those who achieved the target BP goal set by JNC VIII which are <150/90 mmHg for elder patients aged above 60 year and 140/90 mmHg for those aged less than 60 years.

Global assessment regarding safety was evaluated by recording any adverse event or any complaint during the therapy in every visit. Safety outcomes include mainly symptoms related to hypotension like blurred vision, confusion, dizziness, nausea or vomiting, weakness and others. Patients were interviewed and asked about the appearance of any adverse events at every visit throughout the study period of 120 days.

Statistical analysis:

Data analysis on patient demographics and various outcome measures were performed using graph pad prism 6. Comparison between the baseline values with the value on the 15th, 30th, 60th and 120th day of treatment were

made, as well as comparison in between these days were made by applying one way analysis of variance and the Turkeys multiple comparison test. Value of P<0.05 were considered as significant.

Table 1: Baseline characteristics of patients

Baseline characteristics of patients	
Males	26 (63.4%)
Females	15 (36.6%)
Age range	45 – 75 years
Number patients over 60 years	23 (56.1%)
Number patients below 60 years	18 (43.9%)
SBP (Mean ± SD) mm Hg	171.0 ± 8.89
DBP (Mean ± SD) mm Hg	100.0 ± 4.30

RESULTS:

SBP and DBP were recorded at baseline and at every visit throughout the study period of 120 days. In addition, overall efficacy and tolerability was assessed at the end of the study period. The baseline characteristics of patients are summarized in the Table 1.

Systolic Blood Pressure (SBP):

The SBP was measured at base line and then subsequently at 15th, 30th, 60th and 120th days of treatment. The baseline SBP Mean ± SD was 171.0 ± 8.89 mmHg. The mean SBP at 15th, 30th, 60th and 120th days of treatment were 163.0 ± 7.34mmHg, 146.0 ± 8.82 mmHg, 135.0 ± 8.23 mmHg and 130.0 ± 2.73 respectively. There was statistically significant (p<0.0001) decrease in SBP from the baseline to the 15th, 30th, 60th and 120th day of treatment (Tables 2 and 3). SBP decreased by 8.0 ± 1.55 mmHg, 25 .0 ± 0.07 mmHg, 36.0 ± 0.66 mmHg and 41.0 ± 6.16 mmHg from the baseline to 15th, 30th, 60th and 120th day of treatment respectively.

Table 2: Effect of triple drug therapy on systolic blood pressure

	Baseline	Day 15***	Day 30***	Day 60***^	Day 120***^
Mean ± SD mmHg	171.0 ± 8.8	163.0 ± 7.3	146.0 ± 8.8	135.0 ± 8.2	130.0 ± 2.7

*** p<0.0001 vs. baseline, ^ p<0.0001 vs. Day 30

Table 3: Change (∆) in SBP from baseline

	Day 15	Day 30	Day 60	Day 120
∆ SBP from baseline (mmHg)	-8.0 ± 1.55	-25.0 ± 0.07	-36.0 ± 0.66	-41.0 ± 6.16

Diastolic Blood Pressure (DBP):

DBP was measured at base line and then subsequently at 15th, 30th, 60th and 120th days of treatment. The baseline DBP Mean ± SD was 100.0 ± 4.30 mmHg. The mean DBP at 15th, 30th, 60th and 120th days of treatment were 92.9 ± 3.64 mmHg, 87.0 ± 4.32 mmHg, 82.6 ± 3.09 mmHg and 77.0 ± 4.05 respectively. There was statistically significant (p<0.0001) decrease in DBP from the baseline to the 15th, 30th, 60th and 120th day of treatment (Tables 4 and 5). DBP decreased by 7.1 ± 0.66 mmHg, 13.0 ± 0.02 mmHg, 17.4 ± 1.21 mmHg and 22.5 ± 0.25 mmHg from the baseline to 15th, 30th, 60th and 120th day of treatment respectively.

Achievement of JNC VIII goal:

Target BP goal is set by JNC VIII based on age and complications. Recommended target goal for patients >60 years old is 150/90 mmHg and 140/90 mmHg for patients of age <60 years. During and after the treatment following are the percentage of patients achieving the target BP goal (Tables 6 and 7).

Table 4: Effect of triple drug therapy on DBP

	Baseline	Day 15***	Day 30***	Day 60***^	Day 120***^
Mean ± SD mmHg	100.0 ±4.30	92.9±3.64	87.0±4.32	82.6±3.09	77.5±4.05

***p<0.0001 vs. baseline, ^p<0.0001 vs. day 30th

Table 5: Change (∆) in DBP from the baseline

	Day 15	Day 30	Day 60	Day 120
∆ DBP from baseline (mmHg)	-7.1 ± 0.66	-13.0 ± 0.02	-17.4 ± 1.21	-22.5 ± 0.25

Table 6: Percentage of patients (>60 years) achieving the target BP (<150/90 mmHg)

	Day 30	Day 60	Day 120
% of patients (n)	(17/23) 73.9%	(21/23) 91.3%	(22/23) 95.7%

Table 7: Percentage of patients (<60 years) achieving the target BP (<140/90mmHg)

	Day 30	Day 60	Day 120
% of patients (n)	(12/18) 66.7%	(16/18) 88.9%	(17/18) 94.4%

Global Assessment of Efficacy and Tolerability:

As discussed in Efficacy and Safety Evaluations, Efficacy was considered in three grades: Excellent, Good and Poor. On the 30th day of treatment 73.9% and 66.7% of patients of age group >60 years and <60 years respectively showed efficacy as excellent. Similarly on 60th day of therapy 91.3% & 88.9% of patients aged >60 years and <60 years respectively showed efficacy as excellent. 95.7% and 94.4% of patients of age group >60 years and <60 years respectively showed efficacy as excellent after the completion of study period of 120 days. Overall clinical efficacy as good and poor on 30th and 60th day of treatment without regarding the age differentiation were 19.5% (8/41) and 7.3% (3/41) respectively. Only 4.8% (2/41) of patients showed poor efficacy after the completion of study period of 120 days. Moreover 2 out of 41 patients complained about the side effects mainly related with the symptoms of hypotension which were mild in nature and do not warn the safety concern.

DISCUSSION:

Different clinical studies using fixed dose combinations of angiotensin receptor blocker (ARBs) / hydrochlorothiazide (HCTZ) and ARBs/Amlodipine (Calcium channel blocker: CCB) have been shown to be efficient and safe in reducing BP [6,7]. Moreover it is proven that delaying BP control by strategies of increasing dose, increases the risk of cardiovascular events in comparison with the initial use of combinations therapy [8]. Ample evidences are available from the different clinical studies that multiple antihypertensive therapies are often required for effective control of blood pressure. European guideline and many more guideline suggest the need of fixed dose combination therapy for the treatment of hypertension [9,10]. Based on cumulative data from different clinical trials, 25% of patients required triple drug combination therapy to achieve target BP [11].

In this study we evaluated the efficacy and safety of triple drugs fixed dose combination of Telmisartan 40 + Amlodipine 5mg+ Hydrochlorthiazide 12.5 mg in the management of hypertension. The results of the present study are in line with the results of previous studies [12,13,14].

