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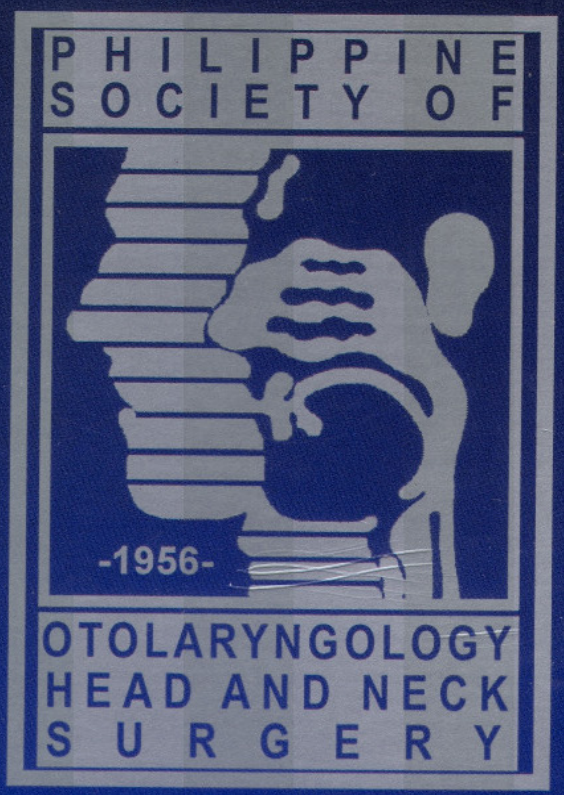

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ELECTROCOCHLEOGRAPHY FINDINGS IN NORMAL AND PATHOLOGIC EARS: A LOCAL EXPERIENCE*

CECILIA MARICXIE C. FRANCO, MD**
CHARLOTTE M. CHIONG, MD, FPSO-HNS***

ABSTRACT

OBJECTIVES: 1. To establish the normal electrocochleography values at the Hearing and Vestibular Laboratory as represented by SP and AP amplitudes, and SP/AP amplitude ratio of waveforms taken from a range of 20-90 dB, 2. To study the effect of click intensities on the measures of SP, AP, SP/AP ratios, 3. To establish the effect of gender on electrocochleography values by comparing the normative data of male and female subjects, 4. To compare the electrocochleography findings of normal-hearing individuals with those of patients with inner ear pathologies (i.e. Meniere's disease/endolymphatic hydrops)
STUDY DESIGN: This is a prospective study on deriving normative values of electrocochleography among Filipino subjects.
SETTING: This study was done at the hearing and vestibular laboratory of a tertiary hospital.
PATIENTS: The normal group included 16 subjects, 7 males and 9 females (n = 21 ears) satisfying the inclusion criteria such as: 1. Filipino citizen, 2. Age: 18-45 years old, 3. No known history of middle ear inflammation since childhood, congenital abnormalities, subjective hearing loss, nor intake of ototoxic drugs, 4. No known history of upper respiratory tract or external ear infection within three consecutive months prior to testing, 5. No exposure to unusually loud noises. Patients were all subjected to Pure Tone Audiometry (PTA) prior to EcochG to determine their audiologic status using the Hughson-Westlake method at 0.5KHz to 4KHz with the diagnostic audiometer. Subjects whose PTA results were normal hearing thresholds (25dB hearing tone average) were then included in the study and proceeded with electrocochleography. Patients diagnosed with Meniere's disease/endolymphatic hydrops (3 female patients, n = 5 ears) underwent electrocochleography. These values were then compared with the data derived from the normal group.
RESULTS: Sixteen subjects (7 male, 9 female) with audiologically normal hearing taken by pure tone audiometry were subjected to electrocochleography. Meniere's disease patients were compared to the normal female study group with the different parameters used. The t test was utilized to analyze the data. A p value of ≤ 0.05 was set to determine the level of significance. A comparison was made regarding the use of different click stimuli intensities of 80 and 90dB. Statistical analysis of the data showed no significant difference between click stimuli intensities. Intergender differences were not noted. However, SP amplitudes between the normal female group and the pathologic group showed a statistical difference at both click intensities used.
CONCLUSION: From the results derived, the following conclusions were made: 1) No significant difference was seen in the values derived from different click stimuli intensities (90 dB and 80 dB) in all three groups that were studied i.e. normal males, normal females, and the pathologic group. 2) No statistically significant difference was noted between normal males and normal females at the click stimuli intensities tested. 3) In the comparison between the normal study group and the pathologic group (Meniere's disease), there was a statistical difference noted in the SP values derived. This is consistent with foreign literature stating that SP is a sensitive indicator of hydrops. 4) The normative values derived from both male and female normal subjects were comparable with foreign literature.

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INTRODUCTION

Cochlear potentials in humans have been studied as far back as 1930's during the discovery of the cochlear microphonic by Wever and Bray.[1,2] However, very little attention has been paid to the clinical application of these potentials until the discovery in the early 1970's and eventual application of the auditory brainstem response (ABR). Since then, the utilization of the auditory evoked potentials has grown in an exponential rate. More sophisticated tools have been developed to record the very early and the small voltage changes that occur in the ear when sound is introduced. This has led to the revived interest in the clinical application of the stimulus-related potentials of both the cochlea and auditory nerve. The general technique for recording these potentials is referred to as electrocochleography (EcochG).[2]

Electrocochleography is an electrophysiological technique of the recording stimulus-related response of the cochlea and auditory nerve by electrodes placed as close to the cochlea as possible. This procedure continues to be an important tool in the evaluation of the inner ear and auditory nerve function. It is particularly important in the diagnosis, assessment, and monitoring of certain otologic disorders specifically Meniere's disease/ endolymphatic hydrops. Gibson et al have shown a high percentage of hydrops in the contralateral ear of patients diagnosed with Meniere's disease.[4] Adamonis et al have utilized electrocochleography in monitoring the response to gentamycin treatment for Meniere's disease.[5] It is also useful in the enhancement of Wave I of auditory brainstem response in patients with substantial amount of hearing loss. A study by Schoonhoven[6] et al in severely hearing-impaired children have shown that in many cases were no ABR can be elicited, 68 percent have produced detectable electrocochleographic responses in the 1000-4000Hz range. They noted that in infants expected to suffer from hearing losses greater than 70dB, EcochG provides information on the amount of residual hearing in the majority of subjects in whom no ABR can be elicited.[7]

Electrocochleography is also a valuable tool in the intraoperative monitoring of the peripheral auditory structures at risk of the permanent damage secondary to surgically-induced trauma. Intraoperatively, EcochG has also been used to diagnose the presence of a perilymphatic fistula with no visible leak of fluid into the middle ear.[8]

Components of EcochG routinely analyzed for these purposes include a) cochlear summating potential (SP) = a direct current potential which appears as a + or - shift from the CM baseline; b) cochlear microphonic (CM) = an attenuating response which mimics the waveform and the polarity of the stimulus at low to moderate stimulus levels; c) auditory nerve action potential (AP) = series of brief negative peaks which results from synchronous firing of large number of fibers of the 8th cranial nerve. It is now well documented that in suspected cases of Meniere's disease, the amplitude of the SP is greater than normal especially in comparison with the amplitude of the first negative peak of the AP. There are two general approaches for the recording of EcochG 1) Transtympanic (TT) which is an invasive procedure that involves the passing of a needle electrode through the tympanic membrane (TM) to rest on the cochlear promontory and 2) extratympanic (ET) performed with electrode resting against the skin of the ear canal on the lateral surface of the TM. The development of the noninvasive ear canal electrodes capable of providing responses that approximate those obtained with the more invasive procedures has greatly increased the clinical practicality and popularity of EcochG among clinicians.

Normative values for Filipinos are yet to be set for EcochG application and interpretation. At present, no local studies have yet been done to investigate and determine the normal values for EcochG. Currently available normative values for EcochG application are from foreign literature. It is primarily this purpose that the study wishes to pursue.

MATERIALS AND METHODS

Subjects:

The normal group included 16 subjects, 7 males and 9 females (n = 21 ears) satisfying the inclusion criteria such as:

1. Filipino citizen
2. Age: 18-45 years old
3. No known history of middle ear inflammation since childhood, congenital abnormalities, subjective hearing loss, nor intake of ototoxic drugs.
4. No known history of upper respiratory tract or external ear infection within three consecutive months prior to testing.
5. No exposure to unusually loud noises.

Patients were all subjected to Pure Tone Audiometry (PTA) prior to EcochG to determine their audiologic status using the Hughson-Westlake method at 0.5KHz to 4KHz with the

diagnostic audiometer. Subjects whose PTA results were normal hearing thresholds (25dB hearing tone average) were then included in the study and proceeded with electrocochleography. Patients diagnosed with Meniere's disease/ endolymphatic hydrops (3 female patients, n = 5 ears) underwent electrocochleography. These values were then compared with the data derived from the normal group.

Electrodes

The silver tympanic membrane electrode is a ball-tipped wire measuring 17cm. This is protected with a silastic tube on its tipped end. The opposite end is attached to several finer silver wires intertwined and insulated with a transparent tube measuring 40cms and attached to an adapter that would fit the amplifier lead.

Nihon Kohden MEB 2200

This machine was utilized to amplify and average electrode responses coming from the subjects' tympanic membrane.

Procedure

In a non-commercial sound-treated room, patients were allowed to lie down in a supine position. Ear canals were all examined using an otoscope prior to insertion of the electrode. Topical anesthesia (EMLA) was then applied on the tympanic membrane, fifteen minutes before the procedure. Prior to insertion, a small amount of electrode gel was placed on the ball tipped end to provide a conductive interference. Using a Lumiview, the electrode was gently inserted through the ear canal until it rested against the tympanic membrane at the postero-inferior quadrant area. After insertion, the electrode was gently bent inferior to the tragus and is attached to the cheek with an adhesive tape. A standard headphone was then gently placed onto the ear being tested.

EcochG potentials were recorded between the active electrode resting against the tympanic membrane and the reference disk electrode on the opposite earlobe with a forehead disk serving as ground. Responses were amplified and averaged using a *Nihon Kohden MEB 2200* with filters set at 5-3000 Hz and the first ten milliseconds averaged across 1000 stimulus per trial. The stimulus used was a 100 usec broad band alternating polarity clicks at a rate of 10/ sec through a standard headphone. Initial responses were recorded at 90 dB Hearing Level.

The stimulus was later reduced to 80, 70, 60, 40, and 30 or until all responses were absent. The wave tracings recorded by the examiner were analyzed and measured using the following parameters 1) AP amplitude distance component, 2) SP amplitude - height of the shoulder preceding the AP component and 3) SP/ AP amplitude ratio.

At the end of each session a repeat otoscopic examination was done.

Analysis

For the 21 ears, the SP, AP, SP/AP ratios were determined and tabulated. The mean latencies and standard deviations were calculated accordingly. The mean latencies and standard deviations for the nine male ears at 90 decibels were calculated and compared with those at 80 decibels. The same procedure was done on the 12 female ears as well as for the pathologic group (Meniere's disease patients). Mean latencies and standard deviations for the nine male ears were also compared with the twelve female ears. The twelve female normal ears were also compared with the pathologic ears. The t-test was used and confidence intervals were calculated at a p value of 0.05.

RESULTS

The results were tabulated into different click stimuli intensities (90 dB compared with 80db) in the normal study group (male and female) and the pathologic group (Meniere's disease). Intergender differences were also tested (Table 9). Lastly, the pathologic group was compared with the normal female study group (Table 10). The mean values, +/- SD, and p values were determined for SP, AP, SP/AP ratio at two levels of intensity stimuli (90dB and 80dB). In testing for any statistical significance, the t test was used since the 2 populations being compared are not the same. The accepted level of significance was set at a p value of ≤ 0.05.

Tables 3-5 show the different SP, AP, SP/ AP ratios derived from all the study patients included. With regard to the different click stimuli intensities, tables 6-8 show the means and standard deviations for the normal study group and the pathologic group. For purposes of data analysis, the normal group was divided and analysed separately in order to investigate if there is gender specific variables that may be affected. For the three groups studied, there was no significant difference noted with regard to the click stimuli intensities used. Table 9 shows the comparison between the normal male study group and the normal female study group. No significant statistical difference was noted between the values derived from the two groups. However, the comparison between the normal female study

group and the pathologic group (table 10), only SP was noted to have a significant difference where at SP80 p=0.05 and SP90 p= 0.02.

Figures 1 and 2 show illustrative tracings. Differences in the amplitude of SP, AP, SP/AP can be appreciated in the figures shown.

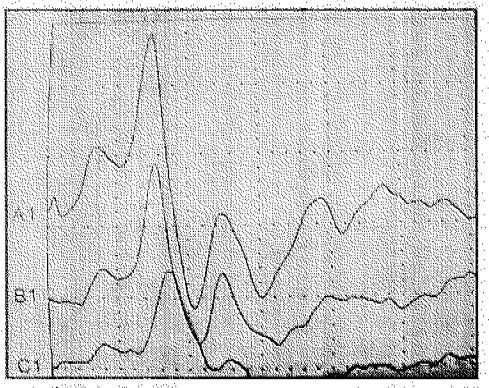

FIGURE 1: Electrocochleography tracing taken from a normal individual

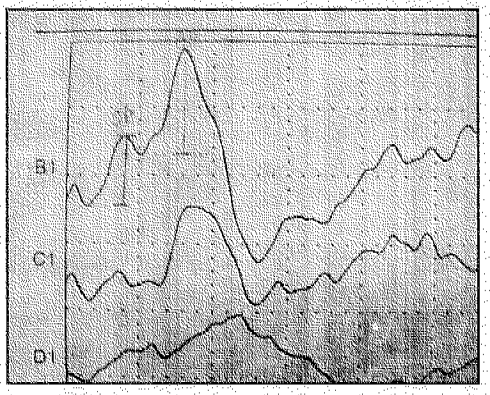

FIGURE2: Electrocochelography tracing taken from a patient diagnosed with Meniere's Disease

DISCUSSION

Several studies have been made on formulating normative values on patients, because of its clinical importance in diagnosing and monitoring such diseases like Meniere's disease, or endolymphatic hydrops. The components of interest for its interpretation may include the SP (Summation Potential of cochlea) and AP (action Potential of auditory nerve), recorded individually or in combination. Its characteristics in turn, are dependent on several factors such as location, signal averaging parameter and stimuli features, which are subject for several studies.

The first recorded potential from the eight nerve is attributed to Wever and Bray[1,2]. Saul and Davis[2] were able to separate the electrocochleogram into its main components: the cochlear microphonic and the compound action potential. Ruben started to record human cochlear microphonics and auditory nerve action potentials routinely, obtained with an electrode placed directly on and through the round window membrane.

One of the significant studies was that of Arts et al.[2], who provided an overview of diagnostic testing for endolymphatic hydrops. He cited the study of Badrel-Dine et al.[2] that examined the relationship between electrode location and summating potential(SP) /auditory nerve action potential (AP) amplitude ratio in guinea pigs. The ratio was found to be highly dependent on electrode location for transtympanic recordings. In contrast, Krueger and Wagner[2] noted no significant difference in the SP/AP ratio between round window and promontory recordings in humans and that waveform patterns that led to the diagnostic interpretation of the electrocochleogram (EcochGm) were the same at both recording sites. In another study, Wuyts et al[2] reviewed instrumentation settings and analysis procedures for TT (transtympanic) and ET (extratympanic) EcochG. Upper limits of normal (ULN) was also defined for SP/AP amplitude ratio to clicks and the SP amplitude for tone bursts. For TT recordings these values were 0.35 and –2 microvolts, respectively, while ET –SP/AP amplitude ratios was 0.42. He also noted an advantage associated with the TT approach which allows for a more favorable signal –to-noise ratio (SNR) than ET methods. However, Ferraro and Krishnan noted that both TT and ET responses could have poor SNRs due to improper or unstable electrode contact.

A study on standard method for measuring TT responses was made by Sass et al.[2] to facilitate clinical applications and uniform interpretation of the EcochGm . This was based on an analysis of factors related to testing environment, stimuli and electrodes. In support of his study, Ferraro and Krishnan[2] described procedures for recording and interpreting EcochGms from the TM. Both of these studies advocated the use of clicks and tone bursts as stimuli. Sass et al[2] also included the measurement of latency difference (LD) between APs evoked by condensation versus rarefaction clicks and noted that AP-LD is prolonged in the case of Meniere's disease /Endolymphatic hydrops. In addition to measuring AP-LD, Ferraro and Krishnan[2] described a method developed by Tibbils and Ferraro[9], allowing the assessment of both amplitude and duration features of the response through the use of alternating clicks and a software routine for measuring the area under the curve. He found out that patients suspected of having Meniere's disease and endolymphatic hydrops had abnormal SP/AP area ratios in the

presence of normal amplitude ratios.

In a local study, Hardillo and Chiong[1] compared the use of silver and copper tympanic membrane electrodes in a non invasive EcochG among normal hearing Filipinos. This showed that mean AP amplitudes, mean SP amplitudes, AP/SP amplitude ratios and mean AP latencies for both electrodes have no significant difference at $p<0.05$. The results indicate that both electrodes are capable of recording reliable EcochG waveforms. The purpose of their study was to look for an alternative material for the electrode, as the silver electrode is quite expensive and unavailable locally.

In a study made by Pappas Jr et al[10], he correlated extratympanic EcochG results and Meniere's disease, and demonstrated a predictive value of 0.74 of patients who have the disease for SP:AP > 0.50. Ferraro and Tibbils[9], however, showed in their study that SP/AP area ratios greater than 1.37 and amplitude ratios greater than 0.41 were considered abnormal.

In this study, the authors were unable to note any statistical difference using different click intensity stimuli. Intergender differences were not noted either. However, the differences in the value of SP was noted to be statistically significant when the normal and the pathologic group were compared. This is verified by Ferraro and Tibbils[9]. Only 60% of the general Meniere's disease population will show an elevated SP/AP ratio. This shows that the SP is a sensitive indicator of hydrops. Reviewing the data derived from the normal subjects (table 1), SP/AP ratios are comparable to those seen in foreign literature (table 2).

TABLE 1
Normative values derived from audiologically normal males and females taken at 90dB and 80dB

	mean	SD	Range
SP80NF	0.15	0.06	0.09-0.21
SP80NM	0.17	0.09	0.08-0.26
SP90NF	0.19	0.13	0.06-0.32
SP90NM	0.26	0.15	0.11-0.41
AP80NF	0.44	0.25	0.19-0.69
AP80NM	0.53	0.24	0.29-0.77
AP90NF	0.55	0.39	0.16-0.94
AP90NM	0.66	0.31	0.35-0.97
SP/AP80NF	0.38	0.11	0.27-0.49
SP/AP80NM	0.33	0.09	0.24-0.42
SP/AP90NF	0.38	0.13	0.25-0.51
SP/AP90NM	0.39	0.12	0.27-0.51

TABLE 2
Summary of some recent studies comparing mean AP/AP amplitude ratios to click stimuli for normal subjects [2]

	SP/AP ratio Mean ± SD	Approach	N
Campbell et al	0.27 ± 0.15	TM	17
Levine et al	0.31 ± 0.11	TM	13
Margolis et al	0.26 ± 0.09	TM	53
Koyunco et al	0.24 ± 0.20	Ear canal	20
Roland et al	0.21 ± 0.09	Ear canal	17
Densert et al	0.16 ± 0.06	TT	17
Aso et al	0.24 ± 0.05	TT	29

CONCLUSION

From the results derived, the following conclusions were made: 1) No significant difference was seen in the values derived from different click stimuli intensities (90 dB and 80 dB) in all three groups that were studied i.e. normal males, normal females, and the pathologic group. 2) No statistical significant difference was noted between normal males and normal females at the click stimuli intensities tested. 3) In the comparison between the normal study group and the pathologic group (Meniere's disease), there was a statistical difference noted in the SP values derived. This is consistent with foreign literature stating that SP is a sensitive indicator of hydrops. 4) The normative values derived from both male and female normal subjects were comparable with foreign literature.

RECOMMENDATIONS

1. A bigger sample size with regard to the normal group and the Meniere's Disease group should be employed in further studies so as to obtain more values and increase the reliability of the data gathered.
2. Wave morphology, latency periods for the SP/AP complex should be measured as well to account for the other changes that may occur in the inner ear that could affect the electrocochleography tracings.
3. Further studies may compare or include other peripheral vestibular disorders or inner ear diseases so as to validate the pathologic changes that can occur/deviate from the normal.
4. Electrocochleography should be done on Meniere's Disease patients in the active state of the disease so as to get an accurate measurement of the derangements brought about by the disease. This will give a better baseline and monitoring of the progression and resolution of the Meniere's Disease attacks.

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TABLE 3
SP, AP, SP/AP levels taken from normal males at 90dB and 80 dB

MALE	90dB SP	80dB SP	90dB AP	80dB AP	90dB SP/AP	80dB SP/AP
1	0.4	0.1	0.8	0.5	0.5	0.2
2	0.2	0.2	0.9	0.6	0.22	0.33
3	0.1	0.1	0.4	0.2	0.25	0.5
4	0.4	0.35	0.85	0.85	0.47	0.41
5	0.3	0.2	1.0	0.8	0.3	0.25
6	0.5	0.25	1.0	0.8	0.5	0.31
7	0.1	0.1	0.2	0.25	0.5	0.4
8	0.2	0.15	0.45	0.4	0.44	0.37
9	0.1	0.1	0.35	0.4	0.29	0.25

TABLE 4
SP, AP, SP/AP levels taken from normal females at 90dB and 80 dB

FEMALE	90dB SP	80dB SP	90dB AP	80dB AP	90dB SP/AP	80dB SP/AP
1	0.3	0.2	1.0	0.55	0.3	0.36
2	0.1	0.1	0.2	0.2	0.5	0.5
3	0.35	0.25	1.1	0.8	0.27	0.31
4	0.2	0.2	1.0	0.7	0.2	0.29
5	0.5	0.25	0.85	0.8	0.58	0.31
6	0.1	0.1	0.3	0.4	0.33	0.25
7	0.1	0.1	0.2	0.4	0.5	0.25
8	0.1	0.1	0.25	0.2	0.4	0.5
9	0.1	0.1	0.2	0.2	0.5	0.5
10	0.2	0.2	1.0	0.65	0.2	0.31
11	0.1	0.1	0.25	0.2	0.4	0.5
12	0.1	0.1	0.3	0.2	0.33	0.5

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DETERMINING THE NEURO-ENDOCRINE FUNCTION OF THE HUMAN VOMERONASAL ORGAN USING NEURON-SPECIFIC ENOLASE*

EDWARD ANTHONY G. PUEY, MD**
CORNELITO E. TIPLES, MD****
BENJAMIN S.A. CAMPOMANES JR., MD, FPSO-HNS***

ABSTRACT

OBJECTIVES: (a). To determine whether Neuron-Specific Enolase (NSE) is present in the vomeronasal organs (VNO) of live human subjects, (b) to determine if it is exclusively present in the VNO, and (c) to know whether there is a significant difference between the presence or absence of NSE in the septal pit/ VNO and the other sites in the nasal septum.
DESIGN: Analytical.
SETTING: A University – based tertiary hospital.
PATIENTS: All patients ages 18 – 60 years old, regardless of sex, admitted for nasal surgery under general anesthesia. Inclusion criteria: Those granted cardio-pulmonary clearance for surgery, with identifiable septal pits, and those who are to undergo non-malignancy related nasal surgeries. Exclusion criteria: those denied of cardio-pulmonary clearance, those undergoing surgery for nasal malignancies, and those without identifiable septal pits. There were 29 candidates for the study but 7 were excluded.
RESULTS: There were a total of 22 subjects, 13 males and 9 females with a mean age of 38.5 years. Fifteen were diagnosed with nasal polyposis; 2 had nasal polyposis with septal deviation, 1 had purely septal deviation, and 4 were cases of nasal bone fractures. Biopsies done on the septal pits, representing the VNO, showed that 19 were NSE positive and 3 were negative. Biopsies done on the other sites of the septum showed that 18 were NSE positive and 4 were negative. There were no subjects who showed negative NSE staining results on both the septal pit and the other sites. By applying the Z-Test for 2 Proportions, there is no significant difference between the presence or absence of NSE in the septal pit and the other sites of the septum.
CONCLUSION: The authors conclude that the human VNO do contain neuro-epithelial receptors and has therefore retained some of it's neuro-endocrine functions. These neuro-epithelial receptors are not exclusive to the VNO's alone, but can also be found scattered around the other sites of the septal mucosa. The authors recommend that search for the human pheromones be continued so that they may be identified, studied, understood, and therefore be put to good use.

INTRODUCTION

Aristotle famously counted five human sensory modalities: hearing (audition), sight (vision), taste (gustation), touch (tactile sense), and smell (olfaction). Since then, his list has expanded to include such potentially novel modalities as pain (nociception), and orientation with respect to the gravitational field and awareness of limb position (proprioception). Among these, olfaction is probably the least explored modality. In this area, there is a sensory system in humans of which we have only recently become aware of: the *vomeronasal system.* Many mammals have an identifiable pit or groove along the anterior-inferior aspect of the nasal septum that contains chemosensitive cells[1]. This structure, which is also seen in humans, has been called the *vomeronasal organ* (VNO) or *Jacobson's organ/ pit.* In some situations, this system has been shown to be receptive to *pheromones*, which are pervasive throughout the subhuman animal kingdom[2]. The search for a human pheromone has been going on for many years, and attempts to refine various biological odorants like human urine, axillary and vaginal secretions have been done with no conclusive results[2]. Despite the limited number of evidence of the neuro-endocrine

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functionality of the VNO, numerous fragrances, or additives to fragrances, whose advertisements perpetuate the myth that an odor can make one irresistible to members of the opposite sex, have been or are being sold. Although making physiological recordings in humans is generally prohibited, both anatomical and behavioral evidence can and has been collected that indicates the presence of this unconscious sensory system in our species. *Neuron-Specific Enolase* (NSE) is a cytosolic protein that is exclusive to neurons. NSE staining is a form of immuno-histologic staining technique used to determine the presence of neuroepithelial cells, thereby demonstrating the presence of even the minutest nerve endings. It is currently being widely used in the detection of tumors of neuroepithelial origin[3]. It is relatively more economical (P870/test) and easy to perform as compared to post-mortem dissections and electron microscopy (P3,000/test) of tissues, which have been done by past authors. The question raised by the authors of this research is whether the human VNO possesses neuro-endocrine functions as demonstrated by the presence of NSE.

OBJECTIVES

The objectives of this research are: (a) to determine whether NSE is present in the VNO of live human subjects, (b) to determine whether NSE is exclusively present in the VNO, and (c) to know whether there is a significant difference between the presence or absence of NSE in the septal pit/VNO and the other sites of the nasal septum.

MATERIALS AND METHODS

All patients, regardless of sex, aged 18 to 60 years (18 being the age of consent, and 60 being the commonly agreed upon age when atrophic changes start to set in) undergoing nasal surgery under general anesthesia in a University-based tertiary hospital, were considered candidates for this research. *Inclusion criteria*: (a) those cleared by the Department of Internal Medicine to undergo nasal surgery under general anesthesia, (b) those scheduled for surgery of benign nasal lesions (e.g. inflammatory nasal polyps) or corrective nasal surgery (e.g. septoplasty, close reduction of nasal bone fractures, etc.), and (c) those with discernible antero-inferior septal pits on nasal endoscopy prior to surgery. *Exclusion criteria:* (a) those denied of cardio-pulmonary clearance due to other underlying medical problems, (b) patients undergoing nasal surgery for malignancies, and (c) those with no identifiable septal pits. The study was clearly explained and a written consent was acquired from each of the included subject prior to the proposed procedure. Intra-operatively, nasal mucosal tissue biopsy were done using a Storz straight-biting "through cut" Blakesly forceps under endoscopic guidance (Storz 0 degree rigid nasal endoscope). Full thickness tissue samples were taken from only one side of the nasal cavity. First from the identifiable pits, representing the VNO, on the nasal septum, then on another site of the septum (either the posterior or superior portion) at least 2 centimeters away from the pit. Hemostasis was achieved by applying oxymetazoline soaked cottonoids directly unto the biopsy sites. Tissues taken were then labeled and sent to the Section of Anatomic Pathology for processing and staining with NSE. The slides were read by three board certified pathologists and results were signed out as either positive (+) or negative (-) for NSE. The pathologists were blinded and only the authors were aware of codes on the labeled slides. In cases where findings differed from each of the pathologists, the majority was counted as the official reading. No post-operative morbities were encountered in all of the cases. Results were then gathered and tabulated.

FIGURE 1
The VNO/Jacobson's pit (left)

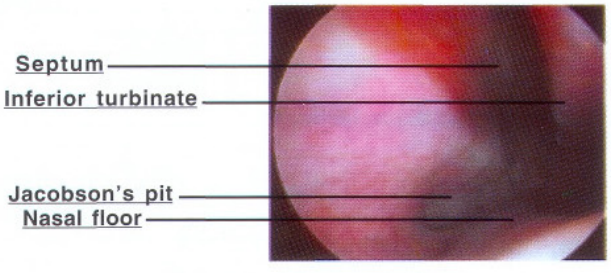
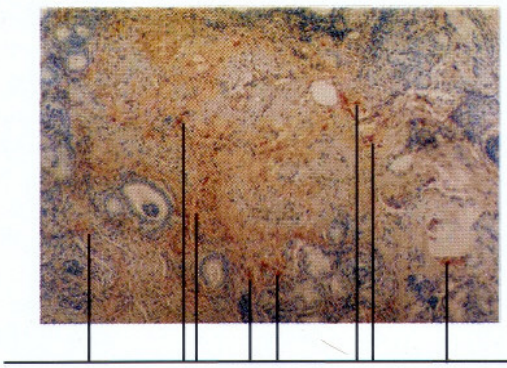


FIGURE 2
Instrumentations

FIGURE 3
NSE staining kit

FIGURE 4
NSE Positive Tissue



Deep red cluster of NSE stained cells due to the cytoplasmic uptake of neuronal epithelium

RESULTS

TABLE 1
*FESS (Functional Endoscopic Sinus Surgery)

Name/ Age/Sex	Diagnosis	Surgery Performed	NSE Staining PIT	NSE Staining Other Sites
J.I./22/M	Nasal bone fracutre	Close reduction	+	+
M.T./59/F	Nasal polyposis	FESS	+	+
B.H./29/M	Nasal polyposis	FESS	+	-
R.B./27/M	Nasal polyposis	FESS	+	+
L.B./41/F	Nasal polyposis	FESS	-	+
E.B/18/M	Nasal polyposis	FESS	+	+
K.C./25/F	Nasal polyposis	FESS	+	+
R.P./31/F	Nasal polyposis	FESS	+	-
E.F./19/F	Nasal polyposis	FESS	+	+
L.T./46/M	Septal deviation	Septoplasty	-	+
E.M./33/F	Nasal polyposis w ith	FESS w ith	+	+
	Septal deviation	Septoplasty		
W.F./54/M	Nasal polyposis	FESS	+	+
H.I./29/M	Nasal bone fracutre	Close reduction	+	-
J.P./32/M	Nasal polyposis	FESS	-	+
J.L./35/M	Nasal polyposis	FESS	+	+
E.A./47/M	Nasal bone fracutre	Close reduction	+	+
S.P./27/F	Nasal polyposis w ith	FESS w ith	+	+
	Septal deviation	Septoplasty		
G.F./33/M	Nasal bone fracutre	Close reduction	+	-
R.F./21/M	Nasal polyposis	FESS	+	+
L.B./44/F	Nasal polyposis	FESS	+	+
C.L./26/F	Nasal polyposis	FESS	+	+
A.C./27/M	Nasal polyposis	FESS	+	+

There were 29 candidates for the study. Seven were excluded due to the following reasons: 4 had no discernible septal pits, and 3 were denied cardio-pulmonary clearances due to other medical problems, leaving the total number of subjects to 22. There were 13 males and 9 females with ages ranging from 18 to 59 years (mean of 38.5 years). Fifteen were diagnosed with nasal polyposis and underwent Functional Endoscopic Sinus Surgery (FESS); 2 had nasal polyposis with septal deviation who underwent FESS with Septoplasty, 1 had purely septal deviation and underwent Septoplasty alone. Four of them were cases of nasal bone fractures secondary to trauma that underwent close reduction. NSE staining of the *septal pits* showed 19 were positive (86.4%) and 3 were negative (13.6%) out of the 22. For the other sites, 18 were positive (81.8%) and 4 were negative (18.2%) out of the 22. There were no subjects that showed negative NSE on both the septal pit and the other sites. The 3 tissues taken from the septal pits that were NSE negative were positive on their other sites, while the 4 taken from the other sites that were NSE negative were positive on their septal pits. Application of the Z-Test for 2 Proportions on the results showed a computed score of 0.416 (significance: Z = 1.96).