A study conducted by Duprez D et al [12] has shown that after 6 weeks (42 days) of treatment, reduction in systolic/diastolic ABP (ambulatory blood pressure) were greater in the triple combination (ARB/CCB/ HCTZ) group than in the dual therapy (ARB/HCTZ) group (-22.0/-13.3 vs. -17.4/-8.1 mmHg). Similarly in the present study at 30th and 60th day of treatment reduction in systolic/diastolic blood pressure were 25.0 ± 0.07 / 13.0 ± 0.02 and 36.0 ± 0.66 / 17.4 ± 1.21 mmHg respectively. Thus the results of the present study on 30th day are comparable or even better than the result of the above mentioned study after 6 weeks of treatment.

Another study conducted by Abhichandani et al [13] on triple drug combination (ARB+CCB+Diuretic) in the management of hypertension with or without co-morbidities for 120 days reported change in SBP/DBP from baseline to 60th and 120th day of treatment ($p<0.0001$) as -19.0 ± 2.61 / -16.6 ± 1.38 mmHg and -25.0 ± 4.07 / -21.6 ± 1.37mmHg respectively. Results of the present study are better than the study conducted by Abhichandani et al (-36.0 ± 0.66 / -17.4 ± 1.21mmHg vs. -19.0 ± 2.61 / -16.6 ± 1.38 and -41.0 ± 6.16 / -22.5 ± 0.25 vs. -25.0 ± 4.07 / -21.6 ± 1.37mmHg) at 60th and 120th days of treatment respectively [13].

A study conducted by Maladkar et al used the same triple drug combination for 12 weeks in the management of hypertension [14]. There was statistically significant decrease in SBP/DBP from baseline to 12th week (end of the treatment) of treatment mean ± SD (165.7 ± 15.66 / 100.2 ± 10.31 mmHg vs. 122.5 ± 9.38 / 79.4 ± 6.64 mmHg). Similarly the present study reported statistically significant ($p<0.0001$) decrease in SBP/DBP from baseline to the end of 120th days (171.0 ± 8.89 / 100.0 ± 4.30 mmHg vs. 130.0 ± 2.73 / 77.5 ± 4.05 mmHg). Thus the results of the present study are comparable to the studies done earlier.

Regarding the achievement of target BP; the present study reported higher percentage of hypertensive patients achieving the target BP in comparison to previous studies. In a study conducted by Khemchandani et al use of same triple drug combination for 2 months (60 days) in the management of hypertension resulted in 65% and 85% of patients achieving the target BP at 30th and 60th day of treatment respectively [15]. While in the present study 91.3% and 88.8% of patients of age group >60 and <60 years old achieved the JNC VIII target at the 60th day of treatment respectively.

In the current study treatment was well tolerated but 2 out of 41 patients (4.8%) complained about the side effects like headache, general weakness and dizziness. Side effects were mild in nature and did not require discontinuation of therapy.

Our data indicates that triple drug combination was highly effective in achieving the target blood pressure without any major adverse event.

CONCLUSION:

Triple drug fixed dose combination therapy of Telmisartan, Amlodipine and Hydrochlorothiazide is an effective, safe and convenient treatment approach in achieving the target blood pressure goal in hypertensive patients.

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A CASE REPORT

GROWTH IN THE VENTRAL PORTION OF TONGUE: CASE REPORT

Eshitha Ebrahim, *Prasanna Kumar Rao, Laxmi kanthChatra, Prashanth Shenai, Veena KM, Rachana V Prabhu, Tashika Kushraj & Prathima Shetty

Department of Oral Medicine and Radiology, Yenepoya Dental College, Yenepoya University, Mangalore, Karnataka, India

***Correspondence Author**: drjpkrao@gmail.com

RUNNING TITLE: Traumatic fibroma

ABSTRACT:
Traumatic fibroma, (also called Irritation fibroma, Focal fibrous hyperplasia, Fibrous nodule or Fibroepithelial polyp) is the benign soft tissue neoplasm occurring in the oral cavity. It is a painless, localized, mass of normal color with a smooth surface and a sessile or, occasionally, pedunculated base. The buccal mucosa, labial mucosa, tongue and gingiva are common sites. Here we report a rare case of traumatic fibroma in the ventral portion of the tongue in a patient twenty years of age.

Keywords: Fibrous hyperplasia, Tongue Growth, Traumatic Fibroma.
Submitted: April 2014, Accepted: July 2014

INTRODUCTION:

Irritation fibroma or traumatic fibroma, was first reported in 1846 as polypus and fibrous polyp [1]. It is a common submucosal response to trauma from teeth or dental prostheses and found in 1.2% of adults worldwide. It is a benign exophytic oral lesion [1].

Clinically it appears as a painless, localized, mass of normal color with a smooth surface and a sessile or, occasionally, pedunculated base [2]. It may be formed by the proliferation of dense fibrous "scar" tissue which can result from a single traumatic episode or from repeated, less severe traumatic episodes and chronic inflammation or infection. It is most common in the third to fifth decades of life [2]. The prevalence of oral mucosa fibroma is higher in female (71%) then male (29%) [3]. Irritation fibroma can occur anywhere in the mouth but the buccal mucosa along the bite line is the most common sites [4, 5]. Here we report a rare case of traumatic fibroma in the ventral portion of the tongue in a twenty years old patient.

CASE REPORT:

A 20 year-old male patient, reported to the department of oral medicine and maxillofacial radiology, with the chief complaint of a growth in the ventral portion of the tongue [Figure 1]. The lesion was asymptomatic and had been present for one year. There was an increase in size of the growth since past 4 months. Medical history was uneventful and there was no contributory past dental history.

Patient had tongue thrusting habit since childhood. General and extraoral examinations appeared non contributory. On intraoral clinical examination, a penduculated soft tissue nodule measuring 0.5 x 0.4 mm was noticed in the ventral portion of the tongue, extending superiorly 1.0 mm below from the tip of the tongue along the midline and inferiorly 1.0 cm away from the lingual frenum. Colour of the growth was same as that of the adjacent mucosa, with no surface ulceration, erythema or pus discharge. The lesion was of soft inconsistency, covered by intact mucosa. The surrounding mucosa was normal and the patient's oral hygiene was satisfactory. The incisal edges of left mandibular central and lateral incisors were found to impinge the growth.

Based on the clinical appearance and the lesion's history, the differential diagnosis included mucocele, giant cell fibroma, papilloma, granular cell tumor. The lesion was excised under local anaesthesia and hemorrhage control was achieved. Filing the sharp edges of the offending teeth was also done.

Microscopic examination of the excised specimen revealed a nodular mass of fibrous connective tissue covered by stratified squamous epithelium. The connective tissue is usually dense and collagenized. The lesion is not encapsulated and the collagen bundles may be arranged in a radiating, circular or haphazard fashion. The covering epithelium shows atrophy of the rete ridges and the surface may exhibit hyperkeratosis. Scattered lymphocytes and plasma cells may be seen, most often beneath the epithelial surface [Figure 2].

No postoperative complications were present and the surgical site appeared to have healed well. The patient presented for follow-up examination seven days, fifteen days, and two years postoperatively [Figure 3]. There was no evidence of recurrence of the lesion, and the patient had no complaints pertaining to the lesion.

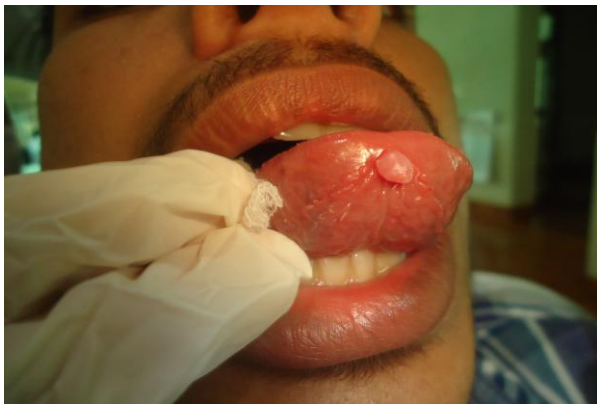

Figure 1: A growth in the ventral tongue

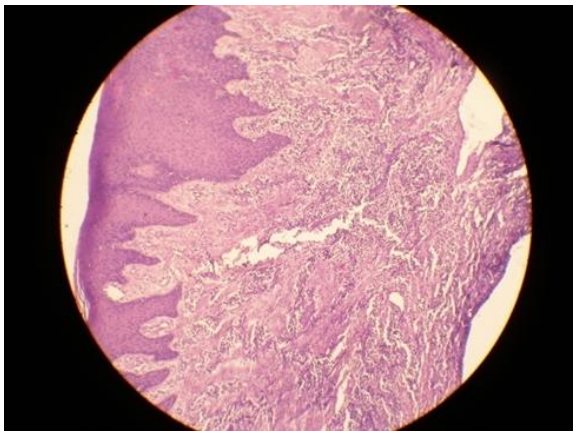

Figure 2: Histopathologic picture showing proliferation of fibroblasts and deposition of collagen fibers in short and cluttered beams

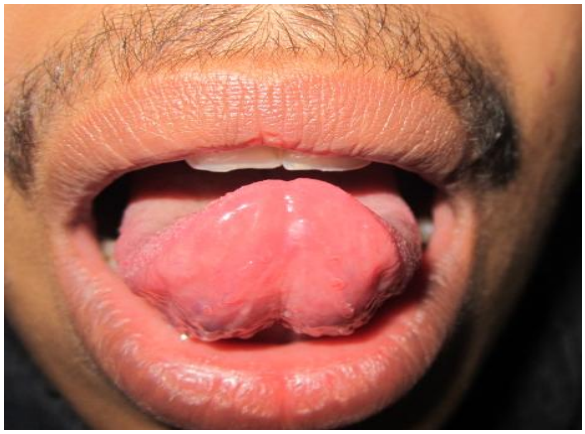

Figure 3: Follow up after 7 days

DISCUSSION:

Traumatic fibroma is most common in the third to fifth decades of life [2]. In the present case, the patient is a twenty year old male. Although irritation fibroma can occur anywhere in the mouth, the buccal mucosa along the bite line is the most common sites, however in the present case the fibroma is in the ventral surface of tongue, which is rare. This inflammatory hyperplasia is the most common oral mucosal mass submitted for biopsy and is usually composed of Types I and III collagen. It is a reactive hyperplasia of fibrous connective tissue in response to local irritation or trauma [3, 6]. Studies on the mean sizes of the different benign tumors have found that the largest of them were lipomas, while on the other hand, the smallest were the fibromas and papillomas [7, 8]. Traumatic fibromas have no malignant potential [9, 10]. Multiple fibromas are seen in conditions like familial fibromatosis, fibrotic papillary hyperplasia of the palate,

tuberous sclerosis, or multiple hamartoma syndromes (Cowden syndrome) [11].

The irritation fibroma is usually treated by conservative surgical excision, electro surgery or soft tissue laser. In the present case surgical excision was the treatment done. Abdulhamed and Merry in their study proved that diode laser provides a marked clinical improvement in excision of soft tissue oral lesions including traumatic fibroma, without the need for surgical intervention [12].

CONCLUSION:

The great majority of soft tissue masses of the oral mucosa are considered to be reactive rather than neoplastic in nature. These benign reactive proliferations are much more common in the mouth than the other parts of body, because of the tendency of mucosa to get traumatized by sharp, hard teeth and prosthetic appliances. The differential diagnosis of irritation fibroma is based mainly on the location of the soft tissue swelling and the final diagnosis should be always based on histopathological examination.

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CASE REPORT

CAPILLARY HAEMANGIOMA – A CASE REPORT

Nidhin Naroor, *Prashanth Shenai, Laxmikanth Chatra, VeenaKM, Prasanna Kumar Rao, Rachana V Prabhu, Tashika Kushraj, Prathima Shetty & Shaul Hameed

Department of Oral Medicine and Radiology, Yenepoya Dental College, Yenepoya University, Mangalore, Karnataka, India

***Correspondence Author**: ydcomr@gmail.com

ABSTRACT:
Haemangioma are relatively uncommon lesions, but head and neck is a common region. Although haemangioma is common in head and neck its rarely seen intraoraly. Haemangioma is histologically classified into capillary and cavernous forms. Ultra sound imaging, Computed tomography (CT) and magnetic resonance imaging (MRI) can be used for volumetric analysis of haemangioma. This article reports a rare case of capillary haemangioma in the tongue.

Key words: Haemangioma, intra oral, vascular malformation
Submitted: June 2014; Accepted: August 2014

INTRODUCTION:

Haemangioma and vascular malformations are diagnosed fairly easily with careful history and physical examination. The head and neck region is the site for haemangioma development which is mostly seen in childhood (about 60% of cases) [1, 2]. The gender of the patient and the size of the haemangioma do not influence the speed or the completeness of resolution among the different localizations of vascular malformations in the head and neck region; the tongue has specific characteristics because it is not only susceptible to trauma, but also may cause speaking or swallowing problems [2].

Here we are reporting a case of haemangioma present on tongue of 46 year old male patient. Ethical clearance was taken from University Ethical department for publishing this case report.

CASE REPORT:

A-46-year old male patient reported to the dental hospital with the chief complaint of decay on lower right back tooth since 6 months. He had history of pain in right lower back teeth region when chewing. His general

physical examination and extra oral examination were non contributory. On intra oral examination dental caries were found in relation to right maxillary second and third molar, left maxillary third molar, left mandibular first, second and third molar and in right mandibular second molar. In the tongue a solitary swelling of size 1.0×1.5 cm was seen on the dorsal surface. It was greyish blue in colour and oval in shape [fig 1]. The patient gave history of bluish discolouration in the tongue which was present during childhood. The surrounding tissue appears to be normal. There was restriction in tongue movement due to tongue tie [fig 2]. On palpation all inspectory findings regarding size, shape and site was confirmed. The swelling was non tender, non fluctuant, non compressible. No bleeding or pus discharge was present on palpation. Diascopy test was performed and blanching was noticed [fig 3]. Based on the clinical presentation and chair side investigation the swelling was provisionally diagnosed as haemangioma. Ultrasonography of tongue shows a small hypo echoic lesion on the ventral aspect of tongue with vascularity on colour Doppler, suggestive of haemangioma.