	Septal Pit	Other Sites
NSE (+)	19	18
NSE(-)	3	4
Total	$22(n_1)$	$22(n_2)$
Percentage	$86.4\%(P_1)$	$81.8\%(P_2)$

Hypothesis
Ho: $P_1 = P_2$
Ha: $P_1 ? P_2$
Statistical test : Z-Test for 2 Proportions

$$P = \frac{\text{no. of (+) in } P_1 + \text{no. of (+) in } P_2}{n_1 + n_2} = \frac{19 + 18}{22 + 22} = \frac{37}{44} = 0.84 \text{ or } 84\%$$

where q = 16

$$Z = \frac{P_1 - P_2}{\sqrt{\frac{(p)(q)}{n_1} + \frac{(p)(q)}{n_2}}} = \frac{86.4 - 81.8}{\sqrt{\frac{(84)(16)}{22} + \frac{(84)(16)}{22}}}$$

Computed value of Z = 0.416
Clinical Significance = Z = 1.96
Ho: $P_1 = P_2$

DISCUSSION

The term *pheromone* - from the Greek roots of *pherin,* to transfer, and *hormone*, to excite - describes a class of chemicals that are communicated between animals of the same species and that elicit stereotyped behavioral or neuroendocrine responses. These chemicals, as opposed to hormones, which act on the same individual, are released by one member of a species and received by another member of the same species, resulting in a specific action or developmental process via the process of olfaction[4]. While pheromones are known to

mediate a variety of behaviors in other mammals, the human *vomeronasal organ* (VNO), which conveys information about pheromone concentration to the brain, was believed to be absent or atrophied in adults[5]. It was also believed to lack any functional receptors or connection to the central nervous system. A recent review (Johnson, Jan 1998) claims that, while the VNO is present in the fetus, the organ is vestigial in adult humans and that no connection to the central nervous system has been found[6]. In many mammals though, it is possible to trace neural pathways from the VNO to the hypothalamus and other brain regions involved in motivation of behavior[7]. Potiquet (1891) observed the VNO in 25% of 200 adult humans. In 1985, Johnson et al. examined 100 human adults specifically for the presence of the opening of the vomeronasal organ on the antero-inferior part of the nasal septum and found it present in only 39% of patients. But in 27 human septums that they removed for post mortem study, these structures were found in 70% of these[7]. Moran in 1991 examined 200 patients and found VNO openings in both nostrils of every one. He suggests that previous studies missed many VNO's because the studies were conducted without magnification. He found that VNO openings can be as small as 0.2 millimeters, which is roughly the maximum resolution of the human eye[8]. Electron microscopy of the organ reveals that the epithelium contains two kinds of cells which may be sensory cells: some microvillar cells and some unmyelinated, intra-epithelial axons (Stensaas, 1991)[9].

Numerous studies for humans pheromones have examined the perception of odors collected on T-shirts and pads from the upper part of the body and the axilla (Russel, 1976; Doty, et al., 1978; Schleit, 1980 & 1981)[10,11,12]. These odors allow individuals to identify their own smell as well as that of their spouses and close kin (Porter & Moore, 1981; Cernoch & Porter, 1985; Hepper, 1988). These studies suggest that chemical cues from the human body contain sufficient differences in the concentration of odorants to allow for discrimination of individuals and phase in the menstrual cycle of female subjects [13,14,15].

In our study, NSE staining done on the tissues taken from the *septal pits* showed positive results in 19 (86.4%) and negative in 3 (13.6%) out of 22. Tissues taken from the *other parts* of the nasal septum, which were at least 2 centimeters away from the identifiable septal pits, were positive in 18 (81.8%) and negative in 4 (18.2%). A positive NSE staining can be clearly seen as a deep red cluster of cells scattered around the field which is due to the diffuse cytoplasmic uptake of the stain by tissues with neuronal epithelium. In this study, the presence of an anatomically distinct septal pit was noted in 25 out of 29 subjects (86.2%). Though the number of subjects in this research may seem small compared to the other studies, based on the test results, the percentage of the anatomically distinct VNO (86.2%) is relatively comparable to those gathered by Moran (almost 100%) in 1991, as compared to those by Potiquet (25%) in 1891, and Johnson (39%) in 1985[8]. Again, this could be explained by the failure of the other authors to use magnification, as stated by Moran. With regards to the NSE staining results, it is very much apparent that neuroepithelial cells are present in the VNO's (86.4%). But biopsies done on the other sites in the septum also showed positive results in the majority of cases (81.8%). With these findings, it would be safe to deduce that neuro-epithelial cells, and therefore receptors, are present in the VNO's but are not exclusive to it. They are likewise scattered all over the nasal septal mucosa. It would also seem prudent to say that the VNO is not necessarily vestigial but may have in fact retained some of its neuro-endocrine function, together with the surrounding nasal septal mucosa. The gradual decline in its capacity as a neuro-endocrine receptor could possibly be explained by the daily bathing and application of scents that practically masks the normal human odor, a practice common in much of the world, thereby losing some and if not most of the pheromone mechanisms[16]. Although a lot still remains to be learned about the human VNO and its connections, there is little room for doubt that the VNO does exist, respond to pheromones, and affect automonic functions.

CONCLUSIONS

With these findings, the authors conclude that the human VNO, together with the other parts of the nasal septal mucosa, do contain neuro-epithelial receptors based on NSE testing and may have therefore retained some of it's neuro-endocrine functions. It is possible that the entire nasal septal mucosa is receptive to pheromones after all. Humans may have had a well developed vomeronasal system, and it is quite understandable why it has through time diminished in its acuity. Humans are the only mammals known to have developed a general distaste for their own natural odors. The natural human odor has been branded offensive, and has since been masked by regular bathing using scented soaps, and by application of perfumes derived from sweet smelling flowers and plants. In the next millenium,

unless this system is given the recognition it deserves, humans may wake up one day and find themselves devoid of this unique gift.

RECOMMENDATIONS

The authors would like to recommend that the search for the human pheromones be pursued. And whenever a research on the pheromones and the human vomeronasal system is being undertaken, one is advised not to put too much emphasis on the VNO alone, but instead to pay particular attention to the whole nasal septal mucosa for they too contain as much neuro-epithelium as that of the VNO. Human pheromones should be identified and studied, so that they can be isolated and put to good use. The search should continue for what could be the elusive, true "sixth sense" – our vomeronasal organ.

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THE EFFECT OF COMMONLY USED NASAL STEROID SPRAYS (BUDESONIDE, TRIAMCINOLONE, MOMETASONE AND FLUTICASONE) ON NASAL MUCOCILIARY TRANSPORT IN NORMAL ADULTS*

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ABSTRACT

Objective: To determine the effect of 4 commonly used nasal steroids on the nasal mucociliary transport of normal individuals.
Design: Non – randomized, single - blind study
Setting: Chicken dressing factory in Bocaue, Bulacan
Methodology: Forty-eight volunteer adults were enrolled consecutively into 4 groups (12 subjects each). Using the Saccharin test, baseline nasal mucociliary transport rate was determined. Two days later, a single burst of Budesonide 64 mcg, Triamcinolone 55 mcg, Mometasone 50 mcg and Fluticasone 50 mcg on both nostrils were administered. Post application nasal mucus transport rate were determined afterwards.
Results: Comparing the baseline and post application Saccharin test for each group, there was no significant difference noted in all 4 groups (p-value >0.05). The same also holds true with the baseline and post application nasal mucus transport rate for each group, no significant difference was detected (p-value >0.05). Although Budesonide tends to hasten nasal mucus transport rate and Mometasone (Nasonex) tends to prolong it, the effect of these drugs was not significant when tested statistically (p value > 0.05).
Conclusion: This investigative study revealed that by administering a single burst of the 4 nasal steroid preparations on both nostrils, nasal mucus transport rate was not significantly affected or altered at all. In the selection of any nasal agents, clinical studies on its effect on the nasal mucus transport system should be taken into consideration. A nasal drug that significantly impairs nasal mucus transport, may further compromise the nasociliary mechanism of a patient already suffering from a nasal disease.

key words – saccharin test, nasal mucus transport rate, nasal steroid spray

INTRODUCTION

Many patients, both adults and children, are now routinely prescribed with nasal steroid spray for the prophylactic treatment of asthma, allergic and non-allergic rhinitis, nasal polyposis and sinusitis. By delivering the drugs directly to the nasal airway, these products maximize the beneficial therapeutic effects of corticosteroids while minimizing the adverse systemic outcome.

The effect of common nasal agents on the nasal mucociliary system has been investigated in the past. [1] One basic finding was that by applying tap or distilled water, ciliary activity ceases and using saline solution promptly restores it. They also learned that oil is a poor vehicle for nasal agents as it impairs ciliary activity. These early studies elevated the standard of intranasal medication, so that before a certain preparation is adopted for use in the nose, their effect on ciliary activity is first determined.

In the past decades, only Budesonide and Fluticasone nasal steroid sprays are available in the market. But during the past 4 years, introduction of new intranasal steroid preparation proliferated such as Mometasone, Triamcinolone and the rest. This highlights the efficacy of nasal steroid in the treatment of nasal problems such as allergic rhinitis. Its popularity lies primarily in its minimal systemic absorption which makes it ideal for long term use compared with other nasal drugs.

To our knowledge, no local study has been done to assess the effect of these commonly

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used intranasal steroid sprays on the nasal mucus transport system of individuals. This is the primary reason why this investigative study was initiated.

OBJECTIVES

General Objective:
To determine the effect of 4 commonly used nasal steroids on the Nasal Mucociliary Transport of normal individuals.

Specific Objectives:

1. To determine if there is a significant difference in the NMTR values before and after administration using Budesonide, Triamcinolone, Mometasone, and Fluticasone.
2. To determine if there is a significant difference in age, sex, nasopharyngeal length, Saccharin test, and Nasal Mucociliary Transport rate among the 4 test groups.
3. To determine which intranasal steroid prolongs the nasal mucus transport rate.
4. To determine which intranasal steroid hastens nasal mucus transport rate.

SAMPLE POPULATION

The study covered the month of January to May 2000. Volunteer, normal adults were included in the study. The subjects were employees working in a chicken dressing factory in Saturo, Bocaue, Bulacan.

The following were EXCLUDED:

a. Pregnant women
b. Patients with Diabetes Mellitus, Kidney disease, Immotile Cilia Syndrome, and COPD.
c. Subjects with current history of URTI, sinusitis, rhinorrhea, epistaxis, postnasal drip or attacks of allergic rhinitis for the past 3 weeks.
d. Inherent nasal anatomical defects or abnormalities brought by disease, and past history of nasal surgery.
e. Currently on nasal steroids spray, oral and systemic steroids, Cromolyn Na, topical or systemic decongestants, cardiac drugs, mucolytics, hormones.
f. Those who exercise heavily few hours prior to testing
g. Smokers

METHODOLOGY

1. Pertinent general data were gathered using a devised data base. (See Appendix A).

A complete physical examination to screen abnormalities and diseases was conducted prior to NMTR testing. A thorough otolaryngologic history and ENT physical examination, to rule out diseases or gross malformations especially pertaining to the nasal area, was done by the ENT resident. If needed, rigid nasal endoscopy was performed using 0^0 Storz Hopkins Telescope to evaluate any questionable rhinoscopic findings.

2. Once cleared, mucociliary transport testing using the Saccharine Test was conducted. The initial Saccharine Test served as the baseline.

SACCHARINE TEST PROCEDURE

One quarter (0.5 mm) of saccharin tablet (Hermesetas ™) was placed under direct vision using a Jansen nasal dressing forceps on the anterior surface of the inferior turbinate, about 2 cm from the opening of the nasal vestibule.

With the use of a stop watch, the exact time of placement of saccharin was recorded. Subjects were asked to sit quietly, without eating or drinking and without sniffing, sneezing, or blowing the nose. They were instructed to swallow every 30 seconds.

They were instructed to notify the examiner on the first definite taste of sweet flavor. If confirmation occurred, the first recorded time was listed.

3. Afterwards, the length from the nasal tip up to the posterior pharyngeal wall of the nasopharynx using a sterile wooden cotton tip applicator was measured in millimeters. This value (mm) divided by the saccharin transit time (min.) equals the nasal mucociliary transport rate (NMTR) expressed in mm per minute (mm/min)

4. After two days, another NMTR determination was done. A single burst (A – Budesonide 64 mcg, B – Triamcinolone, 55 mcg, C- Mometasone, 50 mcg, D- Fluticasone, 50 mcg) of the nasal steroid spray was applied to both nostrils one hour prior to the second NMTR determination.

All bottles were covered and the subject has no knowledge about the drug that is being administered. The subjects were consecutively enrolled with the first subject assigned to group A, the second to group B, the third to group C and the fourth to group D until 4 groups were completed with a total number of 12 subjects each.

STATISTICAL ANALYSIS

1. To determine if there is a significant difference in age and nasopharyngeal length among the 4 groups, one – way ANOVA was computed.
2. To determine if there is a significant difference in sex among the subjects for the 4 groups, Chi-square test was used.
3. To determine if there is a significant difference in the baseline and post-application Saccharin test (mins) and NMTR (mm/min) values among the 4 groups (Baseline A vs B vs C vs D; Post-application A vs B vs C vs D), one way ANOVA was used.
4. Dependent t – test was used to determine if there is a significant difference between the baseline and post-application Saccharin test and NMTR values for each nasal steroid group (i.e. Group A – Baseline vs Group A – Post-application).

RESULTS

Nasal mucociliary clearance, using the saccharin test was evaluated in 48 normal adult volunteers. Four subjects were excluded when they developed signs and symptoms of upper respiratory tract infection prior to treatment. There were 23 (48%) males and 25 (52%) females with a male to female ratio of 1:1.09. The ages ranged from 17-58 with a mean age of 29.85 years.

The 48 subjects were distributed into 4 groups (12 each), with each group assigned a specific nasal steroid spray (A - Budesonide, B - Triamcinolone, C - Mometasone and D - Fluticasone) which was used two days later after the baseline NMTR was established.

Using the Chi-square test, there was no significant difference in sex, comparing the 4 groups (p-value >0.05) and using the one way ANOVA there was no significant difference in the ages of the subjects enrolled (p-value>0.05).

Average nasal length (NL), from the nasal tip to the posterior pharyngeal wall using a wooden cotton tip applicator was 89.25 mms. Group A (Budesonide) subjects had the shortest NL with a mean value of 85.58 mm and Group D (Fluticasone) had the longest with a mean value of 91.58 mm. There was a significant difference noted in the nasal length comparing the subjects of the 4 groups (p-value <0.001).

Mean Saccharin transport time (ST) on baseline determination was 5.68 mins and post application was 5.63 mins. There was no significant difference noted in the baseline Saccharin test results of the 4 groups (p-value of >0.05). Group A (Budesonide) had the fastest ST at 4.77 min. while Group D (Fluticasone) had the slowest Saccharin transit time at 6.21 mins.

Mean saccharin transport time after steroid application was 5.63 mins. Comparing the Saccharin test results of the 4 groups after steroid application using the one way ANOVA no significant difference was noted (p-value >0.05), Saccharin transport time was faster in Group A and B (Budesonide at 4.93 mins and Triamcinolone at 5.73 mins) respectively.

The mean NMTR values of the 4 groups were 16.24 mm/min (baseline) and 16.10 mm/min (post application). Analyzing the baseline NMTR values, there was a significant difference noted among the four groups (A vs B vs C vs D) p value of <0.05, while post steroid application NMTR values also revealed a significant difference (p-value <0.05). Regarding the baseline NMTR, group A (Budesonide) was the fastest at 18.31 mm/min while group D (Fluticasone) was the slowest at 15.05 mm/min. While post application NMTR, revealed that group A (Budesonide) was the fastest at 17.51 mm/min while group C (Mometasone) was again the slowest at 15.56 mm/min.

Comparing the baseline and post application Saccharin test for each group (i.e. group A baseline vs group A post-application), there was no significant difference noted in all groups (p-value >0.05). The same also holds true with the baseline and post application NMTR in each group, no significant difference was noted (p-value >0.05).

Although Budesonide tends to hasten nasal mucus transport rate and Mometasone tends to prolong it, the effect of these drugs was not significant when tested statistically (p value > 0.05).

DISCUSSION

Lund describes the nose as a gatekeeper of the respiratory airway that is continually required to react to environmental change and to rebuff external assault from a variety of agents.[2] Other than this, the nose also secretes enzymes and lysozymes that destroy bacteria causing disintegration upon contact and facilitates their elimination by mucociliary clearance or by coughing and sneezing. [3]

Injury or dysfunction of either the ciliated or secretory cellular components of the mucociliary system may compromise optimal clearance leading to enhanced susceptibility to infection or promoting further tissue injury.

Ciliary movement was shown to be weak in almost a third of patients with chronic recurring

infections in the upper airways. Patients with chronic sinusitis, nasal polyposis, allergic rhinitis, and cystic fibrosis would demonstrate multiple membrane, microtubular, and radine spoke alterations in the ultrastructure of their cilia. [4,5]

In this premise, if and when a nasal agent significantly impairs the nasociliary system, this may further compromise the nasal mucus transport mechanism of a patient actually suffering from a nasal disease.

Among the methods of measuring nasal mucociliary clearance, the saccharin test is a widely accepted, non-invasive, reliable, and simple test in detecting abnormalities in the nasal mucociliary mechanism. The results obtained correlate significantly with that measured with the inert radioactive particles. Measurements of the nasal mucus flow were reproducible even though the climatic conditions were not controlled. [6] Other methods utilize the electron microscope in detecting abnormalities in the ultrastructure of the cilia and by observing ciliary beat frequency.

The effect of common nasal agents on the nasociliary apparatus has been investigated as early as the 18th century.[1] One basic finding was that by applying tap or distilled water ciliary activity ceases and using saline solution restores it. They also learned that oil is a poor vehicle for nasal agents because it interferes with ciliary activity. Mild silver proteins, argyrols also stop ciliary activity while silver nitrate destroys it. Cocaine solution, atropine, camphor, eucalyptus, menthol, sulfathiazole in prolonged use, extreme cold and exposure to radiation impairs ciliary function. On the contrary, Ephedrine solution and Penicillin 250 "u" exhibit no change at all.

A few years ago, a local study by Cabungcal was done comparing nasal agents such as Oxymetazoline, otrizine, steam inhalation using menthol and eucalyptus (bronchorub) and 2 nasal steroid sprays as it affect the mucus transport system using the saccharin test. [7] Although Budesonide tend to increase the nasal mucus rate in that study, it was not significant when tested statistically.

In the past years, Budesonide and Fluticasone are the only available nasal sprays in the market. But recently, new intranasal steroid preparation proliferated such as Mometasone, Triamcinolone and the rest. This is because topical nasal steroids are potent and the most popular treatment for allergic rhinitis and other upper respiratory conditions. Within the recommended dosage, there is minimal evidence for systemic effects because of low systemic absorption and first pass metabolism in the liver. [8,9]

The mean baseline saccharin transit time of the 48 subjects in this study was 5.68 mins. This is comparable with some of the local studies conducted in the past.[8] The slightly faster Saccharin transit time maybe attributed to the fact that majority of the subjects reside in the rural setting. This was supported by a study by Ramos which showed that nasal mucus transport rate tends to be faster among rural dwellers.[11]
In this study, subject variability maybe eliminated by using one set of subjects only and apply the 4 steroid sprays in a given time interval. However, difficulty in convincing a given subject to undergo 4 applications was anticipated. Four applications is too taxing and annoying to an individual volunteer. Nevertheless, the statistics would show that the 4 groups were proximate in age and sex.

A 2-day "wash out" period (prior to application of the nasal steroid) was chosen because a longer period may predispose the subject to respiratory illnesses, which happened incidentally to 4 of the initial volunteers. At 48 hours, the initial saccharin which traverse the nose could have cleared thoroughly compared with a one day "wash out" period.

In this study, the nasopharyngeal length appear to influence the NMTR values. Group A (Budesonide) had a shorter nasopharyngeal length hence it recorded a relatively faster post application NMTR. While Group D (Fluticasone) got a slower post application NMTR because the group had a relatively longer nasopharyngeal length. Although it appeared that this parameter influence the results, however, this was not statistically significant when the baseline and post application NMTR results were compared. This also holds true with the rest of the nasal steroids preparation utilized.

A single burst on both nostrils was chosen because it was the safest to begin with when done in a normal subject. The steroid preparation was primed to make sure that the applied spray was a full burst. Budesonide has a higher dose at 64 mcg/puff which seemed to be manifested in its group which had a faster NMTR compared with the rest of the steroid sprays at 50 mcg/puff. However, this was not significant.

The nasal steroid preparation could have been given in a longer time frame, however, normal individuals were included in this study and giving the nasal steroid in a longer span of time would not be of benefit to our subjects and worse, adverse effect may develop such as mucosal irritation.

There are several reasons to consider why all 4 groups yielded no significant difference on analysis of the baseline and post application NMTR values.

1. The number of subjects may be small

to manifest and detect a significant difference in the nasal mucus transport rate, hence a larger population is required.

2. The single burst of the nasal spray may not be adequate to produce any alteration in the nasociliary clearance. Since most of these preparations have a delayed onset of action, clinical improvement may take up to 7-10 days.

3. The steroid preparation may contain additives which may likewise affect the results.

CONCLUSION

1. Nasal mucociliary clearance using the saccharin test (ST) was evaluated in 48 normal subjects using the following nasal steroid preparations (A – Budesonide, B – Triamcinolone, C – Mometasone and D – Fluticasone).
2. Although Budesonide tends to hasten the nasal mucus transport rate, and Fluticasone tends to prolong it, there was no significant difference noted in all 4 groups.
3. This investigative study revealed that by administering a single burst on both nostrils using the 4 steroid sprays, nasal mucus transport rate was not significantly affected or altered at all.

RECOMMENDATIONS

For further studies,

1. Additional number of subjects are required to evaluate the nasal mucus transport rate using steroid preparations.
2. Actual patients affected with nasal problems except those with structural defects should be considered.
3. A longer interval of steroid use for a period of one, two or three months is suggested.
4. Nasopharyngeal length of prospective subjects should be proximate with each group because it may influence NMTR results.

BASELINE DATA

GROUP A (Budesonide)

Age	Sex	Saccharine test (before) (in minutes)	Nasopharyn-geal Length (in mm)	NMTR (Before) (mm/min)	Saccharine test (After) (in minutes)	NMTR (After) (mm/min)
21	F	4.56	87	19.08	4.58	19.00
23	M	5.14	78	15.17	4.36	17.89
21	F	5.41	80	14.79	5.5	14.55
23	M	5.16	79	15.31	5.18	15.26
58	M	3.31	87	26.28	4.1	21.22
40	F	4.36	89	20.41	5.25	16.95
28	F	5.14	85	16.54	5.1	16.67
43	M	5.32	89	16.73	5.45	16.33
32	F	5.17	90	17.41	5.15	17.48
34	M	4.34	91	20.97	5.1	17.84
22	F	5.25	85	16.19	5	17.00
21	F	4.18	87	20.81	4.36	19.95

GROUP B (Triamcinolone)

Age	Sex	Saccharine test (before) (in minutes)	Nasopharyn-geal Length (in mm)	NMTR (Before) (mm/min)	Saccharine test (After) (in minutes)	NMTR (After) (mm/min)
17	M	7.34	93	12.67	6.43	14.46
24	M	63	89	14.13	6.5	13.69
23	F	7.17	93	12.97	7	13.29
24	M	6.33	95	15.01	5.59	16.99
23	F	5.44	85	15.62	6	14.17
40	M	4.47	89	19.91	5	17.80
31	M	5.25	90	17.14	5.15	17.48
42	F	5.41	90	16.5	6	14.7
33	F	5.31	90	16.95	5.4	16.67
33	F	5.1	91	17.84	5.25	17.33
32	M	5.1	92	18.04	5.13	17.93
25	F	5.23	87	16.63	5.27	16.51

GROUP C (Mometasone)

Age	Sex	Saccharine test (before) (in minutes)	Nasopharyn-geal Length (in mm)	NMTR (Before) (mm/min)	Saccharine test (After) (in minutes)	NMTR (After) (mm/min)
19	F	7.41	85	11.47	6.36	13.36
23	F	8.47	86	10.15	7.17	11.99
27	F	4.43	93	20.99	5.7	16.32
25	M	6.18	92	14.89	6.18	14.89
40	F	7.3	90	12.33	7.1	12.68
19	M	6.43	85	13.22	6.5	13.08
22	F	5.41	89	16.45	5.39	16.51
31	M	4.36	89	20.41	4.45	20.00
29	F	5.55	93	16.76	5.6	16.61
37	F	6.13	93	15.17	5.25	17.71
41	M	5.19	90	17.34	5.23	17.21
31	F	5.37	89	16.57	5.45	16.33

GROUP D (Fluticasone)

Age	Sex	Saccharine test (before) (in minutes)	Nasopharyn-geal Length (in mm)	NMTR (Before) (mm/min)	Saccharine test (After) (in minutes)	NMTR (After) (mm/min)
35	F	5.31	95	17.89	6.09	15.60
24	M	5.59	90	16.10	5.21	17.27
24	F	6.07	89	14.66	6.5	13.69
26	M	7.17	96	13.39	6.18	15.53
24	M	6.53	95	14.55	6.5	14.62
57	M	8.7	96	11.03	7.4	12.97
37	M	5.45	85	15.60	5.53	15.37
31	M	5.45	89	16.06	5.4	16.48
33	F	5.13	90	17.54	5.1	17.65
29	M	6.3	90	14.29	6.1	17.75
28	M	7.5	91	12.13	6.5	14.00
28	F	5.36	93	17.35	5.45	17.06

TABLES

TABLE 1
Characteristics of the subjects

		N (%) = 48
Sex	Male	23 (48%)
	Female	25 (52%)
Age (in yrs)	Mean ± SD	29.85 ± 8.90
	Range	17 – 58
Length of Nasopharynx	Mean ± SD	89.25 ± 4.02
(in mm)	Range	78 – 96

TABLE 2
Comparison of the over- all results

	Before	After	P value Dependent Test
Time in : Mean ± SD	5.68 ± 1.11	5.63 ± 0.77	>0.05 (NS)
Range	3.31 – 8.70	4.10 – 7.40	
NMTR: Mean ±SD	16.24 ± 2.99	16.16 ± 2.02	>0.05 (NS)
(mm/mins) Range	10.15 – 26.28	11.99- 21.22	

TABLE 3
Comparison of the different variables of the four groups

		Group A Budesonide	Group B Triamcinolone	Group C Mometasone	Group D Fluticasone	P Value
Sex:	Male	5	6	4	8	0.05 (NS)
	Female	7	6	8	4	(chi-sq test)
Age:	Mean±SD	30.50±11.60	28.92±7.49	28.67±7.63	31.33±9.17	>0.05 (NS)
	Range	21 –58	17 – 42	19 – 41	24 – 57	ANOVA
Length:	Mean ± SD	85.58 ± 4.38	90.33± 2.74	89.50±2.97	91.58±3.42	<0.001(S)
	Range	78 - 91	85 – 95	85 – 93	85 - 96	ANOVA
Time Before(mins)						
	Mean±SD	4.77 ± 0.63	5.71 ± 0.88	6.02±1.23	6.22±1.09	0.004(S) (NS)
	Range	3.31-5.41	4.47-7.34	4.36-8.47	5.13-8.70	ANOVA
Time After(mins)						
	Mean±SD	4.93±0.46	5.73±0.65	5.87±0.81	5.99±0.68	0.001(S)(NS)
	Range	4.10-5.50	5.0-7.0	4.45-7.17	5.10-7.40	ANOVA
NMTR: Before(mm/mins)						
	Mean±SD	18.31±3.36	16.12±2.14	15.48±3.33	15.05±2.14	<0.05(S)
	Range	14.79-26.28	12.67-19.91	10.51-20.99	11.03-17.89	ANOVA
NMTR:After(mm/mins)						
	Mean ±SD	17.51±1.88	15.92±1.72	15.56±2.39	15.66±1.61	<0.05
	Range	14.54-21.22	13.29-17.93	11.99-20.2	12.97-17.65	ANOVA

TABLE 4
Comparison of the Saccharin test time (in minutes)
pre and post steroid administration in each group

Group	Before (Mean± SD)	After (Mean±SD)	P value (Dependent T-test)
A (Budesonide)	4.77±0.63	4.93±0.46	>0.05(NS)
B (Triamcinolone)	5.71±0.88	5.73±0.65	>0.05(NS)
C (Mometasone)	6.02±1.23	5.87±0.81	>0.05(NS)
D (Fluticasone)	6.22±1.09	5.99±0.68	>0.05(NS)
Mean	5.68	5.63	

TABLE 5
Comparison of the NMTR (mm/min) in
pre and post steroid application in each group