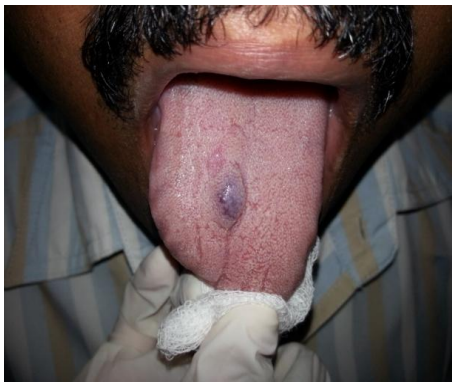

Fig 1- Bluish discolouration seen on dorsum of tongue

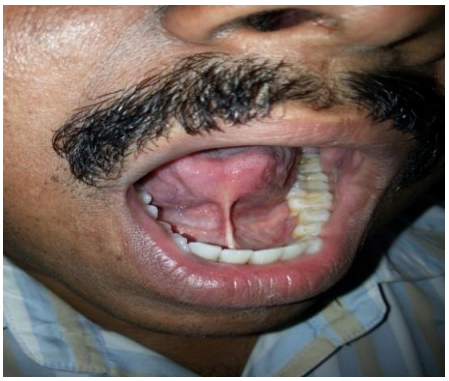

Fig 2- Tongue tie

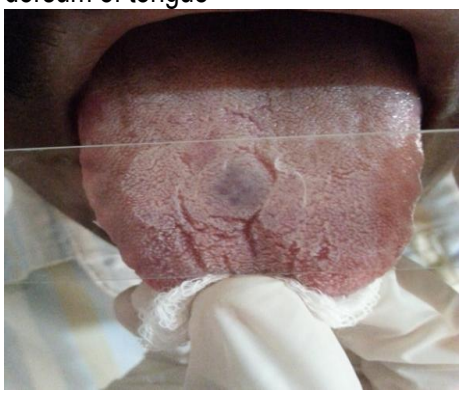

Fig 3- Blanching seen in diascopy

DISCUSSION:

Haemangioma and vascular malformations are diagnosed fairly easily with a careful history and a physical examination. Haemangioma is histologically classified into capillary and cavernous forms. Capillary haemangioma is composed of many small capillaries lines by a single layer of endothelial cells [2]. Supported in a connective tissue stroma of varying density, Cavernous haemangioma are composed of large, irregular, deep dermal and subcutaneous blood-filled channels that impart a purplish discoloration to the overlying skin [3]. In our present case it was diagnosed as capillary haemangioma. Haemangiomas are typically soft, poorly defined, and readily blanch with compression, giving them a characteristic "bag of worms" feel. Often, a capillary component overlies a cavernous component, and it may be difficult to distinguish these components histologically [3]. Our present case also showed similar features. It has a higher prevalence in females than in males. The head and neck is more commonly affected especially the face, oral mucosa, lips, tongue and trunk [4, 5]. In the present case lesion was present on dorsum of tongue in 46 year old male patient. Clinically haemangioma can be characterized as a soft, smooth or lobulated, sessile or pedunculated and may be seen in any size from a few millimetres to several centimetres [5]. The colour of the lesion ranges from pink to red purple and tumour blanches on the application of pressure, and haemorrhage may occur either spontaneously or after minor trauma. They are generally painless [6]. In our present case the colour of the lesion was greyish blue and painless. Even though haemangioma is considered one of the most common soft tissue tumours of the head and neck, it is rarely seen in the oral cavity and uncommonly encountered by the clinicians. Radiographic imaging is indicated preoperatively in selected cases where large lesions may impinge on vital anatomical structures, such as the facial nerve or orbit. Ultra sound imaging, Computed tomography (CT) and magnetic resonance imaging (MRI) can also be used for volumetric analysis of haemangioma and vascular malformations [4]. In this case the Ultrasonography of tongue shows a small hypo echoic lesion on the ventral aspect of tongue with vascularity on colour Doppler, suggestive of haemangioma. Management of haemangioma depends on a variety of factors, and most true haemangioma requires no treatments. However, 10-20% requires treatment because of the size, exact location, and stages of growth or regeneration [6]. There are many treatment modalities reported in the literature for head and neck haemangioma, including wait and watch policy, for spontaneous involution, intralesional and systemic corticosteroid treatment, embolization, excision, electrolysis and thermocautery, immunomodulatory therapy with interferon

Alfa-2a, and laser photocoagulation [7]. Recently, Sclerotherapy has been employed largely because of its efficiency and ability to conserve the surrounding tissues [4] Growing haemangioma can be treated effectively by using systemic drug therapy, sclerotherapy, laser therapy or combined therapy. Surgery is usually indicated when there is no response to systemic treatments, or even for aesthetic reasons, surgery is also performed as a simple excision in combination or not with plastic surgery. Kutluhan [8] used plasma knife surgery for excision of haemangioma of tongue. In this present case surgical excision of the lesion was advised to the patient, but the patient was not willing for the treatment procedure. Patient was recalled for review after one month, but the patient did not come for follow up.

CONCLUSION:

Oral hemangiomas are a rare clinical finding. However, they can be easily diagnosed provided care is taken in eliciting a proper history and careful clinical examination. Surgical therapy has proved successful in most cases, could be performed safely.

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CASE REPORT

CHRONIC ARTHRITIS IN JUVENILE BEHCET'S SYNDROME: A RARE CASE

***^Tapaswini Bagh, *Laxmikanth Chatra, **Manjunath Shenoy, *Prashanth Shenai, *K M Veena, *Prasanna K. Rao and *Rachana V. Prabhu**

***^**Department of Oral Medicine and Radiology, Yenepoya Dental College, Yenepoya University, Mangalore, Karnataka, India; **Department of Dermatology, Yenepoya Medical College, Yenepoya University, Mangalore, Karnataka, India.

^Correspondence Author: tapaswinibag@gmail.com

Running Title: Behcet's syndrome

ABSTRACT:
Behçet's syndrome is a chronic multisystem vasculitis characterized by mucocutaneous, articular, neurological, gastrointestinal and ophthalmological lesions. Behcet's syndrome is a disease of uncertain etiology. It may be due to immune dysregulation including circulating immune complex, autoimmune cytokines and heat shock proteins are major factor in the pathogenesis of Behcet's syndrome. Patient's positive pathergy test suggests a diagnosis of Behcet's disease. Corticosteroids and immunosupressive drugs are the first line of treatment. This is a case report of juvenile Behcet's syndrome in a thirteen year old girl associated with arthritis.

Key words: Juvenile Behcet's syndrome, Arthritis, Oral ulcer, Pathergy test
Submitted: July 2014; Accepted August 2014

INTRODUCTION:

Behcet's syndrome [BS] is a multi-system disorder, described by Turkish dermatologist Hulusi Behcet in 1937 as a triad of symptoms: recurrent oral ulcer, recurrent genital ulcer and uveitis. [1]. It is a systemic disease, but also involves visceral organs such as the gastrointestinal tract, musculoskeletal, cardiovascular and neurological systems. It is called Behçet's disease, Morbus Behcet, Behcet-Adamantiades syndrome or Silk Road disease [2, 3]. The highest prevalence of BS is seen in young adults between second and third decades and more common in males [4].The first manifestation is usually appearance of oral lesion followed by genital, occular, skin and arthritis. In this article we discussed the clinical, hematological and immunological features of

BS, highlighting culture sensitivity, pathergy test as investigation. The ethical clearance for the publication of this case report was obtained from the university ethics committee.

CASE REPORT:

A 13 year old female patient reported to our dental clinics with a chief complaint of recurrent ulcer on labial aspect of lower lip since five days [Figure 1]. It aggravates spontaneously and regress itself within 7 to 14 days. She had history of similar kind of oral ulcer in the same region three times per month since last one year. It was associated with fever, dry cough, pain, weakness, difficulty in eating, speech and recurrent genital ulcer. She was admitted for the same in Paediatric ward and gave history of itching of left eye, early morning stiffness of metacarpal joints and temporomandibular joints [Figure 2]. She was diagnosed as conjuctivitis and chronic juvenile arthritis from the department of Opthalamology and Orthopedics. Complete blood examination and RA factor for C-reactive protein were carried out. Her Hemoglobin percentage [Hb%] was reduced to 7.9 gm/dl, erythrocyte sedimentation rate [ESR] was increased to 60 mm/1 hour and RA factor for CRP was 23.2mg/l. Her peripheral blood smear showed mild macrocytic anaemia. She was a known case of Hypothyroidism. Patient was under following medication when she reported to dentist [tablet thyroxine 50 mg one and half dose daily since last 1 year]. This was patient's first visit to dentist. Her personal history revealed as she did not have any deleterious habits and cleaned her teeth once daily with tooth brush and tooth paste. She was predominantly a non–vegetarian. On general physical examination, she was conscious and cooperative, moderately built and poorly nourished, well oriented in time, place and person. All vital signs were within the normal limits except temperature which was febrile. There were positive signs of pallor, icterus. On extra oral examination, she had competent lips, with convex profile. No gross asymmetry of the face was seen. Her ears and nose showed no abnormality except for her swollen eyes, multiple papules like erythematous lesion on flexural surface of fore arm, feet and finger nails were brittle. Temporomandibular joint examination revealed tenderness on bilateral temporomandibular joints while opening, no deviation,clicking sound were seen, right submandibular lymph node was tender and palpable. No abnormality was detected on examination of muscles of mastication.On intra oral examination of the soft tissues the buccal mucosa, tongue, floor of the mouth, palate showed no abnormalities except for labial mucosa which showed a solitary ulcer. Examination of the gingival status revealed her oral hygiene status to be fair with moderate stains and calculus deposits. On hard tissue examination she had a normal complement of teeth except some carious teeth were noticed

with respect to maxillary anterior teeth, mandibular right and left posterior premolars and molars. On local examination a solitary ulcer was seen on labial aspect of lower lip which was approximately 3-4 mm in diameter, oval shape surrounded by erythematous halo, sloping edge with yellowish-white floor, no sinus or discharge of pus was evident. Inspectory finding regarding the site, size and location of the lesion were confirmed on palpation. The ulcer was tender, soft in consistency. The adjacent mucosa was normal. Based on history and clinical examination patient was provisionally suspected as Behcet's syndrome along with additional diagnosis were given chronic pulpitis in relation to mandibular right first molar, dental caries in relation to maxillary anterior and mandibular right and left premolars and molars, root stumps in relation to maxillary left second deciduous molar and mandibular left first molar, Chronic generalized gingivitis. Patient was referred to department of pedodontics for restoration of decayed teeth, Root canal treatment, extraction of retained tooth and oral prophylaxis. Patient was advised to use antiseptic gel [Hexigel] in lower labial mucosa twice daily for 7 days and nutrient supplement once daily for 30 days [tablet Neurokind plus] from department of Oral medicine and Radiology. Patient was referred to department of dermatology for further investigation. Pathergy test was performed on flexural surface of left forearm, it showed 2 mm diameter of papules after 48 hours of insertion of 20 gauge of sterile needle which was considered as positive results [from department of dermatology] and advised to apply Diprovate- G ointment twice daily for 15 days.

Culture sensitivity for urine showed heavy mixed bacterial growth of E.coli after 48 hours of aerobic incubation which were sensitive to broad spectrum antibiotics except Ampicillin and Ceftazidime. Liver function test showed increased in total protein level to 9.3gm/dl, serum globulin to 5.9gm/dl and albumin/globulin ratio was decreased to 0.6. Serum calcium level was decreased to 8.4 mg/dl. Renal function test showed decreased in blood urea level to 11mg/dl and creatinine level to 0.4 mg/dl. Based on clinical examination, laboratory tests, pathergy test, patient was finally diagnosed from department of dermatology as chronic arthritis in juvenile Behcet's syndrome. Patient was prescribed the following medication after confirmation from different departments including Dermatology, Medicine, Ophthalmology and Endocrinology: Tablet Dapsone - 100mg half dose daily, Folic acid - 5mg, Neurokind plus once daily, Naproxen - 250mg twice daily, Methotrexate - 5mg, Capsule Indomethacin - 25mg, prednisolone eye drops along with Tablet thyroxine - 50mg one and half dose once daily. Patient was discharged from the hospital after 7days and was followed up to three months.

During this duration she had a mild recurrence of joint symptoms, oral ulcer, which responded well to medication. [Tablet Methotrexate and Antiseptic gel].

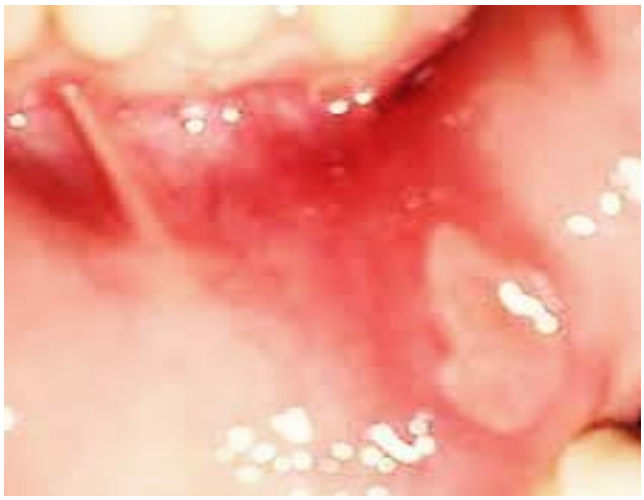

Figure 1: Recurrent apthous ulcer in vermillion border of lower lip

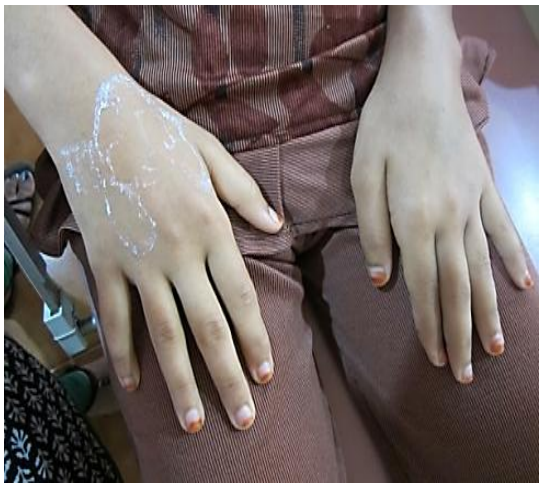

Figure 2: Phalangarthritis of carpal and metacarpal joint

DISCUSSION:

Childhood - onset, Behcet's syndrome is uncommon, accounting for 3-7% of all cases. Our patient had a classical triad of Behcet's syndrome: recurrent apthous ulcer, genital ulcer and conjuctivitis [4, 14]. The highest incidence occurs in the Middle East and Japan, with a lower frequency in northern Europe, United States. The exact etiology has not been established. Behcet's syndrome has an immunogenic basis because of strong association of certain Human leukocyte antigen types [HLA]. HLA B-51 genotype is most frequently linked to BS especially in Asia [5]. However in our case E.coli bacteria was found and it was not related to genetic predisposition.