Group	Before (Mean± SD)	After (Mean±SD)	P value (Dependent T-test)
A (Budesonide)	18.31±3.36	17.51±1.88	>0.05(NS)
B (Triamcinolone)	16.12±2.14	15.92±1.72	>0.05(NS)
C (Mometasone)	15.48±3.33	15.56±2.39	>0.05(NS)
D (Fluticasone)	15.05±2.14	15.66±1.49	>0.05(NS)
Mean	16.24	16.16	

ANOVA – Comparing the difference of 3 or more numerical data (Mean)
Dependent T – test- comparing the difference of 2 numerical data that are paired

FIGURE 1
Mean Nasopharyngeal Length (mm) of the 4 groups

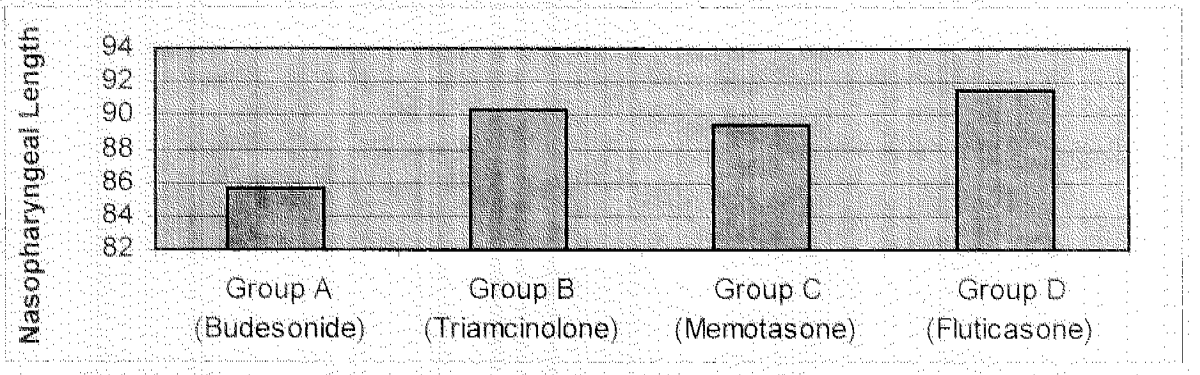


FIGURE 2
Saccharin Transit time (mins.) (Baseline vs. Post-application)

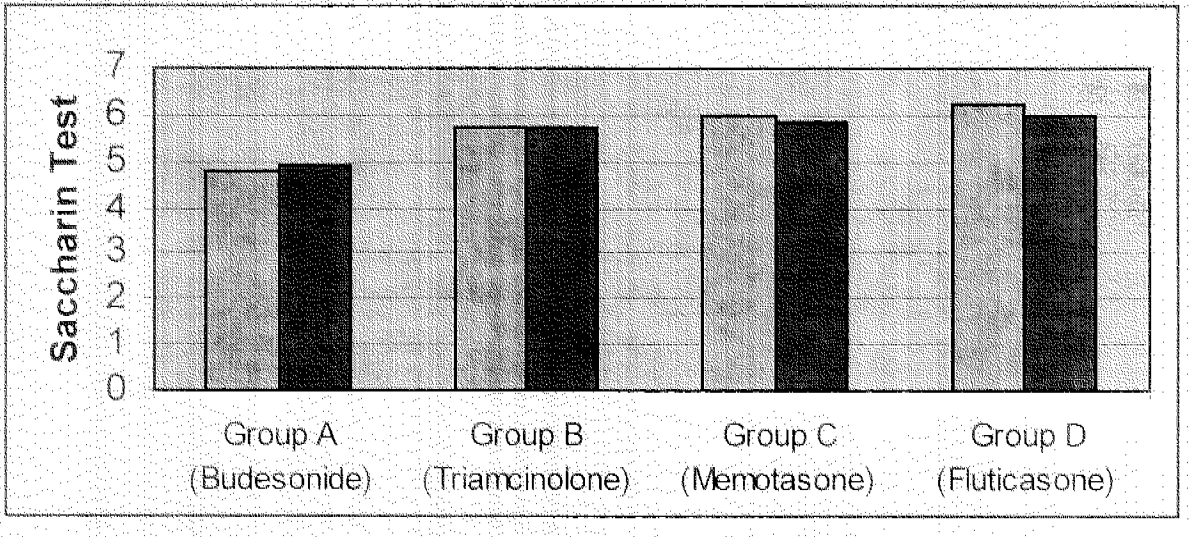
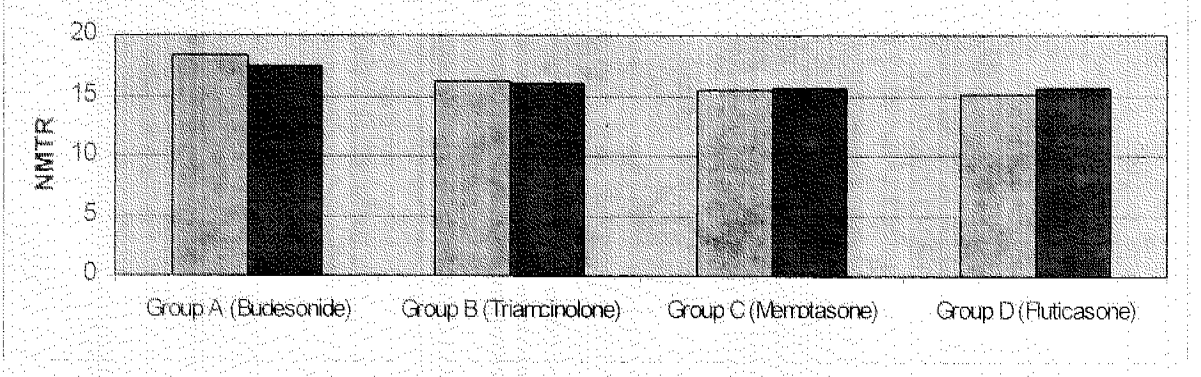


FIGURE 3
Baseline vs Post-application NMTR (mm/min)



APPENDIX

DATA BASE

NAME:
ADDRESS:
AGE:
SEX:
GROUP:
NASAL STEROID:

ENT PHYSICAL EXAMINATION

ANTERIOR RHINOSCOPY: POSTERIOR RHINOSCOPY:

OTOSCOPY: ORAL CAVITY:

NASAL ENDOSCOPY: OTHER FINDINGS:

BASELINE:
SACCHARINE TEST:
NASOPHARYNGEAL LENGTH:
NMTR

AFTER STEROID SPRAY (2 DAYS LATER):
SACCHARINE TEST:
NMTR:

CONSENT

I _____ of legal age and with residence and postal address at _____ hereby consent to be one of the subjects in the experiment given by _____.

_____
NAME OF PATIENT

This consent was given after a have been informed with the use of simple adequate understandable language, the nature of the research, purpose of the research and the risk involved and other possible consequence of the experiment.

I further consent to the performance of spraying the drug to me thru the nose by the ENT physician.

_____
Signature Patient

Signed in the presence of _____
Date_____

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THE EFFECT OF METHAMPHETAMINE HYDROCHLORIDE ("*shabu*") ON NASAL MUCOCILIARY FUNCTION AMONG SHABU USERS*

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FRANCISCO F. VICTORIA, M.D.***

ABSTRACT

Objectives:
General Objective: To compare the mucociliary clearance rates among shabu users and non-users.
Specific Objectives: 1. To determine the mean mucociliary transit time among shabu users and non-users, 2. To determine if the mean mucociliary transit time among shabu users is different from non-users, 3. To determine if there is a correlation between duration of shabu use among the shabu users and mucociliary transit time.
Design: This is a comparative cross-sectional study using stratified sampling of subjects. The mean Saccharin nasal transit time (SNTT) of the shabu users and controls were measured. Statistical analysis was calculated using the student's unpaired *t*-test to compare the difference of the means between the two groups. A confidence level of 95 percent was given or a probability (p) of 0.05 was used.

The degree of association between the 2 variables, namely the duration of exposure of the users to shabu and the rate of the nasal mucociliary system (via Saccharin transit time) was measured using coefficient of correlation.
Setting: Tertiary Hospital
Patients: Forty methamphetamine hydrochloride users, 18 years old and above (mean = 31.075), were included in the study from January 2000 to June 2001. There were 25 males and 15 females. A history of at least 5 years of heavy methamphetamine hydrochloride use was required for the inclusion. For the control group, the same number of neither non-shabu users nor cigarette smokers was included in the study.
Results: Our findings revealed that the saccharin nasal transit time (SNTT) was prolonged among methamphetamine users as compared to non-users. The mean SNTT for shabu users was 35.08 minutes (+/- 7.39 SD), this being significantly prolonged as compared to the SNTT for non-users, which has a mean of 14.89 minutes (+/- 5.11 SD). Our data also showed a positive linear correlation between the duration of methamphetamine hydrochloride use and the nasal transit time using coefficient of correlation (r = +0.833).
Conclusion: In this study, the result suggested that there is a prolonged nasal mucociliary function among methamphetamine hydrochloride users as compared to the non-users. The authors also noted that the length of years of methamphetamine hydrochloride use had a positive correlation with the rate of the mucociliary clearance.

INTRODUCTION

Amphetamine was first marketed in the 1930s as Benzedrine in an over-the-counter inhaler to treat nasal congestion. By 1937, amphetamine was available by prescription in tablet form and was used in the treatment of the sleeping disorder narcolepsy and the behavioral syndrome called minimal brain dysfunction (MBD), which today is called attention deficit hyperactivity disorder (ADHD). During World War II, amphetamine was widely used to keep the fighting men going; both dextroamphetamine (Dexedrine) and methamphetamine (Methedrine) became readily available.[1,2]

Amphetamines are generally taken orally or injected. However, the addition of "ice," the slang name for crystallized methamphetamine

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hydrochloride, has promoted smoking as another mode of administration. Just as "crack" is smokable cocaine, "ice" is smokable methamphetamine. Both drugs are highly addictive and toxic.[2,5,6]

As use of amphetamines spread, so did their abuse. The effects of amphetamines, especially methamphetamine, are similar to cocaine, but their onset is slower and their duration is longer. Methamphetamine is a central nervous system stimulant with a high potential for abuse and dependence. In general, chronic abuse produces a psychosis that resembles schizophrenia and is characterized by paranoia, picking at the skin, preoccupation with one's own thoughts, and auditory and visual hallucinations. Violent and erratic behavior is frequently seen among chronic abusers of amphetamines.[2,3,4]

Methamphetamine is a central nervous system stimulant with a high potential for abuse and dependence. A synthetic drug, methamphetamine is closely related chemically to amphetamine, but produces greater effects on the central nervous system. The drug's euphoric effects are similar to but longer lasting than those of cocaine. It is a powerful stimulant manufactured illicitly using *ephedrine* or *pseudoephedrine* as starting materials.[3,4]

The effects of amphetamines, especially methamphetamine, are similar to cocaine, but their onset is slower and their duration is longer.

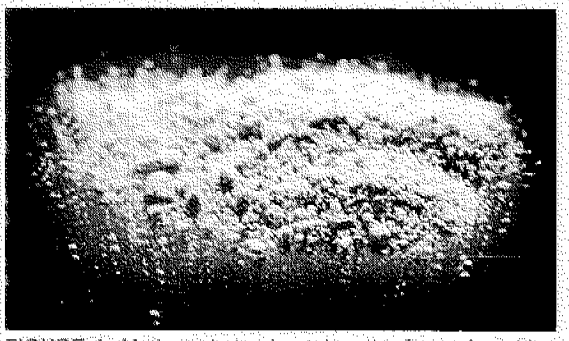

FIGURE 1: Methamphetamine takes the form of a white, odorless, and bitter-tasting crystalline powder, readily soluble in water or alcohol. Street methamphetamine is referred to by many names including "meth", "speed", "zip", "go-fast", "cristy", "chalk", and "crank".

FIGURE 2: Pure methamphetamine hydrochloride, the smokable form of the drug, is called "L.A." or -because of its clear, chunky crystals-"ice", "crystal", "glass", or "quartz".

Amphetamine and other stimulants can cause increased heart and respiratory rates, elevated blood pressure, dilated pupils, and decreased appetite. In addition, users may experience sweating, headache, blurred vision, dizziness, sleeplessness, and anxiety. Extremely high doses can cause a rapid or irregular heartbeat, tremors, and loss of coordination, even physical collapse. An amphetamine injection creates a sudden increase in blood pressure that can result in stroke, very high fever, or heart failure.[4,6,7,8]

The prevalence of the abuse of methamphetamine hydrochloride *("shabu")* in the Philippines has not changed over the years. Since its emergence as the number 1 drug of abuse in 1994, Shabu has consistently ranked first among the most abused drugs. In fact, until now its popularity still rises. Significantly, there is an increasing number of newly reported cases every year. Its percentage of abuse over Marijuana recorded a very significant difference of 51.5% in 1999 and 66.16% in 2000. This, despite the fact that the Philippines is a Marijuana-cultivating country. The rise in the shabu abuse may be attributed to the drug trade being a mega business and to the continued proliferation of clandestine laboratories.[9]

The nose serves not only as the organ for olfaction but also as a filter – the first target for all airborne attack, thus not sparing the nasal mucosal epithelium from the direct effects of various particulate matter such as some inhalational substance of abuse. The integrity of the ciliated epithelium is essential in maintaining adequate clearance of the mucus blanket towards the nasopharynx. Measurements of ciliary beat frequency have been done *ex vivo* under different conditions to demonstrate alterations in ciliary activity.[10,11,12,13] Electron microscopy has also been used to further elucidate the ultrastructural changes occurring within the nasal epithelial cell.[14] Furthermore, impairments in human nasal mucociliary transport system have been assessed *in vivo* using the Saccharin method.[15,16,17] Smoking has been known to be harmful for many years and its depressant effect on ciliary activity has been demonstrated. Prolongation of the mucociliary transit time may predispose an individual nasal entry of virus and/or bacteria. Mucociliary dysfunction may then cause deterioration and perpetuate inflammation of the nose and paranasal sinuses. It is accompanied by an increased incidence of nasal infections.

Several studies showed significant differences in the nasal mucociliary function between normal individuals and in subsets with various pathologic conditions. However, previous studies provide limited information regarding the effect of meth-

amphetamine hydrochloride abuse on the ciliary activity of the nasal epithelium.

OBJECTIVES

General Objective

To compare the mucociliary clearance rates among shabu users and non-users.

Specific Objectives

1. To determine the mean mucociliary transit time among shabu users and non-users,

2. To determine if the mean mucociliary transit time among shabu users is different from non-users,

3. To determine if there is a correlation between duration of shabu use among the shabu users and mucociliary transit time

MATERIALS AND METHODS

A. Subjects

Forty methamphetamine hydrochloride users, 18 years old and above (mean = 31.075), were included in the study from January 2000 to June 2001. There were 25 males and 15 females. A history of at least 5 years of heavy methamphetamine hydrochloride use was required for the inclusion. For the control group, the same number of neither non-shabu users nor cigarette smokers was included in the study. All the subjects from both groups in the study did not have any nasal nor upper respiratory tract infection at least 2 weeks prior and during the period of the study; had no previous sinonasal surgery nor trauma, were not taking any medications; and had no other systemic or metabolic diseases.

TABLE 1
Most Commonly Abused Drugs (Center-Based)
(Adapted from Dangerous Drugs Board Annual Report 2000)

DRUGS USED/ABUSED	2000		1999		1998		1997		1996	
	No.	%	No.	%	No.	%	No.	%	No.	%
1. SHABU	4730	88.23	4631	91.76	3990	93.51	4214	92.55	3947	88.18
2. MARIJUANA	1183	22.07	1998	40.26	1662	36.61	2064	45.11	1776	39.68
3. EPHEDRINE	152	2.84	-	-	-	-	-	-	-	-
4. TRAZEPAM	95	1.77	128	2.59	64	1.5	123	2.7	115	2.57
5. RUGBY	73	1.36	-	-	82	1.92	76	1.67	134	2.99
6. NUBAIN	48	0.9	92	1.86	61	1.43	-	-	99	2.21
7. BROWNIES/CAKE	43	0.8	150	3.04	-	-	-	-	-	-
8. COREXPLAIN	42	0.78	211	4.27	-	-	-	-	-	-
9. COREX-DM	-	-	246	4.98	158	3.7	246	5.38	198	4.42
10. MENTHODEX	-	-	-	-	-	-	206	4.52	135	3.02
11. PHYDCL	-	-	-	-	-	-	182	4	164	3.66
12. PSEUDOFLEX	-	-	-	-	-	-	177	3.89	195	4.36
13. HYCODIN	-	-	-	-	-	-	77	1.69	81	1.81
14. MERCODCL	-	-	-	-	-	-	69	1.52	-	-

TABLE 2
Summary Number of Newly Reported Cases (Center-Based)
(Adapted from Dangerous Drugs Board Annual Report 2000)

YEAR	NUMBER OF NEWLY REPORTED CASES	% CHANGE
2000	5361	8.57%
1999	4938	15.73%
1998	4267	-6.28%
1997	4553	1.72%
1996	4476	-

B. Methodology

Complete history and physical examinations were done in all the subjects who met the inclusion criteria with particular emphasis on nasal examination. The shabu users were asked regarding the length of shabu use in years. Prior to the study, informed consent from each of the subjects in both groups was taken.

Mucociliary clearance will be measured by the Saccharin method of Stanley, et al, wherein a 1-mm diameter particle of saccharin will be placed on the surface of the inferior turbinate 1-cm behind its anterior end. The time required for the subject to experience a sweet taste (saccharin transit time) was measured.

For the measurement of the mucociliary clearance, both sides will be used. All of the subjects will be treated on two occasions with an interval of one week between the two tests. The average nasal mucociliary clearance rates will then be computed and recorded. The subjects will be asked to sit and instructed not to sniff, sneeze, smoke, eat, nor drink during the test. They will be asked to swallow every 30 seconds and say when the sweet taste was perceived. If no taste will be perceived after 60 minutes, the subject's ability to taste saccharin will be placed directly on the tongue to verify ability to taste. The tests will be carried out under room temperature and humidity.

Saccharin Nasal Transit Time (SNTT) = T2 – T1

Wherein: T1 = time when saccharin was placed on the mucosa of the inferior turbinate
T2 = time when sweet taste was perceived by the subject

C. Study Design

This is a comparative cross-sectional study using stratified sampling of subjects. The mean Saccharin nasal transit time (SNTT) of the shabu users and controls were measured. Statistical analysis was calculated using the student's unpaired *t*-test to compare the difference of the means between the two groups. A confidence level of 95 percent was given or a probability (p) of 0.05 was used.

The degree of association between the 2 variables, namely the duration of exposure of the users to shabu and the rate of the nasal mucociliary system (via Saccharin transit time) was measured using coefficient of correlation.

FIGURE 3: Saccharin Method measures Mucociliary Clearance. A saccharin particle (green)placed on the surface of the inferior turbinate on the lateral nasal wall

RESULTS

The saccharin nasal transit time (SNTT) among the shabu users ranged from 25.20 to 52.51 minutes, with a mean of 35.08 (+/- 7.39 SD). The SNTT among the non-users ranged from 6.37 to 26.64 minutes, with a mean of 14.89 (+/- 5.11 SD).

Using the student's unpaired *t*-test to compare the mean SNTT of the two groups, the computed value of *t* was found to be 14.221. This was more than the stipulated value of $t = 1.67$, when p=0.05. Hence, the longer rate among users as compared to the non-users was statistically significant.

The degree of association between the duration of shabu use and the nasal transit time was determined using Pearson's *r* Correlation Coefficient. The computed value of $r=0.833$. This showed that there is a positive correlation between the two variables.

DISCUSSION

Mucociliary function may be defined as the transport of microforeign bodies entrapped on the mucus from the airway for elimination into the digestive tract.[18] Majority of the nasal cavity is lined by pseudostratified columnar ciliated epithelium, except the antero-inferior portion of the nasal cavity, which is lined by non-ciliated squamous epithelium.[19] The integrity of the ciliated epithelium is essential in maintaining adequate clearance of mucus blanket (a transit time of 6 mm per minute) towards the nasopharynx. The cilia beat in a synchronized and metachronized manner, although the precise mechanism of this synchronization is still not fully understood. The cilia move almost exclusively in the sol phase of secretion. The gel phase is actively transported over the sol phase by the cilia during the fast active beat; however, there is no contact between the cilia and the gel phase during slow recovery beat. The synchronicity and precision of these ciliary movements, which is dependent on healthy epithelium, is vital in maintaining normal mucus transport.[20]

TABLE 3

Saccharin Nasal Transit Time among shabu users and non-shabu users.
Table also shows the duration of shabu use among users.

SHABU USERS				CONTROL		
Subject	Age/Sex	SNTT (min)	Duration of exposure (years)	Subject	Age/Sex	SNTT (min)
1	42/M	38.5	13	1	48/F	14.53
2	38/F	29.75	10	2	19/M	7.49
3	21/F	25.2	6	3	40/M	18.4
4	27/M	34.16	9	4	31/M	24.18
5	24/M	31.79	8	5	24/F	15.25
6	26/M	32.42	8	6	20/M	6.37
7	32/M	35.94	12	7	29/M	11.19
8	19/M	25.45	5	8	38/F	16.43
9	24/M	29.02	7	9	22/M	18.4
10	20/M	28.17	6	10	32/F	14.26
11	21/M	26.45	5	11	42/M	25.28
12	29/F	29.89	13	12	28/M	17.89
13	28/F	30.94	7	13	18/M	10.19
14	40/M	48.39	17	14	33/M	8.45
15	42/M	48.36	15	15	35/F	18.92
16	31/F	33.84	15	16	26/M	15.25
17	31/F	27.58	7	17	30/F	8.39
18	32/M	37.62	16	18	22/M	7.42
19	31/M	39.26	15	19	23/M	20.28
20	30/F	32.58	14	20	32/M	16.69
21	45/M	52.51	18	21	25/M	16.09
22	38/M	46.5	16	22	40/M	15.28
23	34/F	32.39	12	23	37/F	18.52
24	29/F	36.05	11	24	21/M	8.62
25	26/F	28.36	8	25	29/M	15.34
26	28/M	34.03	13	26	25/F	13.39
27	25/F	28.3	7	27	44/M	26.64
28	27/M	30.52	6	28	38/M	22.83
29	35/M	47	16	29	33/F	12.45
30	38/F	30.88	10	30	40/M	18.56
31	34/M	45.7	13	31	33/M	18.32
32	29/M	39.91	8	32	20/M	14.15
33	27/F	27.18	6	33	43/M	8.75
34	35/F	32.73	10	34	32/F	17.15
35	33/M	36.96	9	35	28/F	14.06
36	29/F	28.67	8	36	26/F	8.73
37	37/M	46.61	16	37	22/F	9.36
38	39/M	43.73	15	38	27/M	18.08
39	39/M	40.42	12	39	33/F	12.37
40	28/M	29.3	9	40	30/F	10.95

Shabu Users 31.075
Mean SNTT = 35.08 min
STD deviation = 7.39

Non-users 31.45
Mean SNTT = 14.89 min
STD deviation = 5.11

Sotelo et al (1995), proposed that cigarette smoking is a contributing factor in delay in the nasal mucociliary clearance, which may be attributed to the components of cigarette smoke, noted to be ciliary depressant.[21] Other authors have described the velocity of cilia. They studied both upregulation and downregulation of ciliary beat frequency (CBF) from nasal brushings and cultured nasal respiratory epithelium of humans. Their studies revealed upregulation of CBF via depolarization of the cell membrane secondary to neurotransmitters such as Prostaglandin and Substance P. Downregulation occurred secondary to altered intracellular cAMP-dependent calcium flux or to asymmetric interactions between phosphorylation and protein kinase pathways.[22,23,24,25]

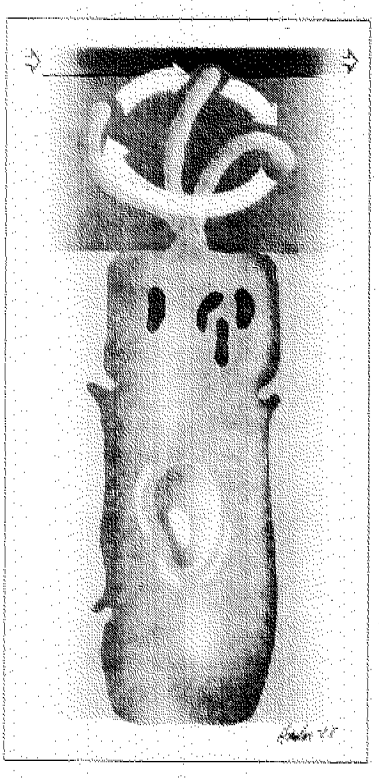

FIGURE 4: An illustration of the mucous blanket, a double-structure, which consists of the sol *"periciliary fluid layer"* and gel *"outer mucous layer"* for effective transport

Nasal mucus is constantly produced. The quantity and composition of the mucus depends among other factors upon environmental conditions such as humidity, pollution, or other airborne external irritants.[20] Several researchers have studied the effects of various inhalational substances on the nasal mucosal epithelium. And others hypothesized on the possible factors that may affect the normal nasal mucociliary clearance. In a recent study by Galvez et al. (1999), the authors hypothesized that chronic pesticide exposure resulted in prolonged nasal mucociliary clearance among farmers due to several contributory factors that may lead to a defective mucociliary transport system.[26]

In the study by Chan et al. (1996), the authors concluded that cocaine directly alters submucosal gland cell function by reducing the basal and stimulated ability to transport ions and fluid after snorting high concentrations of cocaine crystals or smoking the free base form.[27] Active ion transport by airway submucosal gland cells plays an important role in maintaining effective mucociliary clearance. Alterations in the clearance will affect normal airway functions. They showed that cocaine inhibits acetylcholine, which activates the ion transport, by competitively blocking the receptor and the response to isoproterenol by noncompetitive inhibition.[27]

Wang, et al. (1996), determined the effects of amphetamine on the sympathetic function of human nasal mucosa. The effects of amphetamine on the contractile response of isolated human nasal mucosal blood vessels were investigated following electrical field stimulation and methoxamine. The results showed that amphetamine inhibited field stimulation and antagonized the effects on mucosal contraction induced by methoxamine. Amphetamine could potentiate mucosal contraction induced by norepinephrine or epinephrine. It was stated that amphetamine may increase sympathetic function by potentiating the effect of norepinephrine and that high concentration by amphetamine may antagonize a-adrenoreceptor.[28]

Majima et al., (1998), investigated the correlation of rheological properties of mucus and mucociliary transport of middle ear effusion in patients with otitis media with effusion. The outcome of the investigation indicated that there is an optimal viscoelasticity of mucus for mucociliary transport by ciliary beating.[15] The viscoelasticity of nasal secretion from the shabu users group was significantly higher than that of the normal control. These in vitro findings may probably explain in part why nasal mucociliary clearance among the shabu users was significantly longer as compared to the non-users. The duration of shabu use also had a positive correlation with nasal transit time.

The depth of the periciliary fluid layer is critical for the interaction of cilia and mucus.[18] If it is too deep, the tips of the cilia will not catch the outer mucous layer on their effective strokes; if it is too shallow, the cilia will not be able to beat actively. Sakakura et al. (1983), did not observe any significant change in saccharin transit time before and after an administration of normal saline by nebulization in control subjects, whereas in patients with chronic sinusitis, it was significantly faster after nebulization of normal saline than that of before.[29] The result suggested that there is decrease in the periciliary fluid in the nose of chronic sinusitis, and saline nebulization might normalize the reduced periciliary fluid. A tethering

phenomenon that mucous blanket is adherent to the goblet cells by strands of mucus is due to the abnormal releasing of mucus from secretory cells and is one of the pathologic mucous blanket.[29] Therefore, pathologic mucous blanket may lead to mucociliary dysfunction.

Mucociliary clearance is governed by cilia, mucus, and interaction between them. With healthy cilia, suitable mucus and right interaction between them, mucociliary clearance can function. Their functional and structural impairment must be responsible for mucociliary transport dysfunction. If even one of these is impaired, a mucociliary dysfunction will occur.

CONCLUSIONS

The nasal mucociliary transport system among methamphetamine hydrochloride users has been assessed in this study. The results of this study suggest that the prolonged mucociliary clearance among the methamphetamine hydrochloride users as compared to the non-users could be due to methamphetamine hydrochloride exposure. We also noted that the length of years of shabu use had a positive correlation with the rate of the mucociliary clearance.

The three major factors that are considered to be the possible causes of defective mucociliary transport system: (1) cilia, (2) mucus, and (3) cilia and mucus interaction.

The exact mechanism by which methamphetamine hydrochloride exerts their deleterious effects the human nasal epithelium remains uncertain. Nonetheless, defective mucociliary clearance among shabu users has significant implications. The state of health of the nose and the paranasal sinuses depends largely on the integrity of the ciliated epithelium. A vicious cycle in which the infection-induced accumulation of fluid maintains and aggravates airway inflammation was proposed. Bacterial infection causes neutrophil accumulation in the nose and paranasal sinuses and leads to excessive increase in proteases released from neutrophils. In most cases, inhibitor blocks the proteases, and inflammation remits and is cured. If the activity of the proteases exceeds that of inhibitors, they may damage the mucosa of the host and facilitate fluid secretion. These events can lead to mucociliary dysfunction and lead to stagnation of abnormal fluid. Thus, unsaturated proteases may perpetuate inflammation in the nose and sinus. The activity of lysosomal proteases is very high, while that of the thiol protease inhibitors quite weak in nasal secretion of chronic sinusitis. In general, the rheologic properties of this secretion are far from optimum for transport by mucociliary function, and mucociliary transport is further impaired by nasal mucosal changes. Since the ostium of paranasal sinuses is narrowed in chronic sinusitis, stagnation and accumulation of fluid occurs. Stagnated fluid is easily infected, and this is followed by inflammation. This repetition of reinfection-induced inflammation as well as the maintenance of inflammation by mediators are considered serious problems. Thus, the above mechanism was proposed for the pathogenesis

TABLE 4
Factors influencing mucociliary clearance (Adapted from Sakakura)

	FACTORS GOVERNING MOCUCILIARY CLEARANCE	FACTORS IMPAIRING MUCOCILIARY CLEARANCE
CILIA	Number of ciliated cells and cilia	Decrease and disappearance of number of ciliated cells and cilia
	Frequency and amplitude of ciliary beat	Decrease and abnormality of frequency and amplitude of ciliary beat
	Coordination of ciliary beat	Abnormality and disappearance of coordination of ciliary beat
MUCUS	Amount of mucus	Decrease, disappearance and increase of mucus
	Rheologic properties of mucus	High and low viscoelasticity, abnormal spinability and surface properties
CILIA & MUCUS INTERACTION	Depth of periciliary fluid layer	Abnormal depth of periciliary fluid layer (decrease or increase of periciliary layer)
	Releasing mode of mucus from secretory cells	Tethering phenomenon

of chronic sinusitis: a vicious cycle of self-mediated inflammation. Prevention is the rule. Educating our patients on the hazards of smoking methamphetamine hydrochloride, therefore, not only helps them in preventing further aggravation of their condition; it promotes health consciousness of the society as well.

RECOMMENDATIONS

The present study can only demonstrate objectively the effect of methamphetamine hydrochloride on the nasal mucociliary clearance among users. The precise and direct mechanisms by which it influences nasal mucociliary clearance rates remain unanswered. Therefore, it is recommended that further studies be done regarding the direct influences of methamphetamine hydrochloride on nasal mucociliary transport activity such as electron microscopy of the nasal mucociliary layer of users to demonstrate the ultrastructural and or molecular changes brought about by methamphetamine hydrochloride. It is hoped that a better understanding of the destructive changes caused by use on the nasal epithelium and its mucociliary function will lead to conclusive evidences of methamphetamine hydrochloride on the development of nasal and paranasal sinus diseases as well malignancies.

RECOMMENDATIONS FOR FUTURE RESEARCH

A prospective cohort study would be an alternate study design. Nasal mucociliary status of subjects without prior exposure to methamphetamine hydrochloride is initially measured. After exposure, that is, after use of the substance for a specific time, measurements are repeated. Nasal mucociliary clearance rates can then be compared with the subjects who were never exposed and with the methamphetamine hydrochloride users. The effects however may take some time or even years before the changes are evident, and are thus more laborious and tedious. Randomized experiments on humans would not only be unethical but impossible to conduct.

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A COMPARISON OF HEARING THRESHOLDS BETWEEN JEEPNEY DRIVERS OF TANAUAN, BATANGAS AND A HIGHLY SCREENED OTOLOGICALLY NORMAL POPULATION*

RAMON A. KATIGBAK, MD*

ABSTRACT

A comparative cross-sectional study was done to investigate accelerated hearing loss among jeepney drivers of Tanauan, Batangas. Screening audiograms were taken and compared to a general population database to adjust for age-expected hearing loss. Hearing thresholds of 30 male jeepney drivers with a mean age of 32 were taken. These were compared to thresholds at the 50th percentile with normative, age and sex matched hearing data from the International Standards Organization (Database A). At the 50th percentile relative to Database A, jeepney drivers lost about 15 dB, 27 dB and 14 dB at 3000, 4000 and 6000 Hz, respectively. For high frequency hearing loss, the computed relative risk was 1.7 and attributable risk was 12. For broad frequency hearing loss the relative risk is 1.2 and attributable risk is 6. These results are consistent with accelerated hearing loss in excess of age-expected loss among the jeepney drivers.

INTRODUCTION

Hearing loss caused by exposure to occupational noise results in devastating disability that is virtually 100% preventable. Noise induced hearing loss is the second most common form of sensorineural hearing deficit, after presbycusis. Noise induced hearing loss can be prevented by avoiding excessive noise and use of hearing protectors. Avoiding noise exposure stops further progression of the damage. People who are exposed to excessive noise should be screened. When hearing loss is suspected, a thorough history, physical exam and audiometric studies should be performed. If these examinations reveal hearing loss, referral for a full audiologic testing is recommended.

Noise can be described in terms of intensity (perceived as loudness) and frequency (perceived as pitch). Both the intensity and the duration of noise exposure determine the potential for damage to the hair cells of the inner ear. Even sounds perceived as "comfortably" loud can be harmful. Noise induced hearing loss is a sensory neural hearing deficit that begins at frequencies between 3,000 to 6000 Hz and can develop either gradually as a result of chronic exposure to excessive sound levels or from an acute exposure to short term impulsive noise. Excessive shearing forces caused by any sound on the stereocilia of the hair cells of the basilar membrane of the cochlea can cause cell death. Noise induced hearing loss therefore represents excessive "wear and tear" on the delicate middle ear structures. With discontinued exposure, further significant progression of hearing loss stops.

Noise is probably the most common occupational and environmental hazard. Studies done in the United States report that 30 million Americans are exposed to potentially harmful sound levels in their workplaces. Moreover; as many as 10 million Americans have hearing loss caused in part by excessive noise exposure in the workplace or during recreational activities. The economic costs of occupational hearing loss have been estimated to be in the billions of dollars. Noise induced hearing loss has been well recognized since the industrial revolution. In the Philippines however, there is little awareness of the possible deleterious effects of noise on hearing.

The jeepney has been with us since the end of the second world war. Through Filipino ingenuity, military jeeps left behind by the Americans were transformed into a popular mode of mass transport. The extension of the rear of the jeep to accommodate a seating capacity described as "al-

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ways room for one more" as well as the elaborate and ornate decorations have changed little through the years. It has helped shape the Philippine nation by plying its arteries conveying people to every destination across the country. Nowadays, the jeepney has earned a bad reputation for causing traffic accidents and polluting our air with its exhaust fumes. It is postulated that its diesel engines are doing more than just contributing to the noise pollution. The researcher would like to investigate whether the noise generated by jeepneys is enough to cause noise induced hearing loss among jeepney drivers.

OBJECTIVES

1. To investigate the occurrence of accelerated hearing loss among jeepney drivers of Tanauan Batangas.
2. To compare the prevalence of hearing loss between jeepney drivers and a highly screened otologically normal population.

METHODS

Subjects

The study base included jeepney drivers from Tanauan, Batangas with at least 10 years of work experience as a jeepney driver. This cohort was composed of 30 male volunteers with no previous exposure to environmental noise such as military experience or factory work. Also excluded were those with a previous history of ear trauma or infection. An otologic examination was done to include only those with normal appearing ear canals and tympanic membranes.

Medical Examinations

Examination of the jeepney drivers were performed at a private clinic in Tanauan Batangas on October of 2001. All history, physical as well as audiometric examinations were conducted by a single physician. Screening audiograms were taken for 30 subjects using an audiometric booth and an Interacoustics Diagnostic Adiometer Model AD 27. The audiometer was calibrated according to the manufacturer's specifications by a certified technician before the examinations were done. Right and left ear data have been averaged.

Comparison of Jeepney Drivers Threshold Data With Those of a Highly Screened Otologically Normal Population (Database A of ISO 1999)

To predict the effect of noise exposure on hearing, the Internaltional Organization for Standardization developed ISO 1999, Determination of Occupational Noise Exposure and Estimation of Noise Induced Hearing Impairment. This ISO standard represents the most complete knowledge on the effects of noise on hearing sensitivity available today. Database A of ISO 1999 was developed from the hearing thresholds of a large otologically normal population derived from several survey studies. The subjects were screened specifically to study the effect of age (presbycusis) on hearing without confounding caused by otological disease, environmental noise, etc. An otologically normal person is defined as a person in a normal state of health who at the time of testing is free from all signs and symptoms of ear disease or excess cerumen, with no known ear pathology and with no history of undue exposure to noise. This definition is the one that was used to select subjects for the data presented in ISO 7029 (Acoustics – Statistical distribution of hearing thresholds as a function of age). This standard did not account for persons with a history of exposure to potentially ototoxic drugs and familial hearing loss. Comparisons with database A will therefore allow for the estimation of excess hearing caused by factors not related to age. The Standard includes formulas for predicting the distribution of database A hearing thresholds for any age from 18 to 70 years old over frequencies between 125 to 8000 Hz, assuming that the median (50^{th} percentile) hearing threshold for an 18 year old person is 0 dB hearing loss.

For each of the 30 Jeepney drivers, an age-matched male control subject at the 50^{th} percentile of Database A was created. Predicted hearing thresholds of the control subjects at each frequency was determined. As a result, the age distribution of Database A control subjects matched that of the entire cohort of jeepney drivers.

Relative risk and attributable risk for High and Broad Frequency Hearing Loss in Jeepney Drivers Versus Otologically Normal Persons

High frequency hearing loss was defined as an average threshold greater than 30 dB at 3000, 4000 and 6000 Hz. Broad frequency hearing loss was defined as an average threshold exceeding 20 dB across 500, 1000, 2000, and 4000 Hz.[14] The number of jeepney drivers exceeding this criteria for the average of the two ears was calculated.

The number of age matched subjects from database A (P1) as well as the number of jeepney drivers (P2) exceeding the high and broad frequency criterion were taken.

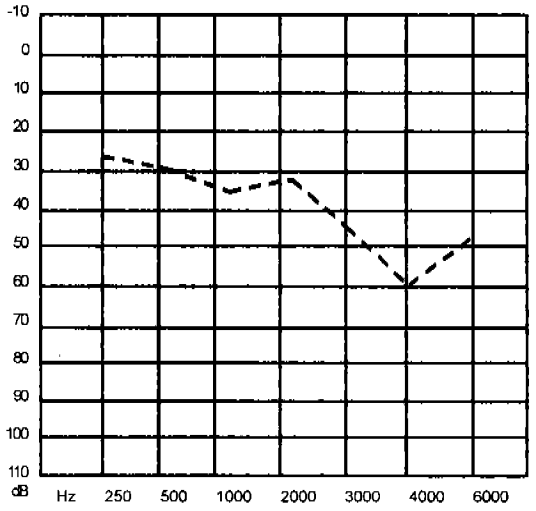
Relative Risk = P2 / P1
Attributable Risk = P2 – P1

RESULTS

The average age of the 30 jeepney drivers and control subjects from database A was 32 years. When results for both ears were averaged, 29 of 30 jeepney drivers had high frequency hearing loss (3000, 4000 and 6000 Hz) compared with 17 of 30 subjects for a database a population with similar age distribution. This yielded a relative risk for the jeepney drivers of 1.7 and an attributable risk of 12. When both ears were averaged, 29 of 30 jeepney drivers had broad frequency hearing loss (500, 1000, 2000, 4000 Hz) compared with 23 of 30 of a database A population of similar age distribution. This yielded a relative risk for the jeepney drivers of 1.2 and an attributable risk of 6.

FIGURE 1 illustrates the mean hearing thresholds over frequencies of 250 to 6000 Hz which were taken from the jeepney drivers.

FIGURE 1
Mean Hearing Thresholds of
Jeepney Drivers in Decibels (dB)



DISCUSSION

Whether hearing loss at high frequency range (3000, 4000, 6000) or hearing loss over a broad frequency range (250, 500, 1000, 2000, and 4000 Hz) was considered 97% of the jeepney drivers met our definitions of hearing loss for the average of both ears. This compares with a much smaller number of 73% and 76% for high frequency and broad frequency range respectively, that would be expected from an age-matched otologically normal population (database A). At the 50th percentile relative to Database A, jeepney drivers lost about 15 dB, 27 dB and 14 dB at 3000, 4000 and 6000 Hz respectively and average

FIGURE 2
Jeepney Drivers Hearing Loss in
Decibels HL and Hearing Loss for
Age-Matched Database A Subjects

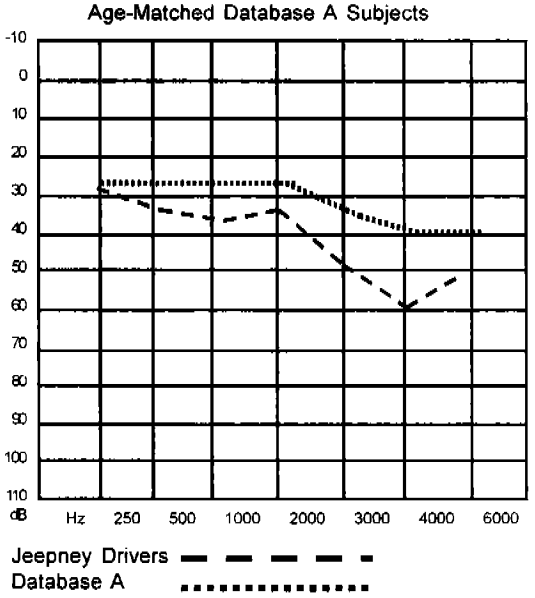


FIGURE 2 illustrates the differences between the jeepney driver's hearing thresholds and those predicted for persons of the same average ages from database A. Over the 3000 to 6000 Hz range, hearing generally became progressively worse relative to the comparison groups.

of 11 dB loss across all frequencies. Therefore, the results suggest that the rate of age-related hearing loss for jeepney drivers are accelerated not only in the 3000 to 6000 Hz range but also across all frequencies. Because these analyses removed the age-expected hearing losses, the threshold shift with increasing age cannot be explained by the effects of normal aging (presbycusis).

The researcher therefore suggests that excess hearing loss among jeepney drivers is caused by occupational noise exposure. Exposure assessments documented using a sound level meter show that jeepney drivers are subjected to prolonged periods of noise exceeding permissible noise exposure levels of the Safety and Health Standards for Federal Supply Contracts (91 dB, 8 hours per day). The finding of exposures combined with apparent accelerated hearing loss in jeepney drivers strongly suggest a noise related health hazard.

The limitation of this study was the lack of information on non-occupational noise exposure and other historical factors that might have affected the hearing of the jeepney drivers. Although these non-occupational factors could not be completely controlled, an independently

derived set of control hearing thresholds from a highly screened otologically normal comparison group (database A) was used. It must be noted though that the control database was derived from studies done on North American subjects. Clearly the use of data taken from Filipinos would have strengthened this study as well as be of use for future investigations on Filipinos. The need for a larger sample size is also wanting.

TABLE 1
Permissible Noise Exposures [8]

Duration Per Day (Hr)	Sound Level dBA Slow Response
8	90
6	92
4	95
3	97
2	100
1 ½	102
1	105
½	110
¼	115

Because of numerous variables and potential confounders, this study cannot conclusively demonstrate that jeepney driver hearing loss is caused by occupational noise. Nonetheless, we have shown that the hearing thresholds of jeepney drivers are deteriorating at an accelerated rate than normal. Furthermore, noise induced hearing loss is an irreversible condition for which there is no effective medical treatment. The irreversible nature of noise induced hearing loss and documented noise hazards thus argue strongly for the widespread implementation of preventive measures. It is recommended that a screening audiometry be advocated for all operators of public utility vehicles so that the magnitude of this problem can be better realized and to enhance target identification. Noise emmission standards should be implemented. We have just only realized this problem that has probably been around since the birth of the jeepney. Therefore, further investigation is merited.

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STATISTICAL EVALUATION OF THE NASAL PEAK FLOW METER*

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ABSTRACT

Objectives:
General: To evaluate the nasal inspiratory peak flow measurements using descriptive and statistical inference
Specific: To determine if there is any significant difference between intra- and inter-trial measurements of peak flow rate. To determine if there is any significant improvement in the peak flow rates of patients before and after sinus surgery. To validate locally the previously established correlation between nasal peak flow meter and rhinomanometer.
Design: Analytical
Setting: Tertiary government hospital
Patients: Ten healthy subjects were chosen to undergo both rhinomanometry and nasal inspiratory peak flow determination. A second phase of the study gathered data from previously operated patients, 27 of whom had separate left and right peak flow readings before and after surgery. Data from another group of 14 patients with simultaneous bilateral peak flow readings before and after surgery were also gathered.
Results: A maximum correlation of -.363 between peak flow and resistance was gathered. Correlation between right peak flow and resistance yielded -.676. An F value of 0.349 and 0.816 for intra- and inter-trial peak flow variability were obtained. Difference of peak flow readings before and after surgery revealed a probability value of .0002.
Conclusion: There was no significant correlation established between the nasal peak flow meter and rhinomanometer. The peak flow readings were consistent through inter- or intra-trial measurements. A significant difference was obtained when peak flow readings before and after surgery were compared.

INTRODUCTION

The importance of evaluating nasal patency cannot be underscored boldly enough. For the ENT specialist, let alone the rhinologist, the cure to a patient's obstructive symptom requires a meticulous assessment of the nasal cavity, its anatomic as well as its functional status.

Objective devices and methods have been in circulation as early as the start of the 21st century. It was only in the 1970's, however that the more standardized rhinomanometer became available.[1] From that time up to the present, it has been the instrument of choice in the objective assessment of nasal patency.[1,3,11,13] Rhinomanometry allows for the simultaneous measurement of air flow and transnasal pressure. From such variables, the nasal airway resistance is derived. Because it is the nature of the anterior rhinomanometer that one nostril be occluded with a foam attached to a silicone tubing leading to the pressure port of the meter, only one nasal cavity is evaluated at a time. Total airway resistance is eventually computed using the values from each of the nasal cavities.

In 1973, Taylor and associates introduced recording of the nasal peak expiratory flow rate with a Wright peak flow meter. Seven years later, Youlten presented a peak inspiratory flow meter which was mainly an inverted mini-Wright peak flow meter.[13] Other versions of the inspiratory peak flow meter has since invaded the commercial scene. This simple device allows for measurement of air flow in a less tedious manner as the rhinomanometer. Furthermore, it has attracted more interest because it is inexpensive, quick and easy to handle by the patient himself.[6] In additional contrast to the rhinomanometer, it was designed to measure

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values with both nostrils devoid of any plugging apparatus.

Literature regarding the correlation between these two devices are currently available.[4,13] The validity of peak inspiratory flow has been evaluated in several studies by assessing the correlation between peak inspiratory flow measurements and other parameters of nasal flow measured by rhinomanometry. The parameters tested are nasal airway resistance as detected by rhinomanometry, and airflow as measured by a peak flow meter. These studies consistently showed strong correlations between peak inspiratory flow and other measurement techniques, rhinomanometry included.[2]

If such correlation exists, then the question arises: can a simpler, more economical peak flow meter substitute for a more complex and costly rhinomanometer? In a developing country like the Philippines, where every possible means to economic progress is indispensable, the substitution of the expensive with the cheap without compromising purpose is in itself sublime. The general objective of this study is:

- To evaluate the nasal inspiratory peak flow measurements using descriptive and statistical inference.

Specifically, it aims:

a) To determine if there is any significant difference among intra-or inter-trial measurements of peak flow rate

b) To determine if there is any significant improvement in the peak flow rates of patients before and after sinus surgery.

c) To validate locally the previously established correlation between nasal peak flow meter and rhinomanometer

MATERIALS AND METHODS

The Subjects

Ten healthy subjects, 6 females and 4 males were included in the study. Age ranged from 25 to 35 years. All subjects were negative for allergic and non-allergic rhinitis, sinusitis, asthma and other chronic obstructive pulmonary diseases at the time of the tests. They were assessed based on their history. Physical examination of the nasal cavities using a 30 degree 4 mm sinuscope were done to corroborate their history. Likewise, visualization of the oropharynx for any sign of infection were done. Each subject also underwent chest auscultation. Normal findings included the lack of septal deviation, nasal discharge and abnormal masses. The absence of post-nasal drip and a clear breath sound completed the criteria for normality.

The Procedure

A table of random numbers was used to decide the order of examination to be done on a patient. As soon as a patient came in, the laterality of the nostril to be tested was first decided upon. Numbers 1 to 3 corresponded to left, numbers 4 to 6 corresponded to right and numbers 7 to 9 for simultaneous testing of both nasal cavities. Zero was disregarded in this particular decision making. The next thing which was decided upon was the kind of instrument to be used first. Was it the peak flow meter? Or the rhinomanometer? Again the table of random numbers was used. Zero to 4 meant that peak flow meter be used first. Numbers 5 to 9 stood for the rhinomanometer. As there were three variables regarding laterality (left, right and bilateral), the table of random numbers was used a second time. Naturally, any number denoting a laterality which was already tested was disregarded. And each time a laterality was chosen, the instrument to be used was automatically decided upon, as well.

The ten subjects came back three times for a repeat of the procedure. They did so following their original order of chronology. There was an approximate time interval of 40 minutes before a subject came back for another trial. This 40-minute interval served as the basis for the computation of inter-trial variability of peak flow measurement.

The Technique

A patient was subjected to an In-Check Portable Inspiratory Flow Meter (Clement-Clarke). To determine the airflow in one nostril, the plastic cap of an oxymetazoline nasal spray served as an improvised apparatus to occlude the non-test nostril. The patient was asked to expire fully. The anesthesia mask which was connected to the flow meter was then snugly fit on his face covering the nose and mouth. He was then instructed to close his mouth and inhale forcefully through his nose for the approximate duration of one second. A patient was asked to do the exercise three times in a row with an approximate interval of 5 to 10 seconds. This 5- to 10-second interval served as the basis for the computation of intra-trial variability of peak flow measurement. The value on the peak flow meter was recorded each time he inhaled.

An Atmos Rhinomanometer 300 was used for each subject. A similar anesthesia mask with an annular diaphragm spiroceptor was used.

This spiroceptor had a hose connected to the machine. A silicone tubing leading to the pressure port of the meter protruded from the anesthesia mask. A foam was attached to this silicone tubing. This foam was snugly inserted into the non-test nostril. The patient was advised to breath normally for 16 seconds, approximately the time it takes for 4 inspiratory-expiratory cycles. The rhinomanometer was specifically designed to test one nostril at a time. Simultaneous testing of both nasal cavities were therefore not possible. After both nostrils were tested, the machine gave out the readings on a thermal paper. The bilateral measurements were computed by the machine and recorded on the same paper.

Data collected were fed into the Stata Version 6.0 Software for analysis. Descriptive data of means and standard deviations were gathered. Multiple analyses of variance were accomplished to determine the compatibility of correlation. Correlations were assessed using Pearson's formula. All possible parameters were correlated with each other. Since related literature pitted airflow against resistance, the study opted to report the same parameters. The unilateral (with the occluding cap) and bilateral (without the occluding cap) airflows were correlated respectively with the unilateral and total resistance. Intra-trial and inter-trial variability of the peak flow measurements were analyzed, as well using the two-way Anova.

Phase two of the study required retrieval of patients' charts. These were patients previously diagnosed of nasal polyposis who underwent nasal peak inspiratory flow determination prior to and after sinus surgery. These patients were seen and treated between June and September, 2001. Peak inspiratory flow measurements of these patients were gathered and tested for significant improvement. One group (n=27) only had left and right peak flow measurements. Simultaneous recording of both nasal cavities were not done in this group. Another (n=14) group only had the simultaneous recording of both cavities without the separate readings of left or right. These groups were analyzed separately. Descriptive data were taken. Differences between pre- and post-operative peak flow measurements were analyzed using the t-test.

Average bilateral nasal resistance at 75, 150 and 300 Pascals (Pa) were 0.23, 0.3 and 0.32 respectively. Average maximum peak flow and mean peak flow were 85.13 and 80.66 respectively (Table 1).

RESULTS

TABLE 1
Descriptive Data For Bilateral Resistance (at 75, 150 & 300 Pa), Maximum And Mean Peak Flow In All Trials

Trial	Res 75	Res 150	Res 300	Max Pf	Mean Pf
1	0.24	0.31	0.32	87	80.83
2	0.23	0.29	0.39	86	80.33
3	0.23	0.31	0.41	83.5	77.83
Average	0.23	0.3	0.32	85.13	80.66

The highest correlation established was –0.363 between the maximum flow and resistance at 300 Pa (Table 2). This was a weakly negative proportion between the two parameters, which simply meant that as resistance increased, the flow decreased.

TABLE 2
Correlation Table Between Bilateral Resistance (at 75, 150 & 300 Pa) Versus Maximum And Mean Peak Flow In All Trials

	Trial 1		Trial 2		Trial 3	
	Max Pf	Mean Pf	Max Pf	Mean Pf	Max Pf	Mean Pf
Res 75	0.244	0.162	-0.092	-0.002	0.157	0.043
Res 150	0.187	0.099	-0.253	-0.154	0.013	-0.174
Res 300	0.125	0.051	-0.363	-0.322	-0.089	-0.262

A correlation between the left nasal cavity maximum airflow and resistance at 75 Pa yielded a value 0.309 (Table 4). This is in contrast to the previous negative relationship between flow and resistance. The highest correlation however was –0.676, which surpassed even that of Wihl's at -0.59 (Table 6). Note, however, that this value was derived from a single cavity, in contrast to Wihl's bilaterally patent cavities.

TABLE 3
Descriptive Data For Airway Resistance (at 75, 150 & 300 Pa) Maximum And Mean Peak Flow Of The Left Nasal Cavity

Trial	Res 75	Res 150	Res 300	Max Pf	Mean Pf
1	0.58	0.79	1.09	55	49.64
2	0.53	0.69	0.97	54.5	48.95
3	0.48	0.62	0.84	59	52.45
Average	0.53	0.7	0.96	38.2	50.34

TABLE 4
Correlation Table Between Airway Resistance (at 75, 150 & 300 Pa) Versus Maximum And Mean Peak Flow Of The Left Cavity In all Trials

	Trial 1		Trial 2		Trial 3	
	Max Pf	Mean Pf	Max Pf	Mean Pf	Max Pf	Mean Pf
Res 75	-0.098	-0.158	0.12	0.048	0.309	0.296
Res 150	-0.101	-0.158	0.089	0.027	0.124	0.138
Res 300	-0.134	-0.183	0.05	0.02	0.098	0.068

TABLE 5
Descriptive Data For Airway Resistance (at 75, 150 & 300 Pa) Maximum And Mean Peak Flow Of The Right Nasal Cavity

Trial	Res 75	Res 150	Res 300	Max Pf	Mean Pf
1	0.45	0.59	0.71	51	46.07
2	0.47	0.6	0.83	45.5	43.97
3	0.51	0.63	0.87	52.5	49.13
Average	0.47	0.6	0.8	49.6	46.39

TABLE 6
Correlation Table Between Airway Resistance (at 75, 150 & 300 Pa) Versus Maximum And Mean Peak Flow Of The Right Cavity In all Trials

	Trial 1		Trial 2		Trial 3	
	Max Pf	Mean Pf	Max Pf	Mean Pf	Max Pf	Mean Pf
Res 75	-0.109	-0.091	-0.275	-0.142	-0.531	-0.617
Res 150	-0.152	-0.145	-0.399	-0.318	-0.416	-0.508
Res 300	-0.088	0.019	-0.676	-0.279	-0.538	-0.632

The two-way anova was used to establish inter- and intra-trial variability of the nasal peak flow. F value of intra-trial variability was 0.349 while that of inter-trial variability was 0.816 (Table 7). The critical value of F is 0.05. This means that a value less than this implies a significant variability in the measurement of peak flow. Our results indicate that no significant change in the peak flow measurements whether they were taken at 5- to 10-second (intra-trial) or 40-minute (inter-trial) intervals.

TABLE 7
Anova Table For Test Of Difference Of Peak Flow Measurements Through Time

Source of variation	Sum of squares	Degrees of freedom	Mean sum of squares	F value
Betw een				
Intra-trial	373.8889	2	186.94445	0.349
Inter-trial	873.8889	2	436.94445	0.816
Interaction	211.1122	4	52.77805	0.0986
Within	43,352.50	81	535.216	
Total	44,811.39	89		
***Critical value of F = .05				

The student's t-test yielded a significant difference between the peak flow measurements before and after surgery. The probability values gathered from the group whose left and right nasal cavities were measured separately were .0006 and .0004, respectively (Table 9). The group with bilaterally patent nasal cavities (no oxymetazoline cap to occlude either nostril) yielded a probability value of .0002 (Table 11). The critical value set was .001. Since computed values were less than the critical, a significant difference of peak flow measurement before and after surgery was established.

TABLE 8
Descriptive Data Of The Average Trials Of Pre And Post-Operative Peak Flow Determination

	Mean	Standard Deviation
Pre-operative		
Left	25.37	21.97
Right	30.92	23.26
Post-operative		
Left	45.74	22.1
Right	52.84	22.47

TABLE 9
Test Of Difference Between The Average Trials Of Pre And Post-Operative Peak Flow Determination (Separate Recordings Of Left And Right Nasal Cavities)

	Mean	Difference	SED	t-value	Prob
Left Pre-op	25.37	-20.37	5.99	-3.4	0.0006
Left Post-op	45.74				
Right Pre-op	30.92	-21.92	6.22	-3.52	0.0004
Right Post-op	52.84				
***Significant at .001 level					

TABLE 10
Descriptive Data Of The Average Trials Of Pre And Post-Operative Peak Flow Determination (Simultaneous Recordings Of Both Nasal Cavities)

	Mean	Standard Deviation
Pre-operative	57.66	15.84
Post-operative	86.21	21.74

TABLE 11
Test Of Difference Between The Average Trials Of Pre And Post-Operative Peak Flow Determination (Simultaneous Recordings Of Both Nasal Cavities)

	Mean	Difference	SED	t-value	Prob
Pre-op	57.66	-28.54	7.18	-3.97	0.0002
Post-op	86.21				
*** Significant at .001 level					

DISCUSSION

From the preceding results and treatment of data, the correlation between nasal peak flow and rhinomanometry in current literature has not been duplicated. The closest correlation ever attained here being -0.363 between the maximum peak flow and resistance at 300 Pascals. However, at one point, the right nasal cavity maximum peak flow attained a -0.676 correlation with resistance at the same pressure (300 Pascals). This is higher than Wihl's correlation of –0.59. Wihl's value however was gathered from a bilaterally patent nose (meaning devoid of any occluding device like our oxymetazoline cap). Several reasons for our failure to reproduce are hereby enumerated.

The rhinomanometer in use has been acquired 2 years hence, and re-calibration of the instrument has never been done. The same instrument was rarely used, generously averaging one patient per week. It is possible that from the time of acquisition up to the time this study was done, accuracy of the instrument might have been altered, its unuse being a contributory factor for inaccuracy. Carney, for one, mentioned that anterior active rhinomanometry has several potential sites for the production of errors,

including the face mask, the anterior pressure probe and the nostril.[1]

The parameters used in this study have not been exactly the same as those in available literature. While Wihl used the corresponding flow and resistance values gathered at a pressure of 200 Pascals our rhinomanometer, on the other hand only had measurements recorded at 75, 150 and 300 Pa. This difference might have caused our inability to come up with similar results.

The values gathered from the peak flow meter were those from the left and the right nostrils, separately taken using the oxymetazoline cap to occlude the non-test nostril. As mentioned, this is not the usual application of the peak flow meter, and definitely not in accordance with its specifications. These same values were compared vis-à-vis the resistance values from the rhinomanometer. It was this method that produced our strongest correlation at –0.676. This is a novelty considering that peak flow meters were designed to measure nasal airflow with both nostrils patent. Our method, though unconventional, may merit validation and further investigation as unilateral measurement may possibly reflect an overall objective assessment of nasal patency.

The nasal cycle is a factor worthy of note. The previous studies used a decongestant to override this factor. This paper did not use any. It has been claimed that rhinomanometry has not been used regularly in clinical practice because of the variability of resistance measurements taken in the un-decongested nose.[1] Our un-decongested noses, then, may have given us variable measurements.