Behcet's syndrome is a clinical diagnosis based on the International study group criteria: An international group of physicians have established a set of guidelines to aid in the diagnosis of Behçet's patients. The criteria put forth by the study group include [6]:

Recurrent oral ulcerations (apthous or herpetiform) at least three times in one year; In addition, a patient must also meet two of the following: Recurrent genital ulcerations, Eye lesions (uveitis or retinal vasculitis) observed by an Ophthalmologist, Skin lesions (erythema nodosum, pseudo folliculitis, papulopustular lesions, acneiform nodules) adult patients not on corticosteroids, Positive "pathergy test" read

by a physician within 24 - 48 hours of testing. Synovitis / Capsulitis (Rare findings)

Oral lesion is the most important criteria for BS and it is the first manifestation in 25% to 75% cases of the BS. Oral ulcer commonly involves the soft palate, oropharynx and labial mucosa of lips. The lesions vary in size with ragged borders and surrounded by erythematous halo [1, 2]. In our case she had an oral ulcer.

The genital lesions are the second manifestation, seen in 75% of the patients. Lesions appear on the vulva, vagina, glans penis, scrotum, and perianal area. The genital ulcerations cause more symptoms in men than in women [2]. In present case patient had a recurrent genital ulcer.

Ocular involvement is the third manifestation, seen in 70% to 85 % of the cases. The most common findings are posterior uveitis, conjunctivitis, corneal ulceration [2]. In our case patient had conjuctivitis.

Other cutaneous manifestations like erythematous papules, vesicles, pustules and erythema nodosum-like lesions.These skin lesions seen in 40 % to 88 % of cases of BS. One of the most important diagnostic points of skin manifestations is the presence of positive "pathergy test" [2]. Our case had an erythema nodosum like lesions on flexural surface of forearm, feet and also pathergy test positive.

Arthritis is one of the more common minor manifestations of the disease and is usually self-limiting and non-deforming. It is seen in around 3-7% of cases. The knees, wrists, elbows and ankles are affected most frequently. [1, 2].

In present case she was diagnosed as chronic juvenile arthritis in metacarpal joints. Cardiovascular, Central nervous system (CNS) involvement is uncommon. Around 10% to 25 % of the patients show CNS involvement. Gastrointestinal, renal systems involvements are common [2]. Our patient had alterations in urine analysis, Hb%, ESR, C-reactive protein, liver and renal function test.

The differential diagnoses were considered Reiter's syndrome (RS), Magic syndrome and Erythema multiforme. RS includes urethritis, arthritis, cutaneous lesions, seen in young adult men but BS mostly seen in children to young adults and oral ulcer is the first manifestation.

Laboratory findings for BS and RS almost similar but genetic markers for RS and BS are HLA B-27 and HLA B-51.

However these tests were not done in present case. Magic syndrome includes oral ulcer, genital ulcer with inflamed cartilage, mostly seen in older individuals with decreased strength in all extremities but BS mostly seen in children to young adults and oral ulcer is the first manifestation. Erythema multiforme target like oral lesion but in BS lesion appears as apthous ulcer. [7]

MANAGEMENT and PROGNOSIS:

As Behcet's syndrome is a multi-system disorder, patient was referred to different departments before starting treatment like dermatology, genitourinary medicine, gynecology, internal medicine, ophthalmology, oral medicine and rheumatology. [8]The management of BS depends on the severity and site of involvement. Patient with eye involvement or CNS lesions require more aggressive therapy with drugs. The oral and genital ulcerations respond well to potent topical corticosteroids: [8] Betamethasone (0.1% cream applied twice daily and 0.5mg 2-4times as a mouth wash) [9].

Patients fail this initial conservative approach often require Thalidomide (Tablet Thalomid 100-300mg daily with water at bed time), low-dose Tablet Methotrexate 5mg /day daily [2, 12]. Severe ocular or systemic diseases combined use of immuno suppressive agents: Azathioprine (Tablet Imuran 1-3mg/kg/day combined with prednisolone).

Contraindicated in pregnancy, concurrent malignant disease, allergic reaction, renal and hepatic insufficiency [7, 10]. Other medication includes levamisole, cyclophosphamide and chlorambucil [9, 10]. Recently the agents that are active against the cytokine TNF-α such as infliximab and ethanercept have found potential effectiveness against mucocutaneous and ocular lesion of Behcets syndrome. [8, 13]

CONCLUSION:

The occurrence of BS in children should be recognized. Awareness of its clinical features in children combined with appropriate investigations will help to delineate this group of children from other forms of chronic inflammatory joint diseases. Behcet's syndrome showed no signs of remission for 3 months in our case. The major features recurrent apthous ulcer, genital ulcer, conjuctivitis, arthritis and skin lesions were noted in present case. In this case the doctor/patient relationship had been under strain for 3 months as BS requires only symptomatic treatment.

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CASE REPORT

FOCAL REACTIVE SOFT TISSUE LESION OF GINGIVA – A DIAGNOSTIC DILEMMA

***^Usha Chikkaiah, **H J Jaikrishna, ***KB Hemavathy, ****Gururaju CR, #Jyothi PA and ##Madhu Kiran**

*^Department of Oral Medicine & Radiology, Sharavathi Dental College and Hospital, Shimoga; **Department of Oral Medicine & Radiology, Shyamala Reddy Dental College & Hospital, Bangalore; ***Department of Oral & Maxillofacial Surgery, Daswani Dental College and Research centre, Kota; **** Department of Oral & Maxillofacial Surgery, Sharavathi Dental College & Hospital, Shimoga, #Department of Prosthodontics including crown & Bridge, Sri Rama Dental College & Hospital, Kanpur; ##Department of conservative & Endodontics, Sharavathi Dental College & Hospital, Shimoga.

^Correspondence author: cushamds@gmail.com

ABSTRACT:

There are different types of focal overgrowths which may occur on the gingiva. These growths of gingiva are common and often result from underlying systemic disease, drug induced, local iatrogenic factors and dental plaque. Many of these enlargements are considered to be reactive rather than neoplastic in nature. These reactive lesions are more common in the oral cavity because of the frequency with which the tissues are injured. Clinically differentiating one from the other as specific entity is sometimes difficult. This case report describes one such reactive growth of the gingiva that is not implicated with any underlying systemic disease or drug induced. Clinical, radiographic, histologic characteristic along with the differential diagnosis, treatment and prognosis are discussed with the importance of the proper communication with the patient as she was more anxious about the possibility of the lesion being a carcinoma.

Key words: Focal, Overgrowth, Gingiva, Reactive, systemic disease, drug induced

Submitted: July 2014; Accepted: August 2014

INTRODUCTION:

Oral mucosa is constantly subjected to external and internal stimulus and therefore manifests a spectrum of disease that range from developmental, reactive and inflammatory to neoplastic [1]. These lesions present as either generalized or localized. Reactive lesions are clinically and histologically non neoplastic

nodular swellings that develop in response to chronic and recurring tissue injury which stimulates an exuberant or excessive tissue response [1, 2].