Subjective factors may also have come into play. The forceful inspiration for one may have had variations within the same subject. Naturally, repeated forceful respirations are tiring, so that latter exercises may not be as comparable in magnitude as the previous ones. Furthermore, repeated forced nasal respirations can markedly influence nasal patency by affecting the blood content in the sinusoid vessels.[1] The mouth may not be tightly shut that air entry per orem may cause a different reading. Alar collapse, likewise, decreases the inspiratory flow in a subject which has a bearing on the amount and rate of air flowing through the nostrils.

However, despite our inability to come up with similar correlation, the nasal peak flow meter exhibited consistency through time. Our intra-trial values (whose maximum interval was 15 seconds) pitted against inter-trial measurements (whose minimum time interval was 30 minutes) reproduced insignificant variability. Our values 0.349 and .816 for intra- and inter-trial measurements, respectively were far beyond the critical F value of .05 to achieve significance. Whether airflow was taken at 15-second or 30-minute interval, the peak flow meter gave a relatively consistent reading.

The peak flow meter can detect change in nasal patency. This was displayed by the significant shift in peak flow values after surgery. In a study by Quine, he mentioned that despite the lack of correlation between objective measures of nasal function and the patient's perception of nasal obstruction, these measures are still essential in assessing the role of surgery in treating nasal obstruction because the patient's assessment of the nose may not relate to the function of the nose as an airway.[11] The patients' assessment of their nasal status were not however included in this study. Suffice however that the values gathered from the separate (right and left) and simultaneous (nose devoid of the oxymetazoline cap) peak flow readings were .0006 for left, .0004 for right and .0002 for both nasal cavities. These are way below the critical value of .001. These figures represent significant difference between the pre- and post-operative peak flow readings.

CONCLUSION AND RECOMMENDATIONS

A statistical evaluation of the nasal peak flow meter is herein presented. Although no significant correlation was established between the nasal peak flow meter and the rhinomanometer, the former can detect post-operative change in nasal patency. Furthermore, the peak flow meter displayed consistency in the measurement of the rate of nasal airflow regardless of time interval.

The authors recommend that detailed duplication of the methods of Wihl et al are to be followed if only to reproduce the same correlation between the peak flow meter and rhinomanometer. This paper also underscores the importance of mechanical re-calibration if only to maintain an accurately performing device. Likewise, we recommend the use of the nasal peak flow meter in patients before and after operation, if only to objectively assess the effect of the surgical procedure.

In a country like the Philippines, where national economy dances on the thin wire of instability, alternative modes from the free to the less costly are openly encouraged. Such modes, as long as compromise to objective is neither impending nor imminent, deserve their place in society. The nasal peak flow meter, though simple

in form and principle is one such mode, sans the crystal display, devoid of the thermal adornments. Its consistency, however, has been proven herein, and so merits our approval as an alternative mode in the evaluation of nasal patency. This is not stinginess. It is ingenuity. This is not backward mentality. It is innovativeness.

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FINE-NEEDLE ASPIRATION BIOPSY IN THE DIAGNOSIS OF THYROID CARCINOMA: A PILOT STUDY*

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ABSTRACT

Objective: To evaluate the usefulness of fine needle aspiration biopsy in the diagnosis of thyroid carcinoma.
Design: Analytic Study
Setting: Tertiary Medical Center
Patients: All euthyroid patients with palpable thyroid nodules where FNAB and subsequent surgery was done at this institution from January 1998 to June 2001.
Result: A total of 155 FNAB's were collated. Of these, 49 patients had surgery. Their FNAB's were correlated with the corresponding 49 histopathological results. The sensitivity of FNAB was 57.14% and the specificity was 97.14%. Positive likelihood ratio was 19.98, and negative likelihood ratio was 45.4.
Conclusion: The high likelihood ratio computed indicates that FNAB is desirable as a screening test for thyroid carcinoma. Its high specificity rate makes it a good diagnostic test. However, the ratio between the positive and negative likelihood ratio is less than expected, suggesting that its usefulness is questionable. The low sensitivity rate proves this point. Despite this negative result, the use of FNAB is still encouraged. Refinement of technique is suggested.

INTRODUCTION

Thyroid nodules are one of the common medical problems that otolaryngologists encounter. In most cases, patients undergo studies, such as ultrasonography, computed tomography/ magnetic resonance imaging, biopsies and blood tests. Depending on the results of these examinations, clinicians may opt just to observe these nodules or to proceed with surgery.

While history, physical examination, thyroid hormone assay, ultrasound and thyroid scans provide valuable information regarding thyroid nodules, the only screening modality which can differentiate benign from cancerous thyroid nodules in most, but not all cases, is the fine needle aspiration biopsy. Aspirates are obtained for cytologic review, and the nodule is either classified as benign, suspicious or malignant. In this regard, FNAB holds a great promise in the detection of thyroid carcinoma. The noted advantages of FNAB are its safety, ease of collection for both the patient and the clinician, and its affordability. Despite all these advantages, there is still remaining skepticism in the abilities of this screening modality. Its validity is still yet to be established in our institution. The results of this study will aid the clinicians of this institution in planning the subsequent appropriate management of thyroid patients.

OBJECTIVE

General Objective:

The objective of this study was to evaluate the usefulness of fine needle aspiration biopsy in the diagnosis of thyroid carcinoma in this institution.

Specific Objectives:

1. To determine the specificity, sensitivity and likelihood ratios of FNAB's of euthyroid patients with palpable thyroid nodules from January 1998 to June 2001 in this institution in the diagnosis of thyroid carcinoma.
2. To identify any source of error in the performance of FNAB in this institution.
3. To offer guidelines in improving the diagnostic efficacy of FNAB in this institution.

*Presented, PSO-HNS Analytical Research Contest, December 04, 2001, Sarabia Manor Hotel, Iloilo City
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MATERIALS AND METHODS

The standard evaluation of patients with thyroid nodular disease in this hospital begins with history and physical examination. Functional state is assessed by T3, T4 and TSH determination, coupled with thyroid ultrasound. Nodules are examined by FNA, using the ultrasound result as guide.

FNA of the thyroid was done using a 1 ½ inch gauge 21 needle on a 20cc syringe. After applying antiseptic, the thyroid nodule was immobilized and aspiration was done, withdrawing the plunger until the first appearance of fluid in the hub of the needle. In cases wherein the nodule is cystic, all the fluid is aspirated and sent for cellblock examination. The specimen was expelled onto a glass slide and smeared by gentle pressure with a second slide. The minimum number of slides obtained was two. These were sent to the pathology department for reading.

Slides examined by the pathologist were classified as nondiagnostic, benign, suspicious or malignant. Nondiagnostic indicates that there is an insufficient number of thyroid cells in the aspirate and no diagnosis is possible. A nondiagnostic aspirate was repeated. Suspicious cytologic diagnoses were considered to be positive for malignancy.

The results of thyroid aspiration biopsies of euthyroid patients with palpable thyroid nodules in this hospital during the period between January 1, 1998 and June 30, 2001 were collected. The cytologic and histologic diagnoses in those patients who underwent surgical intervention in our hospital were then compared.

The results of the final histopathologic diagnosis were used as the gold standard. The results were either classified as benign or malignant tumor. No further classification was made in this study. The clinical usefulness of FNA was evaluated by computing the sensitivity, specificity and likelihood ratios.

RESULTS

A total of 155 euthyroid patients with palpable thyroid nodules were examined by FNA of the thyroid in this institution between January 1998 and June 2001. Of the total number of patients, 121 (78.06%) had nodules that were negative for thyroid malignancy, 19 (12.26%) had nodules that were positive for thyroid malignancy, 4 (2.58%) had nodules that were suspicious for thyroid carcinoma, whereas in 11 patients (7.10%) the specimen was unsatisfactory for diagnosis. (Table 1.)

Histologic specimens were available for 49 patients. Of these, 40 (81.63%) had FNAB result of negative for malignant cells, and 9 (18.37%) diagnosed to have thyroid carcinoma. Thirty-four out of the 40 patients (85%) had a benign nodule on final histopathologic examination. Eight out of the nine patients (88.89%) had thyroid carcinoma. (Table 2.)

TABLE 1
Distribution of FNAB Results

	NUMBER	PERCENTAGE
NEGATIVE FOR MALIGNANT CELLS	121	78.06
POSITIVE FOR MALIGNANT CELLS	19	12.26
SUSPICIOUS FOR MALIGNANCY	4	2.58
NONDIAGNOSTIC SMEAR	11	7.1
TOTAL	155	100

TABLE 2
Distribution Of Histopathologic Examination Results

	NUMBER	PERCENTAGE
BENIGN	34	69.39
MALIGNANT	15	30.61
TOTAL	49	100

Based on the above results, the sensitivity of FNAB was 57.14% and the specificity was 97.14%. False negative rate was computed at 42.85% and false positive rate at 2.86%. Positive predictive value was 88.89% and the negative predictive value was 85%. The overall accuracy for cytologic diagnosis was 85.7%. Positive likelihood ratio was 19.98%, and negative likelihood ratio was 0.44%. (Tables 3, 4 & 5.)

TABLE 3
Correlation Between Cytologic And Histologic Diagnosis

	CYTOLOGY		
HISTOLOGY	NEGATIVE for Malignant Cells	POSITIVE for Malignant Cells	TOTAL
BENIGN	34	1	35
MALIGNANT	6	8	14
TOTAL	40	9	49

TABLE 4
Results Of Statistical Testing*

TEST	RESULT
Sensitivity	57.14%
Specificity	97.14%
False Negative Rate	42.85%
False Positive Rate	2.86%
Positive Predictive Value	88.89%
Negative Predictive Value	85%
Accuracy	85.70%

TABLE 5
Relation Between FNA Diagnosis And The Presence Or Absence Of Malignancy

	Thyroid Ca present at Histology		Thyroid Ca absent at Histology		
FNA Result	Number	Proportion	Number	Proportion	Likelihood Ratio
Positive for Malignancy	8	0.57	1	0.03	19.98
Negative for Malignancy	6	0.43	34	0.97	0.44

*COMPUTATIONS

SENSITIVITY : proportion of patients with disease who have a positive test
= 8/14 X 100 = 57.14%
SPECIFICITY : proportion of patients free of disease who have a negative test
= 34/35 X 100 = 97.14%
FALSE NEGATIVE : proportion of patients with disease who have a negative test
= 6/14 X 100 = 42.85%
FALSE POSITIVE : proportion of patients free of disease who have a positive test
= 1/35 X 100 = 2.86%
POSITIVE PREDICTIVE VALUE : proportion of those with a positive test who actually have the disease
= 8/9 X 100 = 88.89%
NEGATIVE PREDICTIVE VALUE : proportion of those with a negative test who actually are free of the disease
= 34/40 X 100 = 85%
ACCURACY = (8+34)/ 49 X 100 = 85.7%

DISCUSSION

Physical examination of the thyroid, when performed by well-trained physicians, allows the detection of the majority of thyroid nodules. However, physical examination cannot determine whether a nodule is neoplastic or benign. Thyroid ultrasonography permits the detection of thyroid nodules measuring even a few millimeters in size, but a reliable histologic diagnosis cannot be made. FNAB tries to offer a cytologic diagnosis. Biopsy of thyroid nodules usually provides the most valuable information in helping a physician to decide whether a surgical operation is necessary.

A number of clinicians advocate fine needle aspiration biopsy as the first examination after clinical discovery of a thyroid nodule. In our institution, upon discovery of a thyroid nodule, T3, T4 and TSH determination and thyroid ultrasonography is done. Thyroid ultrasonography is used as a guide in performing fine needle aspiration.

An adequate specimen of good technical quality is considered diagnostic or satisfactory and may be benign, suspicious, or malignant. A benign cytologic diagnosis is seen in 50% to 90% of the specimens. From 10% to 30% of FNA cytologic specimens may be suspicious for malignancy or indeterminate (average, 20%). A malignant or positive cytologic diagnosis varies from 1% to 10% (average, 5%). In this study, 78.06% of the specimens were benign, 2.58% was suspicious for malignancy, and 12.26% was malignant. Our nondiagnostic smear composed of 7.10% compared to 2% and 17% in foreign studies.

Foreign literature reports a sensitivity of 91.8%. It is for this reason that in most clinics, FNA has become a standard test in the evaluation of thyroid nodules. It is believed that FNA is the first, and in the vast majority of cases, the only test required for the evaluation of a solitary thyroid nodule.

In our experience, FNAB has a sensitivity of 57.14%. It is relatively low compared to the above studies. However, our results are comparable to other studies. A study conducted by Giard, et.al., (1999) also shows a sensitivity of 57%. They found out that only 41% to 47% of thyroid carcinoma cases were detected cytologically. They concluded that majority of thyroid carcinoma cases are not detected by FNAB.

A similar study by Oertel (2000) regarding the efficacy of FNA's in detecting thyroid cancer also shows a sensitivity of 60%, which is claimed to be a realistic value in a setting where cytopathologic examination is not that common.

The low sensitivity of our test follows a high false negative result. Computed at 42.85%, it is quite high compared to 1.5% to 11% in present literature. A high false negative value translates to a high rate of missed malignancy. However, the value may depend on the number of patients who subsequently have surgery and histologic review. In most retrospective series, not all patients with a benign cytologic diagnosis subsequently have thyroid surgery, suggesting that false-negative rates should be interpreted with some skepticism. Despite this note of caution, most authorities agree that the true false-negative rate is less than 5% if all patients have thyroid surgery.

Very small nodules where accurate needle placement is difficult, and nodules too large to allow proper sampling from all areas, may also cause a high false negative rate. A review of the charts of the patients who had a negative FNA result and a malignant final histopathologic diagnosis was made and it was noted that these patients had palpable nodules bigger than 4 cm.

It is also important to note that accuracy of FNAB declines when follicular lesions are examined. According to Batsakis (1999), delineating follicular neoplasms from adenomatous nodules cannot be definitely accomplished by examining fine needle aspirates. A final histopathologic diagnosis of follicular carcinoma was given to those who had a negative FNA in this study. These would probably account for the high false negative FNAB result in our particular study.

Lastly, however, we cannot discount the fact that false-negative rates are lower in centers

experienced with the procedure and with cytologic interpretation by expert cytopathologists.

The question that is of practical concern to the clinician and the thyroid patient is: "If the results is positive (or negative), what are the chances that the patient has (does not have) the disease?" In this case, the predictive value is of primary importance. Predictive values in this study have a high numeric value. With this result, clinicians can be more confident in saying that a thyroid patient with a negative test result does not have thyroid carcinoma (85%), and that a patient with a positive test result does have thyroid carcinoma (88.89%). It is the best possible estimate of the presence or absence of thyroid carcinoma.

Likelihood ratios (LR) are obtained by dividing the likelihood of obtaining that result among patients with histologically proven thyroid carcinoma and the likelihood of the same cytologic diagnosis among the patients with no thyroid carcinoma at histology. It indicates the desirability of a particular test. A positive LR of more than 1 and a negative LR of less than 1 would make a particular screening test desirable. In our experience, the positive LR was 19.98 and the negative LR was 0.44, indicating that FNAB is a desirable screening test. However, the ratio between the two was computed at 45.4. The ideal ratio is 50 or more, suggesting that its usefulness in our setting is questionable.

CONCLUSION/ RECOMMENDATIONS

The results of the current study show that the cytologic examination of thyroid nodules by FNA is desirable as a screening test for thyroid carcinoma. The high specificity rate makes it a good diagnostic test. However, the ratio between the positive likelihood ratio and negative likelihood ratio is less than expected suggesting that its usefulness is questionable. The low sensitivity rate proves this point. This is contrary to common belief based on current guidelines for the work-up of patients with nodular thyroid disease. The reason for this discrepancy is varied and the following observations/ recommendations are made:

1. The experience as well as the expertise of the cytopathologist is critical in avoiding pitfalls. Determining the adequacy of an aspirate, cellular atypia, application and interpretation of immunostains are but a few of these problems.

2. Larger nodules are more likely to yield false-negative results. To improve sampling, aspirates should be obtained from multiple sites of the nodule rather than repeatedly from one spot. The absence of malignant cells in an otherwise acellular specimen does not exclude malignancy. It is good practice to biopsy all accessible nodules in a multinodular gland

3. FNAB is a relatively simple and inexpensive procedure. To maximize its potential as a diagnostic tool, cooperation among clinicians, pathologists, radiologists and nuclear physicians is maximized.

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ANTERIOR CRANIAL FOSSA LANDMARKS: A STUDY BASED ON FILIPINO CADAVER DISSECTIONS*

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ABSTRACT

Objectives: 1. To measure fixed anatomic landmarks and structures in the anterior cranial fossa of adult Filipino cadavers, 2. To compare some measurements obtained in this study with published values from foreign literature, 3. To demonstrate the clinical importance and application of the measurements obtained in this study
Design: Cross Sectional Study involving dissections of 24 Filipino adult cadaver skulls
Setting: Tertiary government hospital Pathology Laboratory
Materials: 24 adult Filipino cadavers with no gross deformities, craniofacial abnormalities and history of craniofacial trauma
Results: The average length of the anterior cranial fossa obtained in this study is 45.81mm which is not significantly different from published Caucasian value of 47.7mm. There is no significant difference between the means of both sexes. The mean length of the intracranial portion of the optic nerve is 12.97mm on the right and 12.89mm on the left which is significantly different from published Caucasian value of 10mm. There is no significant difference in the mean length of the intracranial portion of the optic nerve between the right and left as well as between males and females. The diameter of the intracranial portion of the optic nerve has an average value of 5.59mm and 5.33mm on the right and left respectively which is not significantly different from published Caucasian value of 4-7mm. There is no significant difference between the mean value on the right and left as well as between both sexes. The average distance between the right and left optic foramen is 13.53mm which is not significantly different between males and females. The angle of the optic chiasm as it bifurcates into the intracranial portion of the optic nerve has an average value of 76.42^0, the mean values being significantly different between sexes, with the males having an average of 79.61^0 and female with 66.83^0. The mean distance from the frontal crest to the anterior wall of the sphenoid sinus and optic chiasm is 44.08mm and 53.26mm respectively with no significant difference between the means of both sexes. (p value=.01).
Conclusion: The mean values for the measurements of anterior cranial fossa structures were noted. Some of the average values obtained in this study are not significantly different from published foreign values except for the mean length of the intracranial portion of the optic nerve. There is no significant difference between the means obtained for both sexes except for the optic chiasm angle. Values derived from this investigation may guide the craniofacial surgeon as to the lateral and posterior most extent that surgery can be performed without jeopardizing intact vital structures such as the optic nerves and orbital contents.

INTRODUCTION

Malignant tumors and even benign but locally aggressive lesions that originate from the paranasal sinuses, particularly those that involve the ethmoid with extension to the floor of the anterior cranial fossa especially the cribriform area often present surgical and management difficulties. En bloc resection through a combined craniofacial approach has been accepted as one of the feasible and encompassing surgical treatment of choice for

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these formidable cases[1-10,14] and has been described in a series by numerous authors, with relatively higher survival rates, lower morbidity and excellent cosmesis[6,7]. A surgical challenge crucial to these cases is that of preserving the integrity of vital structures such as the optic nerves especially in patients with uninvolved orbital contents and good vision.

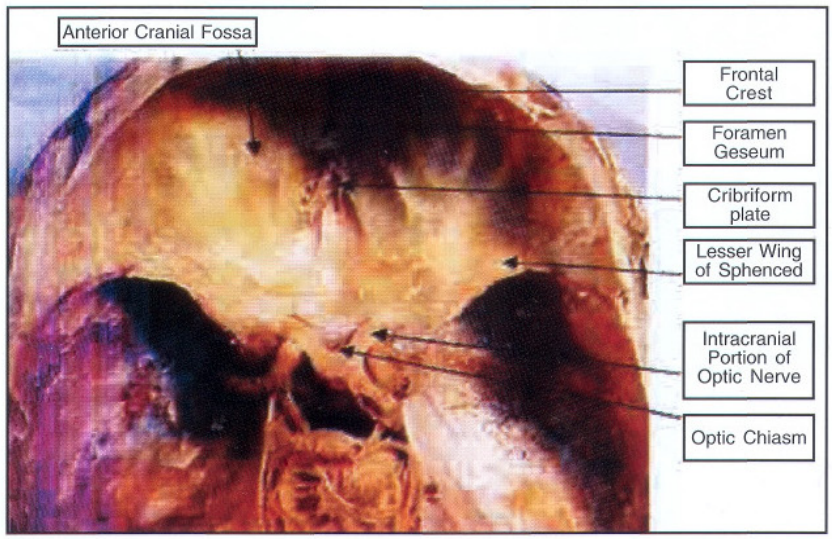
The key to the successful management of the above described tumors lie on the two-team collaborative effort of the head and neck surgeon and neurosurgeon. As such, this study has been undertaken to attempt to provide the otolaryngologist head and neck surgeon a description of anatomic landmarks in the anterior cranial fossa along with the average measurements of important structures and distances between the described anatomic landmarks taken from Filipino cadaver specimens which may serve as a useful guide for the surgeons in the performance of the prescribed craniofacial surgery. The measurements obtained may be able to supply the basis as to the lateral and posterior most extent to which the surgery on the anterior cranial fossa in Filipinos particularly on the area of the cribriform for extensive sinunasal tumors can be performed without jeopardizing intact vital structures such as the optic nerves and orbital contents, in the light that these measurements are wanting in both foreign and local literature.

SURGICAL ANATOMY

The anterior cranial fossa (Figure 1) is formed by the orbital portion of the frontal bone; medially, the cribriform plate (lamina cribrosa) of the ethmoid, which forms a small part of the floor; the lesser wings and anterior part of the body of the sphenoid, contributes posteriorly. The anterior fossa supports the olfactory tracts, bulbs and frontal lobes, and a number of grooves and ridges are found on the frontal bone. This area is the thinnest part of the fossa, and forms the roof of the orbit. The fossa lies at a higher level than the other fossae.

The frontal bone is split anteriorly by the frontal sinus, the median plane of the bone is marked by the frontal crest, to which the falx cerebri attaches. The jugum of the sphenoid separates the fossa from the sphenoid sinus. Anteriorly, the jugum articulates with the cribriform plate, and posteriorly it is grooved by the chiasmatic sulcus, connecting the optic canals. The lesser wings curve away laterally and posteriorly, forming a free overhanging border to the middle cranial fossa, and bear the anterior clinoid processes. The crista galli lies in the midline, which is variable in shape and size and occasionally pneumatized. Anterior to this is the foramen caecum, which often transmits an emissary vein to the superior sagittal sinus. The cribriform plate which divides the nasal and cranial cavities, is so called because of the foramina transmitting the olfactory nerves. The anterior ethmoidal canal usually opens between the orbital part of the frontal bone and the cribriform plate, and transmits the respective nerves and vessels, which runs forwards under the dura to reach the nasal cavity by passing down through a slit at the side pf the crista. Sometimes these structures can pass through a separate foramen in the frontal bone itself. The posterior canal opens at the posterolateral corner of the plate[12].

FIGURE 1
Structures of the Anterior Cranial Fossa



MATERIALS AND METHODS

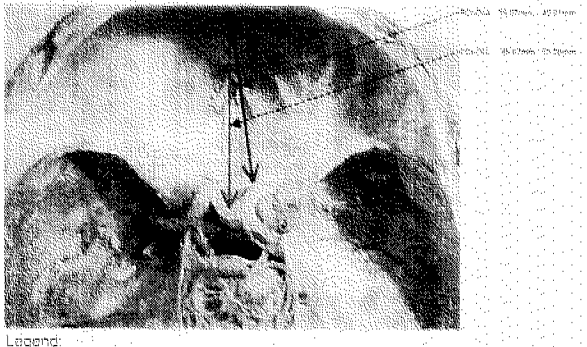
Twenty four well preserved Filipino adult cadavers with no gross deformities nor craniofacial anomalies and history of craniofacial trauma were studied paying particular attention to the anterior cranial fossa structures. Calvarium was removed for exposure of the skull base. Actual measurement of the anterior cranial fossa structures and distances between the anatomic landmarks were made using a Vernier caliper and recorded by 1 of the authors on prepared observation sheets. (Refer to appendix A and B for individual measurements of anterior cranial fossa landmarks). Anatomic variations were observed and likewise noted. Data were recorded and analyzed.

ANTERIOR CRANIAL FOSSA STRUCTURES AND VARIOUS DISTANCES MEASURED

(Fig. 2a, Fig. 2b, Fig. 2c, Fig. 2d, Fig. 2e)

FIGURE 2A

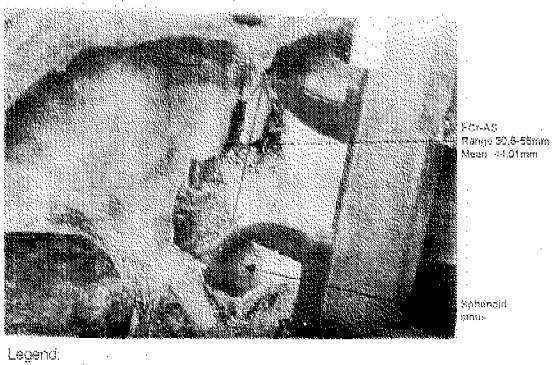
Distance Measured from Frontal Crest to Optic Chiasm and Optic Canal



Legend:
Dark Red Arrow – Frontal Crest to Optic Chiasm (Fcr-OC)*
Dark Blue Arrow – Frontal Crest to Optic Canal (Length of anterior cranial fossa) (FCr-Oca)*

FIGURE 2B

Distance Measured Between Frontal Crest to Anterior Wall of Sphenoid Sinus (Axial view)



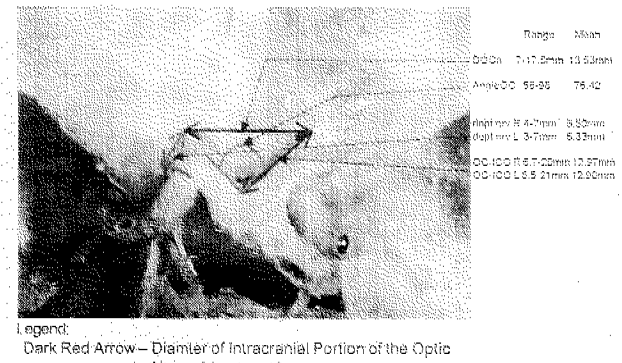
Legend:
Red arrow-Frontal Crest to Anterior Wall of Sphenoid Sinus (Fcr-AS)*

FIGURE 2C

Frontal Crest to Anterior Wall of Sphenoid Sinus (Sagital view). (FCr-AS)*

FIGURE 2D

Distance Measured Between Right and Left Optic Canals Length of Intracranial Portion of Optic Nerve (Distance Between Optic Chiasm to Intracanalicular Potion of Optic Nerve, Diameter of Intracranial Portion of Optic Nerve and Angle of Optic Chiasm)



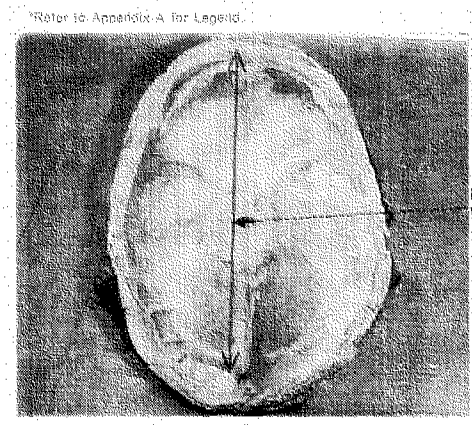
Legend:
Dark Red Arrow – Diamter of Intracranial Portion of the Optic Nerve (d opt nrv)*
Green Perpendicular Line0 – Angle of Optic Chiasm (Angle OC)*
Dark Blue Arrow – (Length of Intracranial Portion of Optic Nerve)-Optic Chiasm to Intracanalicular Portion of the Optic Nerve (OC-ICO)*
Black Arrow – Distance Between Right and Left Optic Canals (DOCa)*

FIGURE 2E

Antero-Posterior Diameter of Skull Base

Dark Red Arrow – Antero-Posterior Diameter of Skull Base (AP Skull)

*Refer to Appendix A for Legend



RESULTS

Table 1 shows the mean values for the measurements of the distances between the different anterior cranial fossa structures in the 18 male and 6 female adult Filipino cadavers in this study. As illustrated, there is no significant difference between the average measurements taken for both sexes except for the angle of the optic chiasm, in which the optic chiasm angle for females is relatively more acute at 66.83 degrees than males at 79.61 degrees (p value=0.01). There is also no significant difference in the mean values of the measurement taken on the right and left side of the intracranial portion of the optic nerve in terms of its length and diameter.

Table 2 shows the combined average measurements of the distances between the anterior cranial fossa structures in the 24 adult Filipino cadaver skulls. These measurements are better illustrated in Figure 2a, 2b, 2c, 2d, and 2e. The reader is referred to Appendix A and B for the indivudual measurements of the distances between the anterior cranial fossa structures of each of the 24 adult Filipino cadaver skulls.