The most common group of hyperplastic reactive gingival/alveolar lesions includes inflammatory gingival hyperplasia, fibrous epulis, oral pyogenic granuloma, irritation fibroma, giant cell fibroma, fibroepithelial polyp, peripheral ossifying fibroma, peripheral giant cell granuloma and pregnancy epulis excluding caries, periodontal and periapical inflammatory disease. Such reactive lesions are less commonly present in other intraoral sites such as cheek, tongue, palate and floor of the mouth [1]. Clinically, these reactive lesions often present diagnostic challenges because of similar clinical features and mimic various groups of pathologic processes [1].

Many of these lesions can be identified as specific entities on the basis of characteristic morphology [3].

The aim of this paper is to provide comprehensive knowledge on the focal reactive hyperplastic gingival lesion. Even though they are non-neoplastic most of the patients are concerned about the malignancy. There is a need for the awareness, proper investigations and histologic evaluation in the management of this lesion.

CASE REPORT:

Presenting concerns: A 56-years-old female reported with a complaint of the swelling in the upper front tooth region. She had initially noticed a small swelling 2 years back, later it had increased to the present size associated with pain and bleeding while brushing and having food. The patient was much tensed due to a recent death of a 40-year-old male patient after surgery in her village that had a similar kind of swelling in the oral cavity and was diagnosed as oral cancer. As her swelling was noticed by all her neighbours they had assumed it was a cancer. Ethical clearance for this study was obtained from the College Ethics committee.

Clinical findings:

On general physical examination, the patient was moderately built and nourished, conscious and co-operative. No abnormalities in gait and posture. There was no evidence of pallor, cyanosis, edema, icterus and clubbing. Right side single submandibular lymph node was palpable measuring about 2.0 x 1.0 cm, firm in consistency, non tender and mobile. All the vital signs were within normal limits. On extra oral examination, lips were incompetent. Fullness of upper lip on right side was noted with a diffuse swelling measuring about 2.0 x 3.0 cm in size. Anterio-posteriorly, the swelling extended from corner of the mouth to 3.0 cm posteriorly and superiorly from ala-tragal line to the upper vermilion border of the lip. No

secondary changes of the skin over the swelling (figure 1). The swelling was tender on palpation and firm in consistency with no local rise in temperature.

Mouth opening was adequate. On intraoral examination a solitary nodular sessile growth seen on the buccal gingiva in relation to teeth 14, 15 measuring about 3.0 x 4.0 cm in size, extending antero-posteriorly from distal aspect of tooth 13 to distal aspect of tooth 17. Superiorly it was obliterating the buccal sulcus in relation to teeth 14, 15, 16, 17 and inferiorly up to the occlusal level of the same involved teeth. The surface was smooth and the overlying mucosa was pink in colour with bleeding spots (figure 2). On palpation, tenderness was present, firm in consistency and bleeding was noted on probing.

General intraoral examination showed generalized bleeding on probing with deposits of calculus and stains. Generalized attrition and gingival recession was noted. Other findings included abrasion of teeth 11, 12; dental caries in relation to teeth 26, 27 and mobility of teeth 14, 15, 26, 31, 32, 41, 43. A provisional diagnosis of pyogenic granuloma of gingiva in relation to teeth 14, 15 was made.

Differential diagnosis:

The various differential diagnoses considered were peripheral giant cell granuloma, peripheral ossifying fibroma and peripheral odontogenic fibroma.

Diagnostic focus and assessment:

The patient was subjected to routine blood investigation and radiographic examination. The blood picture was within normal limits.

Radiographic evaluation:

Intraoral Periapical Radiograph (IOPAR):

IOPAR of teeth 14, 15 showed interdental bone loss in relation to teeth 14, 15, 16 extending upto apical 1/3rd of the root surface and foci of calcification between the crowns of teeth 14 and 15 not in contact with the tooth (figure 3).

Occlusal Radiograph:

Maxillary cross-sectional occlusal radiograph also revealed the foci of calcification on the buccal surface of teeth 14 and 15 measuring approximately 1.0 x 1.0 cm and is not in contact with the tooth or the buccal cortical plate (figure 4).

Orthopantomogram (OPG):

OPG radiograph showed generalized interdental bone loss suggestive of chronic generalized periodontitis. Foci of calcifications were seen in between the teeth 14 and 15 (figure 5). The radiographic diagnosis of peripheral ossifying fibroma was made.

Treatment:

Once the patient was convinced, a prophylactic antibiotic was given and she was subjected to surgical excision under Local anaesthesia . The mobile teeth 14, and 15 was also extracted and

the gross specimen measuring about 3.0 x 4.0 cm was shown to the patient and was sent for histopathological evaluation

Histopathological Evaluation:

The histologic picture showed parakeratinised stratified epithelium with dense, cellular connective tissue stroma with numerous calcified osseous structures. The connective tissue was infiltrated with inflammatory cells and showed few dilated blood vessels engorged with Red Blood Corpuscles. The histologic picture was suggestive of Peripheral Ossifying Fibroma.

Outcome and follow-up:

Based on the clinical, radiological features and histologic characteristics final diagnosis of peripheral ossifying fibroma of gingiva was achieved. The patient was examined one week post operatively with uneventful healing and she also did not complain of any pain and was happy. She was told of the final report that the lesion was a local reactive one and not a neoplastic lesion.

DISCUSSION:

Peripheral Ossifying fibroma (POF) is defined as a well demarcated and occasionally encapsulated lesion consisting of fibrous tissue containing variable amounts of mineralized material resembling bone [4].

There are two types of ossifying fibroma, the central and peripheral types. The central type arises from the endosteum or the periodontal ligament adjacent to the root apex causing expansion of the medullary cavity. The peripheral type occurs solely on the soft tissue covering the tooth bearing areas of the jaws [5]. The peripheral type is a specific entity and does not represent the peripheral counterpart of the central variant [5, 6, 7].

The term Peripheral Ossifying Fibroma was coined by Eversole and Rovin in 1972 [8]. Various terminologies like Peripheral odontogenic fibroma, peripheral cemento-ossifying fibroma, ossifying fibroepithelial polyp, peripheral fibroma with osteogenesis, peripheral fibroma with cementogenesis, and others have been used to describe this lesion [5, 9]. The sheer number of names used for fibroblastic gingival lesions indicates that there is much controversy surrounding the classification of these lesions [10].

The etiopathogenesis of POF is not known, trauma or local irritants such as sub gingival plaque and calculus, ill fitting dental appliances, poor quality dental restoration, masticatory forces, food lodgment and iatrogenic factors may influence the development of the lesion [11].

Many have believed that pyogenic granuloma is an immature form of POF due to their similar clinical and histopathological features [5, 12].