DISCUSSION

Involvement of the cribriform and other anterior cranial fossa structures has been one of the limitations of successful surgery in nasal and paranasal sinus cancers[13]. A feasible and effective method of total extirpation of tumors involving the cribriform plate is by a combined craniofacial approach. The procedure is considered if tumor involves the sphenoid, ethmoid, or frontal sinuses[13]. The combined craniofacial procedure is briefly described and elucidated in this section for correlation later of the clinical importance and application of the present study. The intracranial portion of the combined craniofacial procedure involves initially the full exposure of the floor of the anterior cranial fossa via a shield shaped osteotomy in the frontal bone or frontal craniotomy with bone flap. The frontal lobe and dura is elevated from the floor of the anterior cranial fossa and olfactory nerve

TABLE 1

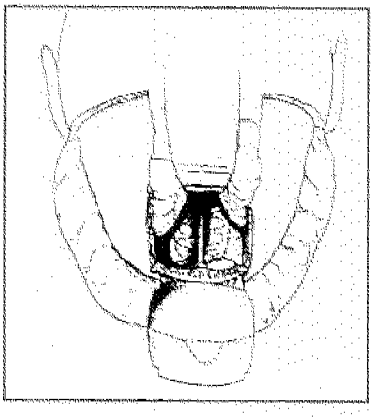
Summary of the Average Measurements of the Different Distances Between the Anatomic Structures in the Anterior Cranial Fossa of Filipino Adult Cadavers (n=24, Male=18, Female=6)

Distances and Structures Measured	Male n=18 Mean (mm)	Male n=18 Standard Deviation	Female n=6 Mean (mm)	Female n=6 Standard Deviation
Length of Anterior Cranial Fossa (Frontal Crest to Optic Canal) (FCr-Oca)	46.48	+/-5.23	43.8	+/-6.15
Frontal Crest to Anterior Wall of Sphenoid Sinus(FCr-AS)	44.23	+/-6.94	43.52	+/-5.15
Frontal Crest to Optic Chiasm (FCr-OC)	53.23	+/-5.19	53.37	+/-8.06
Distance between Right and Left Optic Canal (DOCa)	13.09	+/-2.90	14.83	+/-1.12
Length of Intracranial Portion of Optic Nerve (Optic Chiasm to Intracanalicular Portion of the Optic Nerve) (OC-ICO)	12.94® 12.69(L)	+/-4.16® +/-3.99(L)	13.03® 13.50(L)	+/-3.97 +/-3.88
Diameter of Intracranial portion of the Optic Nerve (dopt nrv)	5.64® 5.36(L)	+/-.800® +/-1.05(L)	5.45® 5.25(L)	+/-.92 +/-1.08
Angle of Optic Chiasm (Angle OC)	79.61 degrees	+/-9.70	66.83	+/-2.83
AP Diameter of Skull (AP Skull)	157.33	+/-7.48	148.9	+/-2.82

TABLE 2
Combined Results of Measurements of Anatomic Structures in the Anterior Cranial Fossa of the 24 Adult Filipino Cadavers

	Mean	Standard Deviation
Length of Anterior Cranial Fossa (Frontal Crest to Optic Canal) (FCr-Oca)	45.81mm	5.46
Frontal Crest to Anterior Wall of the Sphenoid Sinus(FCr-AS)	44.08mm	6.44
Frontal Crest to Optic Chiasm (FCr-OC)	53.26mm	5.84
Distance between Right and Left Optic Canal (DOCa)	13.53mm	2.66
Length of Intracranial Portion of Optic Nerve (Optic Chiasm to Intracanalicular Portion ofthe Optic Nerve) (OC-ICO)	12.97mm right 12.89mm left	4.03 3.90
Diameter of Intracranial Portion of Optic Nerve (dopt nrv)	5.59mm right 5.33mm left	.82 1.04
Angle of Optic Chiasm (Angle OC)	76.42degrees	10.13
AP Diameter of Skull (AP Skull)	150.9mm	10.13

FIGURE 3
A. Frontal Lobe elevated from Anterior Cranial Fossa and Plate
B. Area of Osteotomy for Mobilization of cribriform plate shown by dots and shaded area



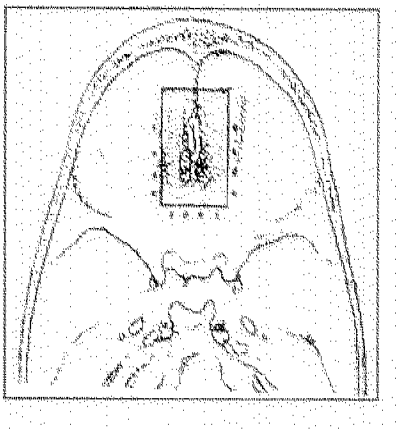
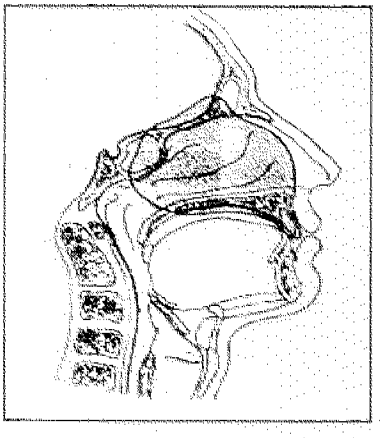
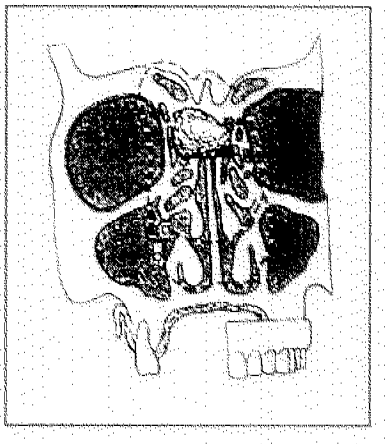


FIGURE 4
Sagital (a) and Coronal (b) view showing extent of osteotomy resection encompassing posteior wall of frontal sinus, cribriform plate, anterior wall of sphenoid sinus, medial wall of orbit, and medial maxillary wall.



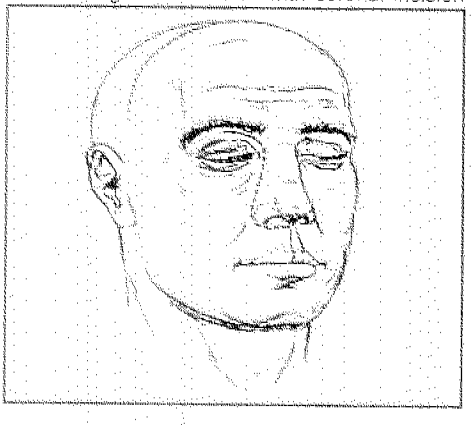


branches passing through the cribriform are transected for complete exposure. This is followed by sharp osteotome dissection of the cribriform plate (Figure 3a and b).

The lateral extent of the intracranial osteotome dissection should be wide enough to encompass the medial walls of both orbital cavities (lateral walls of the ethmoid), being particularly generous on the side of the growth or extension of the primary tumor. The posterior extension will ideally enter the sphenoid sinuses and in so doing partially free the anterior wall of the sphenoid. Anteriorly, the frontal sinus is entered and the entire posterior wall of the frontal sinus included in the resection[5] (Figure 4 a and b).

The facial portion of the operation is approached either via an extended lateral rhinotomy or Weber-Fergusson incision. (Figure 5)

FIGURE 5
The extended lateral rhinotomy or Weber-Fergusson incision with coronal incision



The frontal bone is osteotomized laterally and superiorly and a complete vertical transection made of the nasal septum anteriorly. This permits the retraction of the entire nose to expose the contralateral nasal cavity. The antrum is entered by removing the anterior wall and the orbit is mobilized laterally. Bone cuts are made for medial maxillectomy on the ipsilateral side.

As illustrated, the above-described procedure entails meticulous regard for anatomic details in the anterior cranial fossa to be able to perform an encompassing but safe craniofacial surgery. As a prelude to more successful and sound performance of the described surgical procedure, this anatomic study was embarked upon and deemed important by the authors.

Hence, measurements of certain anterior cranial fossa structures as well as distances between fixed anatomic landmarks were obtained in this investigation. Some of the measurements taken have established values that we have obtained in this study are comparable with published Caucasian values (Table3).

TABLE 3
Comparison of Mean Values from Foreign Literature and Present Study

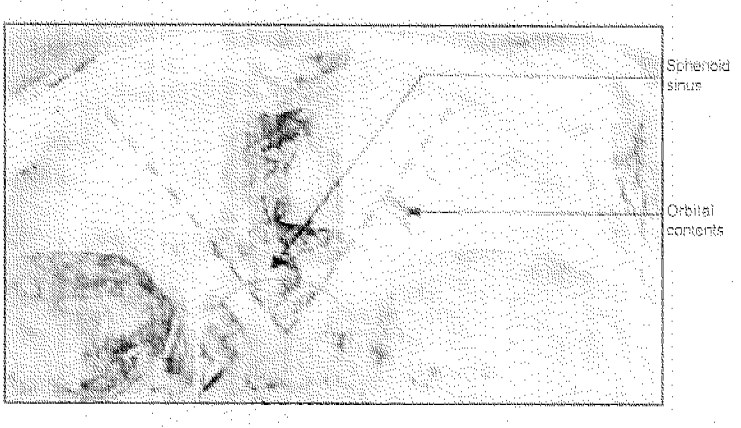
	Foreign Values	Present Study
Length of Anterior Cranial Fossa (Frontal Crest to Optic Foramen)	47.7mm[12]	45.8mm
Length of Intracranial Portion of Optic Nerve (Optic Chiasm to Intra canalicular Portion of Optic Nerve)	10mm[13]	Right: 12.97mm Left: 12.89mm
Diameter of Intracranial Portion of Optic Nerve	4-7mm[12]	Right: 5.59mm Right: 5.33mm

For the measurements taken, which to the authors' knowledge are without existing established foreign data, the clinical importance and applications are discussed. Mean values between sexes were also compared in this study to determine if there is any significant difference. Taking into consideration that certain paired anatomic structures in the human body may not always be symmetrical in configuration, some measurements were taken from the right and left side and compared if there were any significant difference between the mean values.

Indeed, there is considerable morphological variation in the anatomy of the anterior cranial fossa[12]. The average length of the anterior cranial fossa (FCr-Oca) (Figure 2a) obtained in this study is 45.81mm with a standard deviation of 47.7mm[12]. Confidence interval for all the measurements dervied from this study is at p=.01, using the Student t-test for computation of significant difference between the means. The mean diameter of the intracranial portion (Figure 2d) of the optic nerve (d opt nrv) is 5.59mm on the right with SD of 0.82 and 5.33mm on the left with SD of 1.04, the values of which have no significant difference with the published foreign value of 4-7mm. There is also no significant difference between the mean values obtained for males and females as well as between the right and left side. The average length of the intracranial portion of the optic nerve (OC-ICO)(Figure 2d) is 12.97mm and 12.89mm with SD of 4.03 and 3.89 on the right and left respectively. There is significant difference between the values obtained with the published foreign value of 10 mm. Table 3 shows a comparison of the mean values of the measurements obtained in this study with published foreign data.

The average optic chiasm angle (Angle OC) (Figure 2d) as it bifurcates into the intracranial portion of the optic nerves is 76.42 degrees with a SD of 10.1. In this study, there is however a significant difference in the value of the means for the optic chiasm angle of males and females, with a mean value of 79.61 degrees and SD of 9.69 for the former and 66.83 degrees and SD of 2.32 for the latter. Extending the lines (green dotted vertical lines in Figure 6) that form the angle of the optic chiasm will facilitate the delineation of the lateral margins of the dissection (Figure 6).

FIGURE 6
Vertical Dotted Lines (Green) extended from Optic Chiasm Angle Delineate Lateral Limit of Dissection



Therefore keeping the surgical dissection medial and within the boundaries of the described lines will prevent unnecessary injury to the uninvolved orbital contents and optic nerves.

It is noteworthy that the mean angle of the optic chiasm of females obtained in this study is more acute hence this may imply that there is less lateral latitude as to the extent of resection of tumors in this area compared to males.

The above mentioned and observed differences should be noted and taken into consideration for they may be critical especially in the extirpation of tumors encroaching on the area adjacent to the optic chiasm and intracranial portion of the optic nerves. As these values may dictate the posterior and lateral most extent that the prescribed craniofacial surgery may be performed while preserving the integrity of uninvolved optic nerves especially in patients with good vision.

The average distance between the frontal crest and anterior wall of the sphenoid (FCr-AS)(Figure 2b and 2c) and frontal crest and optic chiasm (FCr-OC)(Figure 2a) is 44.08mm with SD of 6.44 and 53.26mm with SD of 5.84 respectively. In this investigation, there is no significant difference in the mean values for males and females. The distances between the above mentioned anterior cranial fossa landmarks have been measured by the authors as the average values obtained may also help determine the anteroposterior scope of the surgery on the anterior cranial fossa that can be done effectively without injury or damage to the area of the optic chiasm, adjacent orbital contents and optic nerves.

LIMITATIONS OF THE STUDY

It would have been ideal to use fresh cadavers for dissections but there is a problem with acquisition of such in the Philippine setting. As such a certain margin of error with respect to the configuration of some of the anatomic structures especially of the optic nerves should be considered. Being an initial anatomical investigation on fixed anterior cranial fossa landmarks and structures, it is highly recommended that these data be validated during dissection in live patients and the study be continued on a larger sample in order to establish the norm representative of the population. It may also be advantageous if the data established be correlated to the age, height and weight of the patient to determine if these factors may have any influence onthe measured values obtained.

SUMMARY

Significant anatomic landmarks and structures in the anterior cranial fossa were described and measured. This study shows that the mean length of the anterior cranial fossa of the Filipino cadavers and the mean diameter of the intracranial portion of the optic nerve does not differ significantly with published Caucasian values. However, the mean length of the

intracranial portion of the optic nerve obtained in this study is significantly different with published foreign data. The mean values measured for the right and left optic nerves are found to be not significantly different. There is no significant difference between the means of both sexes with the above mentioned measurements taken. The mean value for the angle of the optic chiasm is significantly different between the Filipino male and female cadavers. The measurements derived from this investigation may prove useful for the head and neck surgeon and neurosurgeon in the performance of an encompassing craniofacial surgery for sinunasal tumors extending to the anterior cranial fossa as to the posterior and lateral most limits that the surgery can be carried without damage or injury to the intact and uninvolved optic nerves and orbital contents especially for patients with good vision.

APPENDIX

APPENDIX A
Individual Measurements of Anatomic Structures in the Anterior Cranial Fossa of 18 Adult Male Cadavers

	ap skull	fcr-as	dopt nrv r	dopt nrv l	DOCa	FCr-OCa	FCr-OC	OC-ICO R	OC-ICO L	Angle OC
	138	30.5	4	3	7	38	47	6.8	6.8	58
	147	35	4.5	4	10	38	48	8	8	67
	151	36.6	5	4	10	40	49	8	8	70
	152.5	37.7	5	4.5	10	42	49	8.5	8.5	72
	155	39	5	4.5	11	42.5	49	8.5	8.5	75
	155	39.9	5	5	11	44.1	49.2	9	9	78
	155.5	40	5.5	5	12	45	50	12.2	12.2	79
	156	42	5.5	5.5	12.5	45.5	51.3	12.5	13	79
	156	44	5.5	5.5	13	46.5	52	12.5	13	80
	157	47	6	5.5	14	46.5	52	14	13	80
	157	47.5	6	5.5	14	47	53	14	13	85
	158.6	48	6	6	14	49	53	14	14	90
	161	49	6	6	15	49	53	15	14	91
	161	49.5	6	6	15	50	56.1	16	14.5	93
	165.8	50.5	6	6.5	15.7	51.5	59.5	16	16	98
	168	52	6.5	6.5	17	52	60	18	18	82
	168.6	53	7	6.5	17	53	63	20	18	77
	169	55	7	7	17.5	57	64	20	21	79
Range	138-169	30.5-55	4.0-7	3.0-7	7-17.5	38-57	47-64	6.8-20	6.8-21	58-98
Sum	3145.833	885.93	112.8889	107.3611	220.25	929.5778	1548.856	259.1944	254.1944	1591.611
Mean	157.3333	44.233	5.638889	5.361111	13.09444	46.47778	53.22778	12.94444	12.69444	79.61111
Median	156.5	45.5	5.75	5.5	13.5	46.5	52	13.25	13	79
Mode	155	N/A	6	5.5	10	38	49	14	13	79
Std dev	7.818003	6.9421	0.800837	1.05448	2.896544	5.228604	5.19194	4.158793	3.993741	9.696202

*Legend:

ap skull - anteroposterior diameter of skull in millimeters
fcr-as - frontal crest to anterior wall of sphenoid sinus in millimeter
dopt nrv R - diameter intracranial portion of optic nerve right
dopt nrv L - diameter intracranial portion of optic nerve left
DOCa - distance between right and left optic canal
FCr-Oca - distance between frontal crest to optic canal (length of anterior cranial fossa)
FCr-Oc - distance between frontal crest to optic chiasm
OC-ICO R - distance between optic chiasm to intracanalicular portion of optic nerve right
OC-ICO L - distance between optic chiasm to intracanalicular portion of optic nerve left
angle-OC - angle optic chiasm

APPENDIX B

Individual Measurements of Anatomic Structures in the Anterior Cranial Fossa of 6 Adult Female Cadavers

	ap skull	fcr-as	dopt nrv r	dopt nrv l	DOCa	FCr-ICO	FCr-OC	OC-ICO R	OC-ICO L	Angle OC
	149	47	6	6	17	49	56	18	18	70
	152	42	6.5	6.5	15	42	56	16	15.5	63
	150.5	50.5	6	5.5	14	52.5	67	14	14.5	67
	145	36	4	3.5	14	35	45	11	14	67
	146	45.6	5.4	5.5	14.5	42.5	48	6.7	6.5	68
	150.9	40.6	4.8	4.5	14.5	41.8	48.2	12.5	12.5	66
Range	145-152	36-50.4	4-6.5	3.5-6.5	14-17	35-52.5	45-67	6.7-18	6.5-18	63-70
Sum	893.4	261.7	32.7	31.5	89	262.8	320.2	78.2	81	401
Mean	148.9	43.617	5.45	5.25	14.83333	43.8	53.36667	13.03333	13.5	66.83333
Median	149.75	43.8	5.7	5.5	14.5	42.25	52.1	13.25	14.25	67
Mode	N/A	N/A	6	5.5	14	N/A	56	N/A	N/A	67
Std dev	2.821347	5.1476	0.920326	1.083974	1.125463	6.149797	8.065151	3.973244	3.885872	2.316607

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DEMOGRAPHIC PROFILES OF HEAD AND NECK CANCER PATIENTS: A RETROSPECTIVE STUDY*

FERDNAND C. SUPNET, MD**
FRANCO ROMMEL L. REYES, MD**

ABSTRACT

Objectives: To describe patients with head and neck malignancy and to determine the predisposing factors in the development of their disease. Furthermore, to obtain demographic profile of the head and neck cancer patients, to determine the frequencies and site of involvement of common head and neck malignancies admitted in our department and to determine the synergism between alcohol and tobacco smoking.

Design: Retrospective Descriptive study

Patients: Patients admitted in our department with head and neck malignancies from January 1996 to December 2000.

Setting: Tertiary government hospital

Results: The mean age of the study sample is 68.82 years old. Age of patients mostly fall between 71 to 80. Of the total population, 70% were male and 30% were female. Most of the patients have laryngeal cancer followed by oral cavity and nasopharyngeal cancer. Of the 90 subjects, 71% were smokers and 29% were non-smokers. Among the smokers, 78% were male and 22% were female. For the history of alcohol intake, 41% were alcohol drinker and 59% were non-alcohol drinker. Among the alcohol drinkers, 87% were male and 13% were female. The most common co-morbidity is cardiovascular disease followed by pulmonary disease. Among the head and neck cancer patients, only 16% had positive family history. In males, the most common location of cancer is found in the larynx. In female, oral cavity cancer predominates. The most common chief complaint was neck mass. Among the smokers and alcohol drinkers, the most common site of location of cancer is the larynx. Majority of patients have final histopathologic diagnosis of squamous cell carcinoma. There is two-fold increase in the development of nasopharyngeal and laryngeal cancer in smoker and alcohol drinker compared to smoker non-alcohol drinker.

Conclusion: A head and neck cancer patient may be described as an elderly (about 68 years old) male smoker, who may or may not be an alcohol drinker, with no family history of cancer with cardiovascular and pulmonary disease and with a neck mass. The most common primary sites are the larynx, oral cavity, and nasopharynx. Squamous cell carcinoma is the most common final histopathologic diagnosis. Tobacco smoke alone causes a fourfold increase in laryngeal cancer formation as compared to non-smokers. Alcohol intake alone does not promote cancer formation even in the oral cavity. However, when combined with smoking it has a synergistic effect in nasopharyngeal and maxillary cancer which is not present in the larynx.

INTRODUCTION

According to McKillup, at diagnosis, more than half of all cancer patients are above 65 years of age. Patients with squamous cell carcinoma of the upper aerodigestive tract have a mean age of 60 years. Environmental exposure to carcinogens, notably alcohol and tobacco, leading to cancer may be related to duration, which in turn is related to age. Immune dysfunction, the most important of which is cytotoxic T-cell deficit or dysfunction as well as autoimmune diseases are more common with advancing age.[1] Besides the immune system, the body has its own tumor regulatory mechanisms. One mechanism is the use of tumor suppressor genes which include Rb oncogene and the p53 suppressor genes. Mutations, damage or loss of these genes leaves the growth and formation of malignant cells unchecked. Furthermore, it was noted in a study of Johnson et al that drinking alcohol alone does not predispose to cancer formation but synergism appears to exist between smoking and alcohol drinking in carcinogenesis.

Early detection and prevention of head and neck cancer must be instituted, and this requires identifying the risk factors which may be present in the demographic profile of cancer patients.

*Presented, PSO-HNS Descriptive Research Contest, December 04, 2001, Sarabia Manor Hotel, Iloilo City
**Resident, Department of Otorhinolaryngology-Head and Neck Surgery, Veterans Memorial Medical Center

To describe the profile of patients with head and neck malignancy.

SPECIFIC OBJECTIVE

1. To obtain the demographic profile of head and neck cancer patients.
2. To determine the frequencies and site of involvement of common head and neck malignancies in this institution.
3. To determine if there is synergism between smoking and alcohol in the development of head and neck cancers.

METHODS

This is a retrospective case review of patients diagnosed with head and neck malignancies admitted at our ENT Department from January 1996 to December 2000. Cases were reviewed with regards to age, sex, personal/ social history, family history, past medical history, physical examination and final histopathologic diagnosis. Cases were classified according to smoking and alcohol intake to detect the presence of synergism. Descriptive statistics and frequency distributions were determined and tabulated and conclusions were drawn from them.

RESULTS

A total of 112 cases of head and neck cancer patients were reviewed from January of 1996 to December 2000. However, only 90 patients have complete medical records and histopathological studies to warrant inclusion in the study.

The youngest recorded was 15 years of age and the oldest was at 86. The mean age of the study sample is 68.82 years. Majority of patients studied belong to 71-80 years age group (52.2%) as seen in Figure 1.

There is male predominance in the population as seen in figure 2. Of the population, 70% (63/90) were males and 30% (27/90) were females.

The cases were classified according to

FIGURE 1
Frequency of Age Group

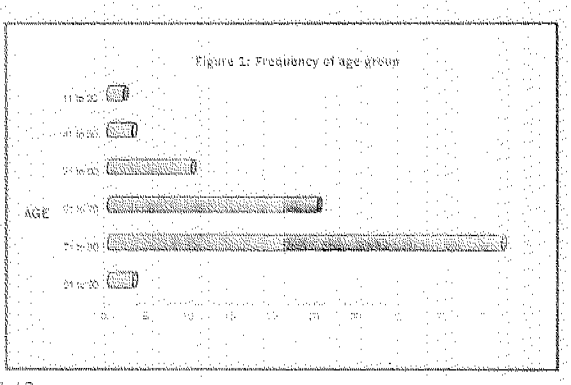


FIGURE 2
Sex Distribution of Patients with Head and Neck Cancer

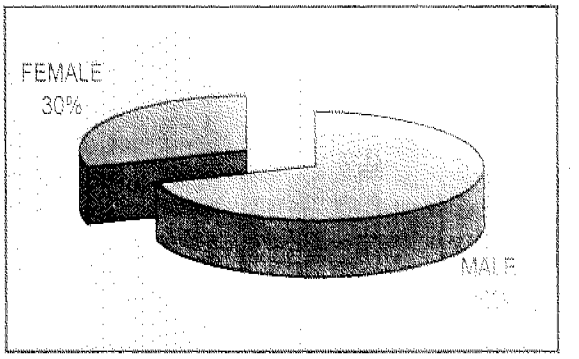


FIGURE 3
Frequency of Site

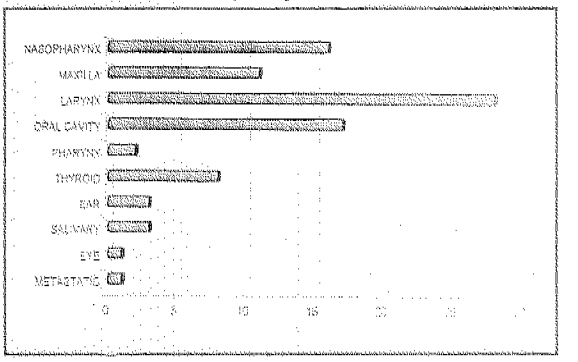


FIGURE 4
Presence of Smoking History

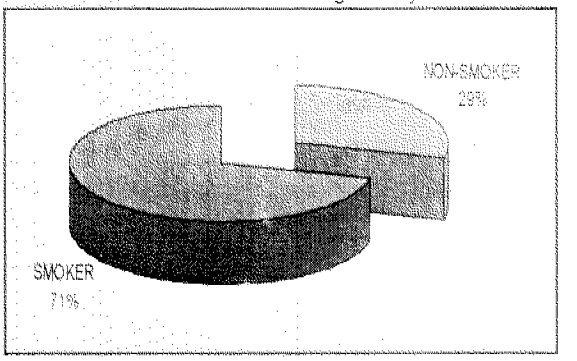
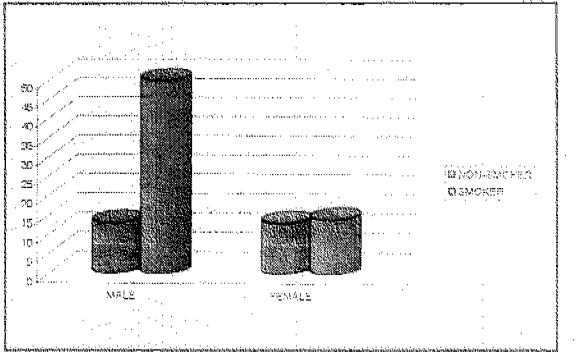


FIGURE 5
Sex Distribution Among Smokers and Non-smokers



their site of involvement as shown in figure 3. Most of the subjects had laryngeal cancer 28/90(31.1%) followed by oral cavity cancer 17/90(18.9%) and nasopharyngeal cancer 16/90(17.8%). Of the 90 subjects, 71%(64/90) were smokers and 29%(26/90) were non-smokers (Figure 4). Among the smokers, 78.1%(50/64) were male and 21.9%(14/64) were females (Figure 5).

Among the cases, 41%(37/90) had positive history of alcohol drinking and 59%(53/90) had no history of alcohol drinking (Figure 6).

Among the alcohol drinkers, 86.5%(32/37) were males and 13.5%(5/37) were females as shown in Figure 7.

Figure 8 lists the co-morbidity of head and neck cancer patients. The most frequent is cardiovascular disease (Hypertension/Heart Disease/Cerebrovascular Accident) followed by pulmonary problem (PTB/COPD/Asthma).

Among head and neck cancer patients, only 16%(14/90) had positive family history of cancer while 84%(76/90) had no family history of cancer. (Figure 9)

Figure 10 shows that in males, the most common site involved is the larynx followed by the nasopharynx. Among females, oral cavity cancer predominates followed by thyroid cancer.

Forty percent (36/90) of head and neck cancer patients presented with neck mass especially in cancer of the nasopharyngeal area. Laryngeal cancer usually presents with hoarseness while cancer of the oral cavity and pharynx usually presents with dysphagia (Figure 11).

By proportion, smoking is common in

FIGURE 6
History of Alcohol Drinking

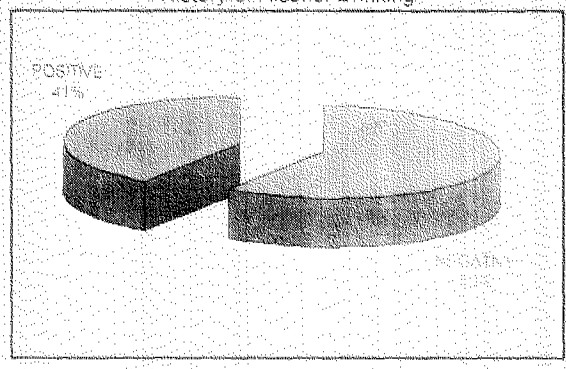


FIGURE 7
Alcohol Drinking vs. Sex

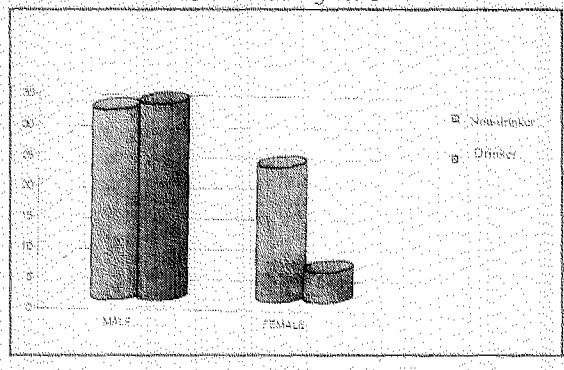


FIGURE 8
List of Co-morbidities

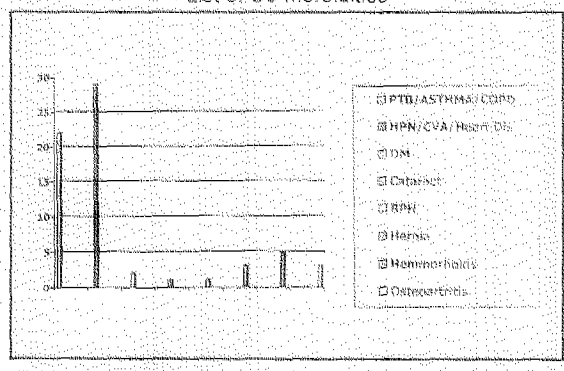


FIGURE 9
Family History of Cancer

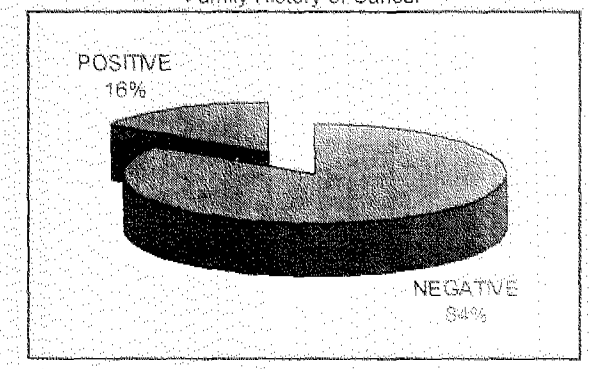


FIGURE 10
Frequency of Site of Cancer in Relation to Sex

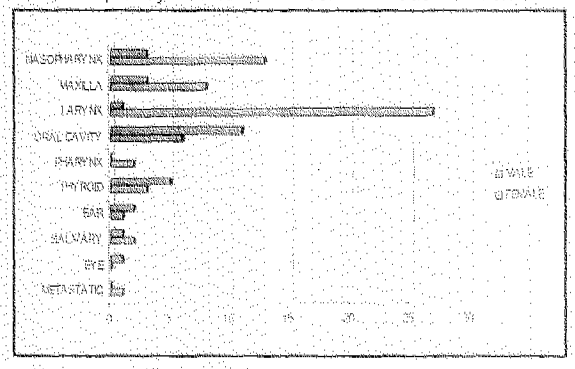
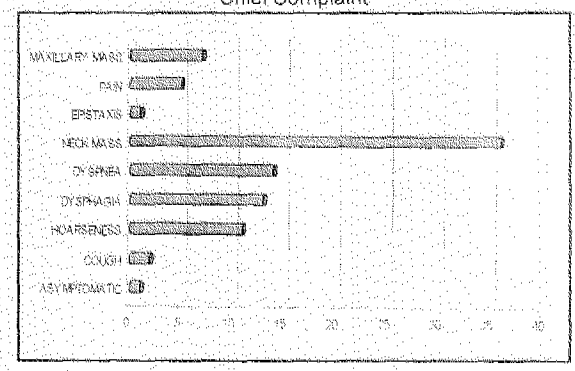


FIGURE 11
Chief Complaint



more than half of cases with primary malignancies of the eye, pharynx, maxilla, larynx, nasopharynx and oral cavity (Figure 12).