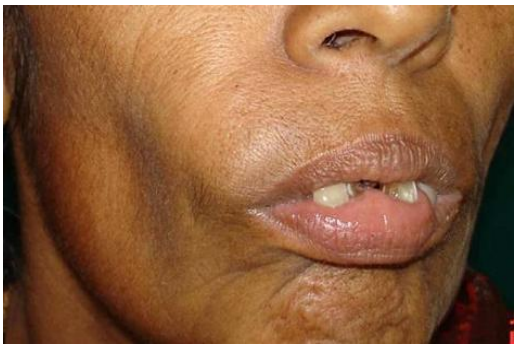

Fig 1: Extraoral swelling on the right side of the upper lip

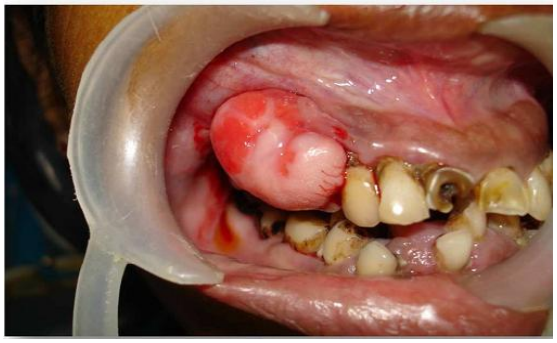

Fig 2: Intraoral view of lesion showing 3.0 X 4.0 cm growth of the gingiva irt teeth 14,15

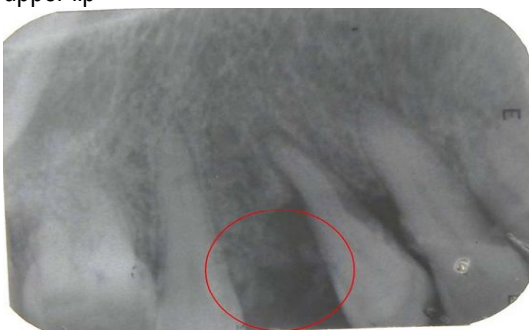

Fig 3: IOPAR showing foci of calcification between teeth 14 and 15

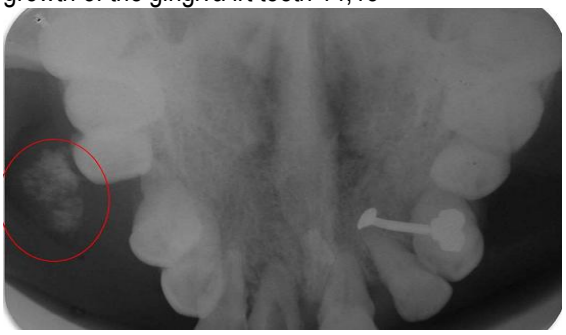

Fig 4: Maxillary cross-sectional Occlusal radiograph, showing foci of calcification on buccal aspect of teeth 14 and 15 measuring about 1.0 x 1.0 cm

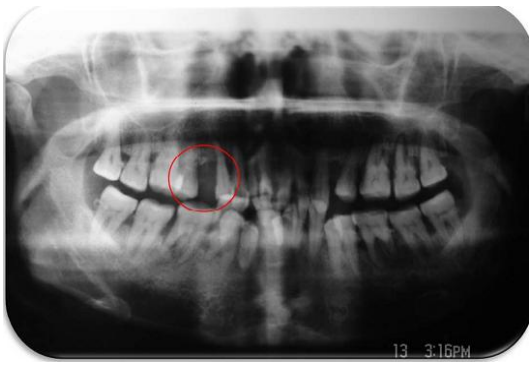

Fig 5: Orthopantamogram showing similar foci of calcification between teeth 14 and 15

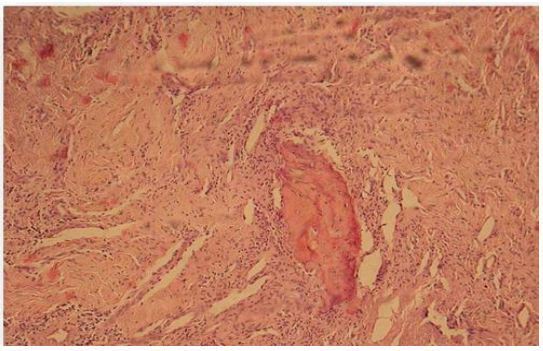

Fig 6: H and E stained section showing foci of calcification suggestive of ossification in dense connective tissue stroma.

The influence of hormone is considered to be the etiological factor in females [10, 13]. In the present case the occurrence of the lesion was due to the local irritant factors like sub gingival calculus and subsequent trauma caused by masticatory forces and brushing.

POF may be presented as pedunculated or sessile mass. These lesions can be red to pink with areas of ulceration and their surface may be smooth or irregular [10, 11, 14]. In the present case the growth was sessile, smooth surfaced with ulceration (figure 2). Although they are generally less than 2.0cm in diameter, size can vary ranging from 0.2 to 3.0cm; 4.0mm to 8.0cm and some lesions may be as large as 9.0cm in diameter. Cases of tooth migration and bone destruction have been reported but not common [10, 11, 14].

The female to male ratio reported in the literature varies from 1.22:1 and 1.7:1 to 4.3:1 [10]; majority of the lesions occur in the second decade with a declining incidence in later years. POF appears to be more common among whites than black and slightly less common among those of Hispanic origin [10, 11, 14].

The lesions may be present for a number of months to years before the excision [10]. Approximately 60% of POF's occur in maxilla and often in anterior region with 55% to 60% present in incisor-cuspid region [10, 14]. In our present case we noted the lesion in an elderly female patient in maxillary posterior region (figure 2). Radiographically POF varies from completely no changes to areas of calcification depending upon the degree of mineralization, superficial bone loss, cupping defect and focal area of calcification have been reported [9]. In the present case, the focus of calcification was located between teeth 14, 15 with drifting of involved teeth and interdental bone loss (figures 3, 4, 5).

Histologically, a typical ulcerated POF can exhibit three zones: [14]

Zone 1: The superficial ulcerated zone covered with fibrinous exudates and enmeshed with polymorphonuclear neutrophils and debris. Zone 2: The zone below the surface epithelium composed almost exclusively of proliferative fibroblasts with diffuse infiltration of chronic inflammatory cells mostly lymphocytes and plasma cells. Zone 3: More collagenised connective tissue with less vascularity and high cellularity osteogenesis consisting of osteoid and bone formation is a prominent feature, which can even reach the ulcerated surface in some cases. The mineralized material may represent mature, lamellar or woven osteoid cementum like material or dystrophic calcification [5, 10, 11].

The non ulcerated POF lesions are similar to an ulcerated type except for the presence of surface epithelium [7, 10, 13, 14]. In our present case the histologic picture showed

numerous calcified osseous structures in dense connective tissue stroma (Figure 6).

Treatment requires proper surgical intervention that ensures thorough excision of the lesion including the involved periosteum and periodontal ligament. Thorough root scaling and planning should be accomplished to remove the irritation [5, 6, 10, 13, 14]. Prognosis is good, but regular follow up of the patients are required as some authors have reported recurrence rates varying from 8.9 to 20% [8, 15]. Cundiff has reported 16% of recurrence rate [8, 16] and Eversole and Rovin have given 20% of the recurrence rate [8].

CONCLUSION:

It is difficult clinically to differentiate between most of the reactive gingival lesions, the lesion must be examined thoroughly both radiographically and histologically. Discussion of the differential diagnosis should be done tactfully to prevent unnecessary distress to the patient and family. Complete surgical excision of the lesion along with elimination of the etiological factors must be achieved to prevent recurrence.

COMPETING INTEREST: NIL

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