Figure 13 shows that by proportion more than half of cases with primary cancers of the eye, nasopharynx, maxilla, and pharynx are alcohol drinkers.

In figure 14, it was noted that majority of head and neck cancer showed a final histopathologic diagnosis of squamous cell carcinoma.

Figure 15 and table 1 illustrates that in the cancer of the nasopharynx and the maxilla, there were more smoker-alcohol drinker compared to smoker non-alcohol drinker and even fewer for non-smoker alcohol drinker. In laryngeal cancer, there was a very high number of smokers and no case of non smoker alcohol drinker. This is significant in the Spearman Rho and Pearson Coefficient statistical analysis.

FIGURE 12
Site of Cancer in Relation to Positive Smoking History

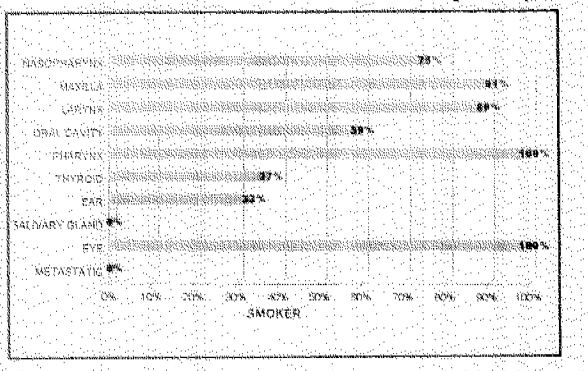


FIGURE 13
Site of Cancer in Relation to Positive Alcohol Drinking History

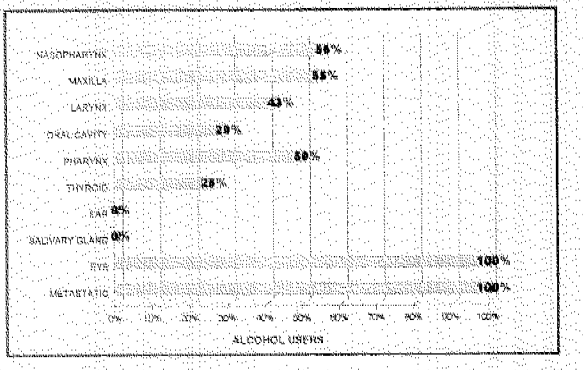
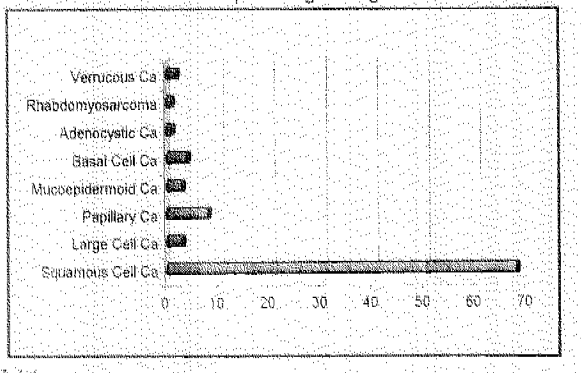


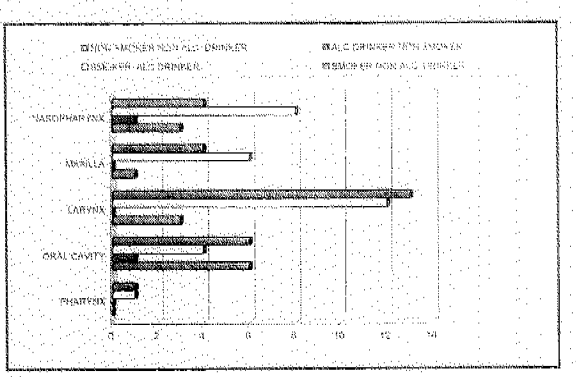
FIGURE 14
Final Histopathologic Diagnosis



DISCUSSION

Transformation of a normal cell into a malignant one may occur as a result of errors in genetic programming or as a consequence of chemical, physical or viral carcinogens.

FIGURE 15
Site of Cancer in Relation to Smoking and Alcohol Drinking History



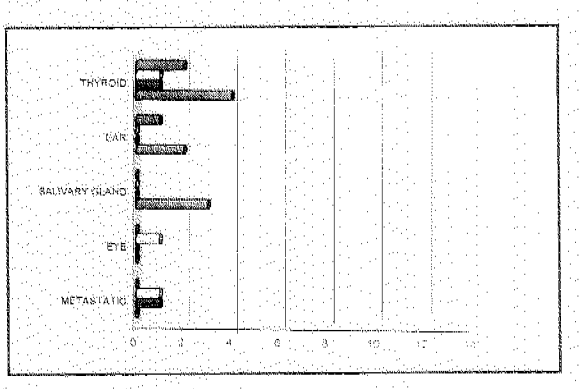


TABLE 1

	SMOKA I.				TOTAL
	NS-NA	S-NA	NS-A	S-A	
Nasopharynx	3	4	1	8	16
Maxilla	1	4		6	11
Larynx	3	13		12	28
Oral Cavity	6	6	1	4	17
Pharynx		1		1	2
Thyroid	4	2	1	1	8
Ear	2	1			3
Salivary Gland	3				3
Eye				1	1
Metastatic			1		1
	22	31	4	33	90

Legend:
NS-NA: Non-Smoker - Non Alc.
S-NA: Smoker - Non Alc. Drinker
NS-A: Non-Smoker - Alc. Drinker
S-A: Smoker Alcohol Drinker

Neoplastic development appears to be a multi-step process of initiation, promotion and progression. Alterations of cellular DNA results in initiation. Promotion is the altered presentation of cell's genetic information. The transformed cells with abnormal phenotypes are clonally produced in progression. This evolutionary process of malignant transformation produces cell with well-recognized characteristics of invasiveness, uncontrolled growth and metastatic potential. Suppression is the body's defense against tumor progression and loss of tumor suppressor genes may induce carcinogenesis. An example of this is the p53 gene located on chromosome 17p13.1. Abnormalities of this gene is common in a wide variety of malignancies including colon, bladder, breast, and other carcinomas, as well as astrocytomas, leukemias, sarcomas, and mesotheliomas. Another suppressor gene is the Rb gene which is the only direct tumor suppressor. Alterations in this gene have been seen in retinoblastomas, sarcomas, leukemias, lymphomas, and carcinomas. Damage, loss, or malfunction of these genes may cause the cells to become susceptible to events that orchestrate the formation of malignant disease (Anderson).

The development of cancer of the head and neck region appears to be influenced by combination of factors such as age, sex, family history and co-morbidity states and choice of lifestyle, that is, excessive smoking and habitual alcoholic beverage drinking.

There appears to be an increasing incidence of head and neck cancer with age as shown in this study. This may be due to impairment of the immune system as person ages and may be further potentiated by history of smoking, chronic alcoholism and malnutrition. Cordes cited that the process associated with aging represents a natural or involutional interference with immunity because cellular immune vigor wanes with increasing age. In a retrospective study done in 740 cases in Brazilian population, by Gervasio et. al., they also noted an increase incidence of cancer in the elderly with an average age of 58.6 years of age.

Among males, excessive smoking and alcohol intake dominated the history as the most probable etiologic factor in developing cancer. Smoking tobacco or cigarette has been shown to induce changes in cellular and humoral immunity. It has been found out that prolonged exposure to tobacco smoke is associated with diminished cytotoxicity and reactivity of the immune system. Moreover, studies in alcohol drinking have demonstrated abnormalities in peripheral B and T lymphocytes (Cordes). With these alcohol and tobacco effects, there is an impairment of the immune response to malignancy. Cigarette smoke contains several chemical carcinogens. Benzopyrene and radionuclides in tobacco (polonium 210 and lead 210) promote cancer formation. Chronic alcohol intake leads to protracted irritation which may not directly lead to cancer but may cause leukoplakia which is good soil for cancer formation if further damage occurs (Robbins). The researcher theorizes that chronic irritation of alcohol on direct mucosal contact is not present in the larynx, which may explain the similar statistics between non-alcohol drinking smokers and alcohol drinking smokers. Alcohol intake predisposes to reductions in the antioxidant mechanisms because of depletion of GSH and Vitamin E, thereby making cells more susceptible to damage (Anderson). In this study, alcohol consumption did not show much carcinogenic effect but seems to potentiate the carcinogenic effects of smoking. In a recent study by Johnson, he also noted that alcohol synergizes with tobacco which increases the incidence of cancer in the upper aerodigestive tract. Another study by Murata and Takayama supported a synergistic effect of alcohol intake and tobacco smoking which they observed also in the upper digestive tract and bladder cancer. Furthermore, Schlect et. al. cited that alcohol may act as promoter for tobacco.

The sites most commonly affected by cancer are larynx (31.1%), oral cavity (18.9%) and nasopharynx (17.6%). In males, the areas commonly affected are the larynx (42.9%) and nasopharynx (20.6%). In female, the oral cavity (40.7%) is mostly affected. These areas are readily exposed to carcinogens which conatantly irritates the mucosal surfaces. Common chief complaints of these patients are neck mass, hoarseness, dysphagia and dyspnea. There are patients who have pre-existing cardiovascular and pulmonary disease however, they are not significant in the development of head and neck cancers. Family history can be a risk factor but it is not significant in this study. Majority of head and neck cancer patients have a final histopathologic diagnosis of squamous cell carcinoma.

CONCLUSION

A head and neck cancer patient may be described as an elderly (about 68 years old) male smoker, who may or may not be an alcohol drinker, with no family history of cancer. He may be a patient with a neck mass and cardiovascular and pulmonary risk factors. The most common

primary sites are the larynx, oral cavity, and nasopharynx. Majority of head and neck cancers are squamous cell carcinoma. Alcohol intake alone does not show any correlation to cancer formation in the oral cavity. However, when alcohol is combined with smoking it showed to have a synergistic effect in nasopharyngeal and maxillary cancer.

RECOMMENDATION

It is recommended that further study may be conducted in a multi-institutional set-up so that we may properly institute measures which may help in the management of this disease.

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HEAD AND NECK MANIFESTATIONS OF NEUROFIBROMATOSIS TYPE 1: A CASE SERIES REPORT*

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ARMANDO M. CHIONG JR., MD, FPSO-HNS***

ABSTRACT

Objectives

1. To present a series of local reports on Neurofibromatosis Type I manifesting as head and neck tumor.
2. To identify patients with Neurofibromatosis Type I based on a criteria developed by the National Neurofibromatosis Foundation.
3. To describe the role of surgery in reconstruction of cosmetically unacceptable, disfiguring lesions of NF Type I.
4. To emphasize the importance of early detection and possibility of malignant transformation of NF Type I.

Design: A case series report

Setting/Patients/Conclusion

Neurofibromatosis or more commonly known as Von Recklinghausen's Disease is one of the most commonly inherited genetic disorder that encompasses a myriad of clinical presentations. It occurs in 1 of every 4,000 population[1,2]. However, the head and neck manifestation is relatively uncommon and causes grave threat to nearby structures. Its potential risk for malignant transformation should be kept in mind; hence, the need for early diagnosis is valuable.

The study was done in a tertiary government hospital in Quezon City. Subjects were patients diagnosed with Neurofibromatosis type I based on a criteria presented by the National Neurofibromatosis Foundation along with patient's biopsy reports. It describes the aesthetic, multi-systemic, as well as psychological effects of this disease condition.

Surgery remains the treatment of choice for resectable lesions and early detection gives favorable results.

INTRODUCTION

Neurofibromatosis is a condition involving an individual's socio-cultural participation and functional, anatomic as well as aesthetic presentation. It is one of the most commonly inherited genetic disorder[1]. Clinically, they are described according to several types. The clinical manifestations are extremely variable and this includes cutaneous features, such as café-au-lait spots and intertriginous freckling in 90% of patients. The presence of benign neurofibromas and the less common plexiform neurofibromas are included although the latter is of special interest due to its ability to cause disfiguration; compromise function and even jeopardize the life of the patient.

Neurofibromatosis type I also known as Von Recklinghausen's Disease is a spectrum of disease conditions affecting multi-systemic functions. The incidence however of head and neck manifestations in patients with the disease varies between 14% to 37%[5].

This autosomal dominant inherited syndrome is manifested by developmental changes in the nervous, skeletal, renal and most importantly the integumentary system. Von Recklinghausen described it in 1882 and Riccardi divided it into 7 types. Type I which comprises 85% of cases is typical neurofibromatosis. Type II, the central or acoustic is distinguished by bilateral acoustic neuromas. Type III "mixed" and

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Type IV "variant" resemble type II but may have numerous neurofibromas and are at greater risk of developing optic gliomas, neurilemmomas and meningiomas. All are inherited as autosomal dominant but Type V, segmental (dermatomal) Neurofibromatosis is considered to arise from postzygotic somatic mutation and is not generally heritable. Type VI has no neurofibromas only café-au-lait spots and must occur in two generations to be diagnose. The last type, late onset Neurofibromatosis begins to manifest neurofibromas no earlier than the twenties and is not yet known if inherited[3].

It is important to consider the risk of development into malignancy associated with the condition, occurring both in adults and children. In younger individuals, most commonly occurring tumors are optic nerve gliomas, brain tumors, leukemia and lymphoma. In adults, neurofibrosarcoma is the most common malignancy specifically associated with Neurofibromatosis type I[2].

The presence of head and neck masses proposes a great deal of challenge to our field for complete excision due to its ability to invade nearby vital structures. Moreover, the surgeon is faced with the problem of reconstruction that the patients usually seek for social as well as personal acceptance brought about by this syndrome.

OBJECTIVES

1. To present a series of cases of Neurofibromatosis Type I manifesting as head and neck tumor.

2. To identify patients with Neurofibromatosis Type I based on a criteria developed by the National Neurofibromatosis Foundation.

3. To describe the role of surgery in reconstruction of cosmetically unacceptable, disfiguring lesions of NF type I.

4. To emphasize the importance of early detection and possibility of malignant transformation of NF type I.

Case I

A case of a 19 year old male, Filipino from Batangas presented with congenital lateral neck mass. It was described as a nodular lesion about 0.5 cm gradually increasing in size and was associated with appearance of multiple cutaneous macular hyperpigmentation seen over the trunk and buttocks. As the patient matured, these lesions increased in size and number. Patient was not brought for consult until his lateral neck mass grew to an extent where it was aesthetically unacceptable. Review of systems, family as well as developmental history was non-contributory. However, the patient is only on his 6th grade due to poor academic performance. Physical examination revealed an 8 x 10 cm (widest diameter) lateral neck mass, movable, non-tender, well circumscribed, doughy with superimposed surface nodularities. Slit lamp examination showed Lisch nodules (iris hamartomas).

The presence of cutaneous lesions (café-au-lait spots) and multiple neurofibromas were prominently seen over the anterior and posterior trunk, buttocks, upper and lower extremities. These cutaneous hyperpigmentations measured more that 15mm in their widest diameter. Axillary as well as inguinal freckling was also present.

Otologic findings were unremarkable. Cervico-lumbar x-ray revealed spina bifida at S1. Neurologic findings were essentially normal. Patient underwent computed tomographic scan of the neck and demonstrated a tumor (lateral neck mass) of neural origin encroaching nearby vascular structures.

Patient underwent excision biopsy and histopathologic evaluation was consistent with neurofibroma presenting as spindle cell pattern. Intraoperative findings noted a doughy mass about 8 x 10 cm with areas of firm nodularities adherent to the right carotid sheath fascia.

Patient was advised frequent follow up for any other developing condition or tumor recurrence.

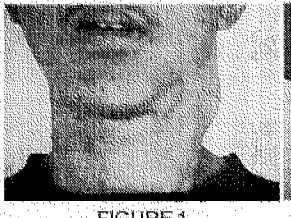

FIGURE 1
19-year old male with Neurofobromatosis

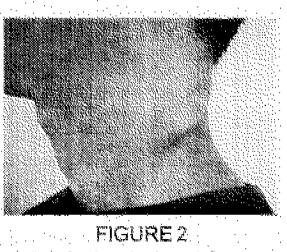

FIGURE 2
Lateral view of neck mass

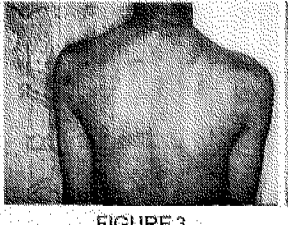

FIGURE 3
Multiple neurofibromas back

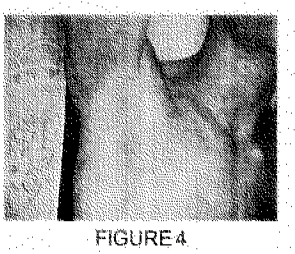

FIGURE 4
Axillary freckling

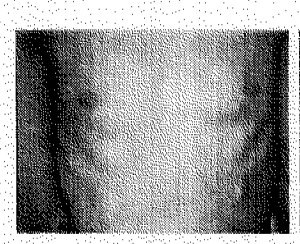

FIGURE 5
Anterior chest wall with neurofibromas

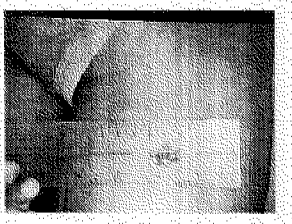

FIGURE 6
Care-au-lait spot measuring > 10mm

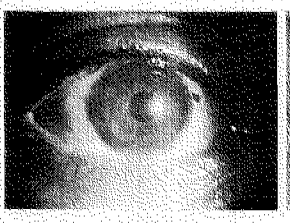

FIGURE 7
Lisch nodules

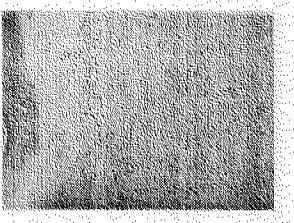

FIGURE 8
Neurofibroma as seen through the microscope(LPO)

Case II

A 19-year-old male from Zamboanga consulted our institution due to a progressively enlarging multinodular lesion of the neck. The patient was noted to have a 1 cm nodular mass over the right lateral neck area associated with multiple cutaneous hyperpigmentation seen since childhood. The lesion exhibited fast growth as the patient grew achieving its widest dimensions at 13 years of age. The lesion at this time was multinodular, fixed, hyperpigmented with areas of hyperemia. Manipulation of the mass may cause bleeding at times. The patient sought consult due to disfiguring effect of the mass over the face.

Upon thorough examination, a very prominent multinodular dispersed irregular mass measuring approximately 28 x 25 cm extending from the right pre-auricular area down to the anterior neck up to about the 2nd rib anteriorly. Posterior lesion covered post-auricular area descending to the subscapular area. The lesion was hyperpigmented, with areas of hyperemia and presented with varying consistency, areas of fixation to the underlying structures.

The patient exhibited Lisch nodules on slit lamp examination. Macular lesions were seen over the entire body but were more prominent over the axillary and inguinal area. There was note of gynecomastia although endocrine assessment was non-contributory. Other findings in the history and physical examination were normal. The patient however also has poor scholastic performance.

The patient underwent cranial and neck CT scan, which revealed a heterogenously soft tissue mass in the carotid and parotid spaces with obliteration of the parapharyngeal space. The said mass encroaches the spinal canal with enlargement of the neural foramen. This was officially signed out as multiple soft tissue neck mass, right, with intradural extension consistent with neurofibromatosis.

Our patient underwent wide resection of cervicofacial cutaneous deformity with reconstruction of defect using Pectoralis Major Myocutaneous Flap. There was no attempt to remove entire lesion due to extension to vital structures. The need for cosmetic reconstruction is one of the primary surgical considerations for this patient.

Final histologic result was consistent with neurofibroma with cellular component composed mostly of diffusely proliferating spindle cells. A plexiform neurofibroma was also present.

FIGURE 9
19-year old with Neurofibromatosis

FIGURE 10
Lateral view showing extent of the mass

FIGURE 11
Plexiform neurofibroma

FIGURE 12
Markings for Pectoralis Major Myocutaneous flap

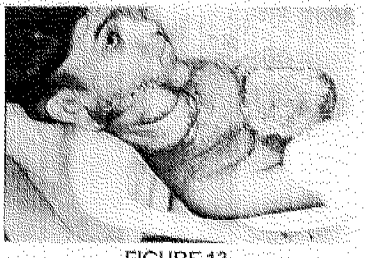

FIGURE 13
The patient post-op

The patient was discharged with a more acceptable cervicofacial appearance and was also advised frequent follow-up for close monitoring of tumor growth and other organ system involvement.

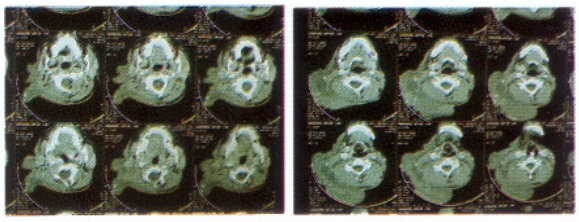

FIGURE 14
CT Scan showing large right lateral neck mass

FIGURE 15
Plexiform Neurofibroma (HPO)

Case III

A 56-year-old male from Quezon City consulted our institution due to a huge, bleeding mass on the face. The mass started to appear 20 years prior to consult as a nodular, firm, nontender left forehead mass about 2 x 2 cm initially. There was minimal growth of the mass until 2 years prior to consult, the mass began to increase rapidly with encroachment to the left orbital and malar region. Patient also had multiple café-au-lait spots over trunk and inguinal area. There was note of multiple neurofibromas over the anterior and posterior trunk.

Upon admission, patient presented with an enormous, friable, fungating mass over left fronto-orbito-malar region with areas of necrosis associated with bleeding and foul smelling discharge. The base of the mass is on the left forehead and cheek though sparing the left eye upon examination. Visual acuity was noted to be counting fingers on the left. Extraocular muscles examination revealed weakness of the left lateral rectus. A slit lamp examination was not feasible due to tumor size. Other examinations were non-contributory.

A cranial CT scan was done which revealed a huge mass on the left side of the head with bony erosive changes on the adjacent temporal and frontal bones. Bony erosive changes were likewise seen over the floor of the middle cranial fossa. A wedge biopsy was done which was read as neurofibrosarcoma.

The plan for surgical extirpation was not feasible due to extent and size of tumor. However, a debulking technique was also contemplated as soon as the patient resumes stability medical-wise. The patient developed pneumonia and severe anemia due to tumor bleed. Neurosurgical opinion did not allow possible craniectomy due to tumor behavior and extent. Along with these, excessive bleeding may cause a grave problem intraoperatively.

FIGURE 16
56-year old male with Neurofibrosarcoma

FIGURE 17
Superior view of the mass

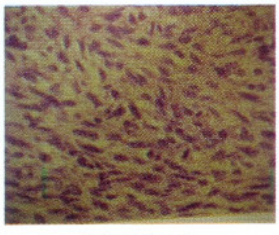

FIGURE 18
Neurofibrosarcoma (HPO)

FIGURE 19
Note extension of the mass to the right eye

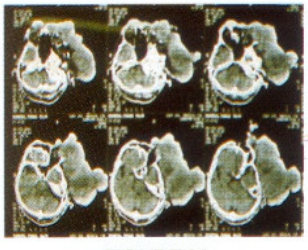

FIGURE 20
CT Scan showing invasion of the infratemporal fossa Left orbit and left frontozygomaticomaxillary area

CASE DISCUSSION

Neurofibromatosis (NF) or Von Recklinghausen syndrome is a neuro-oculo-cutaneous syndrome that affects multiple organ system. Its multi-system involvement can lead to a wide variety of clinical signs and symptoms. More recently, it has been pointed out that neurofibromatosis consists of several distinct autosomal dominant disorders with differing clinical manifestations. Type I or the typical Neurofibromatosis comprises 85% of cases[3].

Head and neck manifestations of NF type I occur in 14 to 37% of the cases[7]. The presence of prominent head and neck lesions carry a poorer prognosis compared to those occuring on the trunk or extremities.

Neurofibromatosis is a genetic abnormality inherited in an autosomal dominant pattern and the gene responsible is the long arm of chromosome 17. It occurs in 1 out of 4,000 people[1,2]. Genetic studies have shown that the gene for Neurofibromatosis type I is on the long arm of chromosome 17 in band q 11.2. The gene is described to be large and codes for a 2818 amino acid protein called neurofibrin. The NF 1 gene is unusual in that one of its introns contains coding sequences for at least 3 other genes, involvement of which may sometimes affect the manifestations in patients with neurofibromatosis type I. Although molecular testing for neurofibromatosis type I is available, it is infrequently indicated clinically. Because of the gene's large size and the fact that many different mutations occur, identification of the specific mutation in the patient has been difficult. Most laboratories have only been able to find mutations in about 15-20% of Neurofibromatosis type I families studied with conventional molecular screening techniques. However, a test based on the protein truncation assay is claimed to detect about 70% of pathogenic mutations in the Neurofibromatosis type I gene[2,11,13].

Information regarding malignancies associated with NF varies and has been said to involve only a small percentage. Plexiform neurofibroma has been identified to have ability to develop into malignant forms[8,9].

The diagnostic criteria developed by the National Neurofibromatosis Foundation are generally accepted. The diagnostic criteria are met in an individual who has two or more of the following features[2,8]:

- six or more café-au-lait macules over 5 mm in greatest diameter in pre-pubertal and over 15 mm in post pubertal individual
- two or more neurofibromas of any type or one plexiform neurofibroma
- freckling in the axillary, inguinal regions
- optic glioma
- one or more Lisch nodules (iris hamartomas)
- distinctive osseous lesions such as sphenoid dysplasia or thinning of the long bone cortex with or without pseudoarthrosis
- a first degree relative (parent, sibling, or offspring) with NF type I by the above criteria

The first case meets four out of seven of the criteria and is therefore included in the diagnosis. The 2nd patient also meets four out of seven of the criteria although he has more propensity to develop malignancy due to presence of plexiform neurofibroma. The 3rd patient only had two features although the initial presentation, which is a nodular lesion on the forehead, may have been a plexiform neurofibroma, which developed into a sarcoma. It is obvious to say that the last case had the poorest prognosis.

The first patient was fortunate to have a resectable tumor, which did not warrant a reconstruction. However, close monitoring is required since the possibility of tumor recurrence is high not to mention the proximity of the excised lesion to significant neurovascular structures.

Our second patient required a more comprehensive approach in management young as he is, the patient had a larger and more extensive mass, which involved not only the head and neck region but also the trunk. Total resection of the tumor was not considered due to widespread cutaneous involvement and extension to vital structures (parapharyngeal space and vertebral area). Primary indication for surgery was for cosmetic reasons, which was also mostly the concern of the patient

It is proper to say that this patient has poorer prognosis due to tumor extent and the presence of plexiform neurofibroma on the final histologic study. Plexiform neurofibromatosis may grown in size and cause serious disfigurement, associated overgrowth or impingement on normal structures. Surgical treatment of such lesions is often unsatisfactory because of their intimate involvement with nerves and their tendency to grow back at the site of removal. A collaborative controlled trial of 13-cis-retinoic acid or interferon alpha-2a for treatment of patients with plexiform neurofibromatosis is currently in progress[2,19]. Other problems of the patient are also being monitored such as the endocrine anomaly (gynecomastia), the presence of Lisch nodules which may progress to optic glioma, the presence of an intradural extension and plexiform neurofibroma which is believed to have the ability to develop into malignancy, Again, a multi-systemic approach is also necessary.

These two patients exhibited poor scholastic performance and it has been said that learning disabilities are one of the most common features in children with NF 1 seen in 40-60% of patients[2].

The most severe among the three cases presented is the third one due to the presence of a malignancy (neurofibrosarcoma), which is assumed to have developed from a previous plexiform neurofibroma.

Along with late consult, the patient had other concomitant medical problems, which made him a poor candidate for surgical intervention.

Patients with Von Recklinghausen's disease have a propensity to develop malignant tumors of the nerve sheath. These tumors are uncommon and account for only 5% of all soft tissue sarcomas, affecting all ages. Only 9 to 14 % are found in the head and neck region[4].

The five year survival for malignant neurofibroma is reported to range from 40-60%. In up to 33% of patients, hematogenous extension has been reported in the lungs and bone[4]. The 5-year, 10-year, and 15-year actuarial survival rates for Neurofibrosarcoma is 76%, 50% and 45% respectively. The decline in survival after 5 years resulted from intercurrent disease unrelated to cancer[20].

Wide excision followed by radiotherapy is the treatment of choice for these cases. Our patient was a poor candidate for this treatment due to other systemic problems. On the other hand, the role of surgery in this case is minimal because of poor prognosis, poor surgical outcome, intraoperative complications and approximation of tumor to the middle cranial fossa.

TABLE 1
Criteria fulfilled by the three cases according to the National Neurofibromatosis Foundation

Criteria	Case 1 (4/7)	Case 2 (4/7)	Case 3 (2/7)
1. Café-au-lait spots (6 or more > 15mm in adults)	+	+	+
2. Two or more neurofibroma or 1 plexiform neurofibroma	+	+	+
3. Freckling (axillary or inguinal)	+	+	-
4. Optic glioma	-	-	N/A
5. Two of more Lisch nodules (iris hamartomas)	+	+	N/A
6. Distinctive osseous lesions such as sphenoid dysplasia or thinning of long bone cortex with out pseudoarthrosis	-	N/A	N/A
7. First degree relative, parent, sibling or offspring with NF 1	-	-	-

CONCLUSION

To our knowledge, there has been no locally reported case series of local reports regarding the occurrence of neurofibromatosis type I in the head and neck region of this tumor.

Surgery remains to be the best management for patients presenting with resectable tumor in the head and neck. Majority of these patients do not come for cutaneous lesions, but primarily due to physical disfigurement brought about by these lesions that cause social withdrawal.

It is important to emphasize the need for early consult for early detection of this syndrome as well as close monitoring to avoid tumor recurrences and development of other related conditions.

Since this is a hereditary problem, they should be reminded of the 50% chance of having an offspring with the same condition. Ideally, the genetic testing for both parents should be performed with location of the gene responsible for containing the protein product neurofibrin[1,2,12,13,14]. However, there is rarely a need for molecular testing for diagnostic purposes. The clinical diagnosis of NF 1 is usually unequivocal in adult individuals. Predictive testing could only be offered to individuals at risk of inheriting an NF 1 mutation from an affected parent, but clinical diagnosis of NF 1 is sufficient in adults.

The life expectancy of patients with Neurofibromatosis Type I is reduced by at least 15 years overall. Cosmetic symptoms that are only mild fare better but others with associated malignancy and hypertension are known to have increased morbidity especially in adults.

Early detection of tumor provides favorable results upon surgery. The Otolaryngologists and Head and Neck specialists comprise one of the limbs of the multilevel approach in the management of this serious condition known as Neurofibromatosis.

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CLINICAL AND VIDEOENDOSTROBOSCOPIC EVALUATION OF LARYNGEAL TUBERCULOSIS: THE VOICE LABORATORY EXPERIENCE*

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MA. CLARISSA S. FORTUNA, MD, FPSO-HNS***

ABSTRACT

Objective. This study is done (1) to present our clinical experience with 22 cases of established laryngeal tuberculosis and (2) to evaluate the changing trends in clinical manifestations of the disease entity in an attempt to contribute accurate and prompt management.
Study Design. This is a retrospective clinical analysis.
Setting. Laryngovideoendostroboscopy (LVES) was done by the investigators at the Voice Laboratory. During the procedure, a thorough history was taken and phonatory tasks during stroboscopic evaluation were recorded on video. Still photographs of the laryngeal structures were reproduced for evaluation in conjunction with the video document.
Patients. All the patients were referred by their attending physicians to the Voice Laboratory because of dysphonia. On LVES, laryngeal lesions were noted. Those with histopathological diagnosis of laryngeal tuberculosis were included in this study.
Results. Patients' ages ranged from 16 to 73 years. Thirteen (13) were male and nine (9) were female. There were nine (9) smokers among the patients. All patients complained of hoarseness.

On laryngovideoendostroboscopy the most common findings are the following: eighteen (18) patients (82%) had vibratory and vertical phase asymmetry while three (3) patients (14%) were symmetrical. Majority (n=13 or 60%) had decreased amplitude on both sides. The periodicity in ten (10) patients were normal while irregular in eight (8). The mucosal wave in five (5) or 23% of patients were normal while abnormal (decreased or adynamic) for the rest (n=17) or 77%. Glottic closure configuration was complete in eight (8) patients, while for the rest (n=14) or 64%, it is either, incomplete, irregular or with posterior chink. Vocal cord paralysis occurred in one patient while another patient was not assessed stroboscopically because of a huge fleshy mass noted at the glottic level.

Based on appearance, 2 (10%) had ulcerofungative mass lesions, 18 (80%) patients had whitish ulcerative lesions and 2 (10%) had polypoid lesions. Fourteen (14) patients manifested as a single laryngeal lesion, all involving the true vocal cords, and eight (8) patients showed multiple lesions, most commonly involving the true vocal cords (8), the false vocal cords (6), the arytenoids (4) and the epiglottis (4).

Fifty five percent of the patients have pulmonary tuberculosis. Among those with pulmonary tuberculosis, 6 (50%) had multiple site-lesions while the other half had involvement of the true cords only. For the remaining patients with normal lung status, 8 (80%) has a single lesion all involving the true cords while 2 (20%) has multiple lesions.
Conclusion. The clinical and videoendostrobscopic findings of laryngeal tuberculosis have been evaluated. The characteristics of laryngeal lesions seem to be more nonspecific and it can even occur as a primary laryngeal infection [6,20]. Typical tuberculous lesions appeared as whitish excrescences or ulcerative lesions not solely confined to the posterior larynx but involve the other glottic structures. It is important to consider tuberculosis in the differential diagnosis of nonspecific laryngeal disease.

INTRODUCTION

In a developing country like the Philippines, tuberculosis is still widely prevalent while the incidence of this communicable disease in industrialized nations is now on the rise [7,18,20]. This is attributed to the rising resistant strains to chemotherapeutic agents and partly due to the ever-increasing number of immunocompromised hosts (e.g. patients with AIDS [3,4,9,10,22] and other

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immunosuppressive diseases[20,24]). As the incidence of tuberculosis increases, laryngeal tuberculosis is also encountered by a growing number of otolaryngologists. Laryngeal tuberculosis is almost always a result of pulmonary tuberculosis [21]. However, recent reports were made on primary laryngeal tuberculosis [23]. The previous mode of infection was direct spread along the airway involving mostly the posterior larynx as it lies in the line of mucociliary clearance from the trachea, but currently it can involve any area of the larynx.

Many clinicians neglect to include tuberculosis in the differential diagnosis of laryngitis resulting in misdiagnosis and inappropriate treatment. A high level of suspicion must be present in all patients with non-specific laryngeal lesions and confirmation with appropriate diagnostic tools leads to proper treatment [19]. This trend urges otolaryngologists to be more alert about the emergence of the laryngeal tuberculosis with atypical clinical manifestations.

In our local setting, where Koch's bacillus is ubiquitous, laryngeal tuberculosis should always be considered in the differential diagnosis of laryngeal lesions. Strong suspicion should be done in all individuals with hoarseness and significant dysphagia and could be confirmed with appropriate diagnostic tools, resulting to proper management.

OBJECTIVE

The objective of this study are (a) to present our clinical experience at the Voice Laboratory with 22 cases of laryngeal tuberculosis and (b) to evaluate its changing trends in clinical manifestations in an attempt to contribute to more accurate and prompt diagnosis and treatment.

The investigators will attempt to: (1) categorize laryngeal appearance videostroboscopically, (2) categorize the lesions according to sites and multiplicity, (3) and compare the patients' lung status with the laryngeal infection.

METHODOLOGY

A retrospective clinical analysis was done on 22 patients diagnosed to have laryngeal tuberculosis by laryngovideoendostrobscopy (LVES) from October 1997 to September 2001 and later confirmed by histopathological report. All were interviewed for a thorough history, including previous results of chest radiographs and biopsy. The patients' age, sex, use of tobacco, symptoms, lesion sites, stroboscopic appearance and lung status were evaluated.

The stroboscopic examination (LVES) was done by the investigators at the Voice Laboratory using the Kay elemetrics computerized laryngeal stroboscope and analyzed by a single interpreter. Perceptual voice evaluation was done prior to the procedure. Laryngeal findings were categorized into: (a) ulcerofungative mass lesion, (b) whitish ulcerative lesion, and (c) polypoid lesion.

Pathological Diagnostic Criteria

The standard diagnostic procedure was direct laryngoscopy with biopsy [13]. The laryngeal specimen was sent to the pathology department for microscopic evaluation. The special staining used was Ziehl-Neelsen stain, which shows acid-fast bacilli as evidence of Koch's infection. Examination under the microscope consists of avascular tubercle with area of central caseation surrounded by palisading epithelial cells and a peripheral zone of mononuclear cells. All 22 cases in our study showed evidence of granulomas histopathologically [27].

RESULTS

The patients' ages ranged from 16 to 73 years with a mean age of 36.8 years. Thirteen (13) patients were male and nine (9) were female. There were nine (9) smokers among the patients with history of tobacco use ranging from 1 to 20 pack years at a mean of 10 pack years. All patients presented with hoarseness as their chief complaint.

On laryngovideoendostroboscopy (LVES) the most common findings were the following: vibratory and vertical phase asymmetry were noted in eighteen (18) patients (82%) while three (3) patients (14%) were symmetrical. Majority (n=13 or 60%) had reduction in amplitude on both sides. The periodicity in ten (10) patients were normal while irregular in eight (8). The mucosal wave in five (5) or 23% of patients were normal while abnormal (decreased or adynamic) for the rest (n=17) or 77%. Glottic closure configuration was complete in eight (8) or 36% patients, while for the rest (n=14) or 64%, it is either, incomplete, irregular or with posterior chink. One patient presented with concomitant vocal cord paralysis while another patient was

not assessed stroboscopically because of severe dysphonia secondary to a huge fleshy mass noted at the glottic level which extended to the subglottis.

Patients were grouped into three different appearances based on the various videoendostroboscopic findings: (a) ulcerofungative mass lesion (n=2, 10%), (b) whitish ulcerative lesion (n=18, 80%), and (c) polypoid lesion (n=2, 10%) [Table1]. Laryngeal lesions in fourteen (14) patients manifested as a single lesion, all involving the true vocal cords, and eight (8) patients showed multiple lesions, most commonly involving the true vocal cords (8), the false vocal cords (6), the arytenoids (4) and the epiglottis (4) [Table 2].

TABLE 1
Categorized Laryngeal Appearance on Laryngeal Videoendoscopy

Laryngeal Findings	Single	Multiple
ulcerofungative mass lesion	2	0
whitish ulcerative lesion	11	7
polypoid lesion	2	0

TABLE 2
Lesions Sites Grouped according to Multiplicity and Location

Laryngeal Appearance by Strobscopy

	True VC	False VC	Arytenoids	Epiglottis
Single	14	0	0	0
Multipl	8	6	4	4

FIGURE 1 & 2
Whitish ulcerative lesions located on both vocal cords.

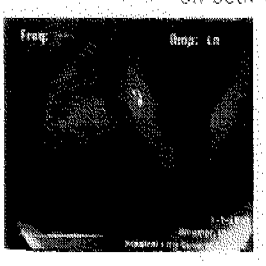
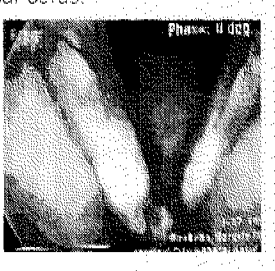



FIGURE 3 & 4
Ulcerofungative mass at the true vocal folds.

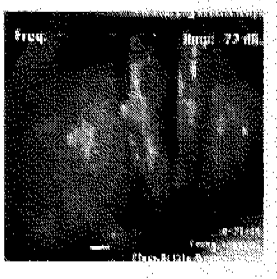



FIGURE 5 & 6
Polypoid lesions located at the free-edges of the vocal folds (left) and early lesions showing irregular edges of the cords (right).

Laryngeal Lesions on Different Sites

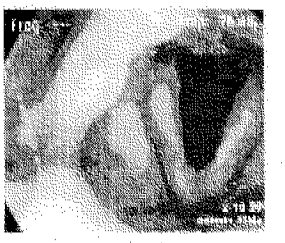
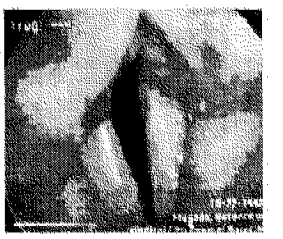



FIGURE 7 & 8
Lesions located at the false vocal cords (left) and the epiglottis (right).

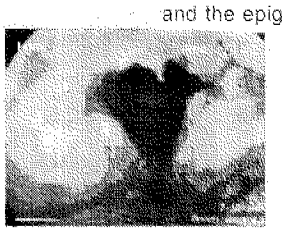
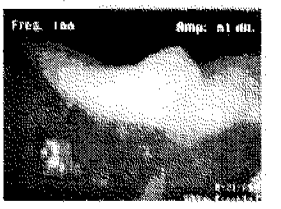
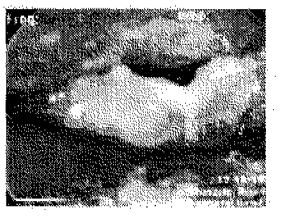
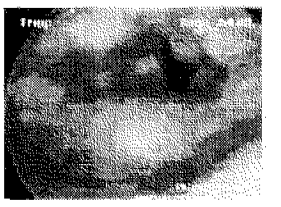



FIGURE 9 & 10
Whitish excrescences located at the epiglottis (left) and a lesion located at the arytenoids (right).

The patients lung status at the time of diagnosis was assessed based on chest x-ray results. More than half of the patients (n=12), i.e. 55%, had pulmonary tuberculosis as documented radiographically. Among those with active pulmonary tuberculosis by chest x-ray, 6 (50%) had multiple site-lesions while 6 (50%) had involvement of the true cords only. In the remaining patients with normal lung status, 8 (80%) had a single lesion involving the true cords while 2 (20%) had multiple lesions.

TABLE 3
Patient's Lung Status

Subjects	Lung Status by Chest X-ray	Multiplicity of Lesions by Endoscopy
22 patients	12 with active PTb	6 with TVC lesions
		6 with multiple-site-lesions
	10 with normal lungs	8 with TVC lesions
		2 with multiple-site-lesions

DISCUSSION

Neglect on the part of the clinician to include Koch's infection in the differential diagnosis of laryngitis could be fatal [25]. At the end of the 20th century. Tuberculosis has emerged as one of the world's leading causes of death from a single infective agent. Laryngeal tuberculosis may come in new and different clinical patterns, thus further investigation by otolaryngologists is warranted. The potential risks of Koch's laryngitis is significantly reduced once prompt and proper treatment is ensured.

Previous investigations reported that the period of greatest incidence of laryngeal tuberculosis is in young adults between 20 to 30 years of age[1]. However, Shin, et al presented in November 2000 a marked shift to older age distribution of patients with laryngeal tuberculosis[20]. In our series, majority were in their second, third and fourth decades. There was also a male sex predominance which was similar in other studies [1]. All the patients presented with hoarseness as they were seen at the Voice Laboratory.

Stroboscopic parameters such as vertical phase symmetry, mucosal wave and glottic closure configuration were all affected by the vocal cord lesions. A decreased to absent mucosal wave was observed in 77% of our patients suggestive of infiltrations of the underlying vocalis muscle. This finding may be clinically indistinguishable from a malignant process and should always warrant a tissue biopsy. Vocal fold mobility can also be impaired when there is compression of the recurrent laryngeal nerve at the hilar area from tuberculous infiltrates. This was evident in one patient.

Based on appearance, majority of the lesions appeared as whitish ulcerative lesions (80%) often appearing as whitish excrescences. The posterior larynx has previously been pointed out in the direct spread along the airway of mycobacterial infection [8]. This was not the case in our study for the involvement of the true cords and the false cords was much more common than the involvement of the posterior commissure. The most commonly involved site was the true vocal cords. The epiglottis is rarely involved in this type of infection [17], except in 4 patients. These findings imply a possible lymphatic or hematogenous spread in laryngeal tuberculosis [18].

Differential diagnosis among laryngeal tumor (e.g. malignancy, papilloma, chronic laryngitis and tuberculous infection) has become more difficult than in the past [2, 11, 15]. Only after biopsy can a true diagnosis be established in spite of technological advances in laryngeal endoscopy and documentation[26]. Carcinoma occurs fairly frequently with pulmonary tuberculosis and occasionally with laryngeal tuberculosis, thus laryngoscopy with tissue biopsy are essential if there is any doubt. Risk factors are important considerations in laryngeal assessment. Age and smoking history are two important factors when considering tuberculosis or malignancy. In our group, most of the patients were in the younger age bracket and a strong smoking history was noted in 41% of the cases.

Primary laryngeal tuberculosis has emerged as a new entity. In the past, it was almost always associated with advanced pulmonary infection [5, 12]. However, reports on patients with an established laryngeal tuberculosis having a negative findings on chest radiograph, negative sputum cultures and negative history of exposure has been made [14]. In our present study, 55% of patients has a concomitant pulmonary tuberculosis while the rest (45%) has primary laryngeal tuberculosis, thus negating previous reports that pulmonary infection with *Mycobacterium tuberculosis hominis* is necessary to harbor the organism at the laryngeal area. We also found that lesions that appear to be more non-specific and located in a single site is seldom associated with pulmonary tuberculosis and when the lesions are more ulcerative and multiple, there was a greater chance of active lung infection.

CONCLUSION

We have presented 22 established cases of laryngeal tuberculosis. Laryngeal stroboscopic findings and lesion sites were discussed and compared with the patients' lung status.

Success in treating patients with laryngeal tuberculosis depends on a high clinical suspicion, prompt diagnosis and early initiation of appropriate anti-Koch's regimen. Clinicians can no longer rely on pulmonary or systemic symptoms alone and must always include tuberculosis as a possible etiological laryngeal lesion.

Based on this series, typical tuberculous lesions appeared as whitish excrescences or ulcerative lesions NOT solely confined to the posterior larynx but involve the other glottic structures. It can also occur as a primary laryngeal lesion.

RECOMMENDATIONS

Tuberculous lesions also require differential diagnosis to distinguish it from neoplasms because they present with similar stroboscopic findings and have no signs of simultaneous and previous pulmonary involvement.

It is equally important to confirm diagnosis of the lesion via laryngoscopy and biopsy to rule out associated carcinoma of the larynx or any other condition where treatment modality could differ significantly.

It is imperative that the otolaryngologist is familiar with the findings of laryngeal involvement of the disease in the face of an increasing incidence of laryngeal Tb.

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A COMPARATIVE REVIEW ON THE PREVALENCE OF THYROID MALIGNANCY IN THE CORDILLERA AND LOWLAND REGIONS

MARY JANE C. TIPAYNO, MD

ABSTRACT

Objective: This study was undertaken to determine if there is a significant difference in the rate of thyroid malignancy in a known goiter endemic region (Cordillera) from that of a non-endemic area (Lowlands), and to determine the prevailing type of carcinoma in these two regions.
Design: Retrospective Descriptive Analysis
Setting: The study was conducted at Baguio General Hospital and Medical Center (BGHMC) from January 1999 to March 2001
Patients: The study involves the review of histologic reports and medical chart records of patients who have undergone thyroidectomy for goiter.
Results: Although not statistically significant, histopathology reports of patients with permanent residence in the Cordillera area show a higher percentage of thyroid carcinoma predominantly of papillary type.
Conclusion: The result supports the worldwide studies that correlate higher prevalence of thyroid carcinoma in goiter endemic regions over the general population. The finding of predominantly papillary type however deviates from the previous results of follicular carcinoma prevalence in iodine deficient regions.

INTRODUCTION

Thyroid carcinoma has been reported on several occasions by foreign authors to have a direct relationship to the prevalence of goiter and Iodine deficiency in a population. Wegelin[1] found thyroid cancer in 1.04% of autopsies in Berne in 1928, when goiter was endemic, but only 0.09%of autopsies in Berlin where endemic goiter was absent.

A study made by Riccabona[2] proposes that carcinoma probably occurs more frequently in populations with endemic goiter. This in part maybe related to the role of TSH as a growth factor for differentiated thyroid carcinoma. In 1987 a national goiter prevalence survey was conducted by the Department of Health in 6 regions that included 38 provinces and 10 cities. Mountain Province (93%)ranked first followed by Bukidnon (71%), Oriental Mindoro (56%), and Abra (41%). No survey was however made on the rate of thyroid malignancy in these regions of the country.

MATERIALS AND METHODS

A retrospective analysis of 81 histopathologic reports of thyroidectomy patients performed at BGHMC is presented. It includes those operated on for all types of goiter from January 1999 to March 2001 and whose medical records fulfill the information required about the age, sex(table 1) and with the same home and provincial address(table 2).

TABLE 1
Classification of Patients

		Group 1 n=36 (Cordillera)	Group 2 n=45 (Lowlands)
Mean Age		36.82	41.27
Sex	Male	5(14%)	6(13%)
	Female	31(86%)	39(87%)

TABLE 2
Provincial Distribution of Goiter Endemic Area (Group 1)

Cordillera area (Endemic region)	n=36
Baguio City	18(50%)
Benguet	13(36%)
Ifugao	2(5.5%)
Kalinga	2(5.5%)
Mt. Province	1(3%)

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Of the 81 patients, thirty-six were from goiter endemic areas (table 3)(Baguio City 50%, Benguet 36%, Ifugao 5.5%, Kalinga 5.5% and Mt.Province 30%) and designated as group one. Forty-five were from the lowland regions, a non-(Table 3) endemic area (Pangasinan 62%, La Union 29%, Ilocos Sur 4.5% and Tarlac 4.5%)were designated as group two. Group one ages ranged from 17 to 75 with mean age of 36.82, consisted of 31 females(86%) and 5 males(14%). Group 2 ages ranged from 20 to 82 with a mean age of 41.27; there were 6 males and 39 females in group two. Uncorrelated t-test was used to analyze the difference between the two groups.

TABLE 3
Provincial Distribution of Non-Goiter Endemic Area (Group 2)

	n=45
Pangasinan	28(62%)
La Union	13(29%)
Ilocos Sur	2(4.5%)
Tarlac	2(4.5%)

RESULTS

Although there was a higher percentage of thyroid malignancy in group one, (table 4) this was shown to be statistically not significant (P>.05). There was predominance of the papillary type (table 2) in both groups occurring in 83% of group one and 75% in group two. Since the carcinoma population was not large, no statistical method was used to carry out the correlation of thyroid carcinoma to age and sex distribution in each group. The mean age of diagnosis was almost equal but it is worthy to mention that the youngest patient in group one was 28 years old compared to 41 from group 2.

TABLE 4
Percentage of Carcinoma

	Group 1 n=36	**Group 2 n=45**
Papillary	5(13.89%)	3(6.66%)
Follicular	1(2.78%)	1(2.22%)
Medullary	0(0%)	0(0%)
Anaplastic	0(0%)	0(0%)
TOTAL	**6(16.66%)**	**4(8.88%)**
t=0.744		
t df=79 at 0.05 and 0.001 is greater than 1		

DISCUSSION

Goiter, a reflection of significant iodine deficiency in a population occurs more commonly in mountainous area as iodine is washed out from the soil. According to a 1987 national survey on goiter, two provinces in the Cordillera were found to have the highest incidence, however no information on the prevalence of carcinoma in these areas is available.

In recent surveys on thyroid cancer in relation to iodine deficiency, Vigneri et al[3] concluded that today, solid evidence has accumulated, both experimental, biological, epidemiological and clinical, that iodine deficiency is a risk factor for thyroid cancer by favoring both initiation, promotion and progression of thyroid tumors. They reviewed the evidence that all conditions that favor prolonged stimulation of cell proliferation are apt to favor premalignant transformation. These include conditions of iodine deficiency at least increased TSH stimulation, increased thyroid cell responsiveness to TSH and increased angiogenesis.

Other studies show that follicular thyroid cancer is more common and papillary thyroid cancer is less common in iodine deficient areas. Williams[4] has summarized these data which show that the ratio of follicular/papillary types exceeds 0.7 in iodine deficient areas, whereas in iodine sufficient areas the ratio is 0.26 or below. Bubenhofer and Hedinger[5] reexamined all their cases of thyroid cancers from Zurich (1924-1974) and they found a relative reduction of anaplastic thyroid cancer after iodine prophylaxis. Different pathologists do not always agree on cancer classifications but slides of tissues from Argentina* before and after iodine prophylaxis, were classified by the same pathologists. Data from Argentina through the iodine transition period(1958-1967) and full prophylaxis (1967-1976) showed a relative reduction in anaplastic carcinoma and a decrease in the ratio of follicular/papillary carcinoma likewise, Cuello et all[6] showed the incidence of anaplastic and follicular thyroid carcinoma in Colombia was greater than in USA (Connecticut)but the incidence of papillary cancer appear to be independent of iodine intake, a probable explanation to the finding of predominant papillary carcinoma in both endemic and non endemic populations in the study.

RECOMMENDATION

To increase the population of subjects and improve the validity of the results, a longer time span of the study is recommended.

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PROFILE OF PATIENTS WITH THYROID MALIGNANCY AT A UNIVERSITY-BASED TERTIARY HOSPITAL: A SIX-YEAR RETROSPECTIVE STUDY (1995-2000)*

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ABSTRACT

Objective: This retrospective study aims to describe the profile of patients with thyroid malignancy who underwent surgery.
Design: Descriptive study
Setting: University-Based Tertiary Hospital.
Patients: Records of 38 patients with thyroid malignancy who underwent surgery were reviewed over a span of 6 years (1995-2000). Data collected from these patients were analyzed and compared with local and foreign literature.
Results: The study showed a male to female ratio of 1:5, a mean age of 41 years old, and a higher rate of papillary Ca (82%) over the follicular variant (18%). Also, a nodular mass (92%) was the most common presentation with lymph node involvement in 40% of the cases. There were also findings of a (+) familial predisposition in 34% of the cases and (+) for radiation exposure in 13%. Most of the cases also belonged to Stage I (55%) based on TNM system and FNAB was very accurate (100%) in diagnosing papillary Ca.
Conclusion: Review of cases revealed a close similarity between profiles of the patients in both local and foreign settings with a significantly younger age group (41 years old) especially among females (38 years old) presenting as a nodular mass, with predominance of the papillary variant (size is usually greater than 4cm in greatest diameter). Females usually belong to stage I while males belong to stage III. A multi-center networking is recommended and active participation in the Tumor Board in order to improve the sampling size and to arrive at more significant findings.

INTRODUCTION

Thyroid malignancy is one of the most frequent endocrine malignancies encountered in clinical practice in the Philippines today. Thyroid cancer ranks 7th overall, 4th in females and 17th in males. It is also the most common cancer of women at ages 15 – 24.[1]

Many prognostic indicators and risk factors such as age, sex, tumor size, nodal spread and distant metastasis, a positive family history or genetic predisposition and prior irradiation exposure have been formulated to assess the behavior of thyroid malignancies and therefore, arrive at the appropriate treatment decisions. With this in mind, it is therefore prudent for us to start analyzing first the characteristics and profile of patients with thyroid malignancy especially in our own university setting. Zantua in his paper entitled "A Ten Year Survey Of Head and Neck Cancer and their Treatment Protocol" reviewed 11 cases of thyroid carcinoma who underwent surgical treatment at a University-Based Tertiary Hospital from January 1985 to December 1995. He also suggested appropriate treatment protocols for these cases encountered.[2]

OBJECTIVE

Thyroid malignancy cases have increased over the past few years at the ENT Department of a University-Based Tertiary Hospital. This retrospective study was conceived to describe the profile of patients with thyroid

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malignancy undergoing surgical treatment. From this, we could compare the profiles of our reviewed cases with that of local studies and foreign literature which may lead us to an earlier diagnosis and treatment.

MATERIALS AND METHODS

Medical records of patients admitted at a University-Based Tertiary Hospital for surgical intervention of thyroid malignancy between January 1995 to August 2000 were reviewed. Data that were collected from these records include: name, age, sex, tumor size in greatest diameter, family history of thyroid disease or cancer, prior irradiation exposure, lymph node involvement at the time of diagnosis, morphology and final histopathological diagnosis of the surgical specimen and surgical treatment. These data were analyzed and relationships were formulated with regards to our own clinical findings and that of other local and international findings. Data collected from these patients were also used to stage each patient at the time of admission using the American Joint Committee on Cancer Staging for papillary, follicular, and medullary thyroid carcinoma.

This paper is a descriptive study which will use frequency distributions to analyze data collected.

RESULTS

A total of 38 cases of thyroid malignancy were reviewed over a span of 6 years (see Table I). There was a female preponderance with 32 (84%) and only 6 (16%) being males. Male to female ratio was placed at 1:5.

TABLE I
Raw Data Tabulated from 38 Patients with Thyroid Carcinoma

Px	Age /Sex	Lym. node	Nodul.	Size	Fam. Hx.	Rad. Exp.	FNAB	Final Histo	Stage	Surgical Tx.
CP	19 F	-	N	5 x 6	-	-	Papillary	Same	I	L lobectomy w / isthmusectomy
SF	58 M	+	N	8.5 x 5.4	+	-	Papillary	Same	III	Total thyroidectomy w / MRND
BB	71 F	-	N	5 x 7	+	+	Papillary	Same	II	Total Thyroidec.
JB	24 F	-	N	4.5 x 3	-	-	Papillary	Same	I	Subtotal Thyroidec
TA	55 M	+	N	5.5 x 5 x 3.5	-	-	Papillary	Same	III	Total thyroidectomy w / MRND
MG	16 F	-	N	4 x 5.7	+	-	Follic Adenoma	Follic CA	I	Total Thyroidec.
CC	28 F	-	N	4 x 3	-	-	Follic Adenoma	Follic CA	I	Total Thyroidec.
JL	24 F	+	N	7.5 x 3 x 3	-	-	Papillary	Same	I	Total Thyroidec. w / paratracheal ND
VF	61 M	+	N	10 x 10	-	-	Papillary	Same	III	Total Thyroidec. w / extended ND
GB	31 F	+	N	7 x 7 x 4	+	-	Papillary	Same	I	Near Total Thyroidec w / MRND
PE	52M	-	N	3 x 4.5	-	-	Papillary	Same	II	R Lobec w / isthmusectomy
PV	56 F	+	M	2 x 3	-	-	Follic Ca	Papill CA	III	Total thyroidectomy w / MRND
EM	69 F	-	N	8 x 7	+	-	Follic Ca	Same	II	Total Thyroidec.
LT	30 F	-	N	4 x 5	-	-	Papillary	Same	I	Completion Thyroide
RD	19 F	+	N	6 x 5.5	+	-	Papillary	Same	I	Total Thyroidec w / PL ND, R; L ND, L
MT	47 F	-	N	4 x 5	-	-	Papillary	Same	II	Near Total Thyroidec
MTF	38 F	+	N	6 x 4	-	-	Papillary	Same	I	Near Total Thyroidec. w / MRND II,L
MD	33 F	+	N	4 x 5	-	-	Papillary	Same	I	Near Total Thyroidec. w / MRND II,R
AS	20 F	-	N	2 x 2	-	-	Papillary	Same	I	Subtotal Thyroidec
TD	59 M	+	M	5 x 5	-	+	Papillary	Same	III	Near Total Thyroidec w / Selective ND
GS	33 F	+	N	3 x 2	-	-	Papillary	Same	I	Total thyroidectomy w / MRND
PS	60 M	+	N	3.2 x 3 x 1.7	-	-	Papillary	Same	III	Near Total Thyroidec w / Selective ND
TF	61 F	+	N	8 x 6	+	-	Papillary	Same	III	Total Thyroidec w / Selective ND
NC	38 F	+	N	4 x 5	+	-	Papillary	Same	I	Completion thyroidec. w / PL ND
HC	52 F	-	N	6 x 2.5	-	-	Follic Ca	Same	II	Total Thyroidec.
DR	18 F	-	N	4 x 4	-	-	Papillary	Same	I	Near Total Thyroidec
JS	22 F	-	N	5 x 4.7	+	+	Papillary	Same	I	Near Total Thyroidec
MR	22 F	-	N	3 x 2.7	-	+	Follic Ca	Same	I	Total Thyroidec.
VT	50 F	+	N	6 x7	+	+	Papillary	Same	III	Completion Thyroidectomy w / RND
FI	36 F	-	N	4.1 x 2	-	-	Papillary	Same	I	Near Total Thyroidec
JD	41 F	-	M	7.5 x 4.5 x 3	+	-	Papillary	Same	I	Completion Thyroidec
BC	50 F	-	N	5 x 5	-	-	Follic Ca	Same	II	Near Total Thyroidec
AA	67 F	-	N	8 x 7	+	-	Follic Ca	Same	II	Near Total Thyroidec
MD	29F	-	N	3 x 2	-	-	Papillary	Same	I	Total Thyroidec.
AR	24 F	-	N	5.5 x 2	+	-	Papillary	Same	I	Total Thyroidec.
MT	37 F	-	N	3 x 4 x 3	-	-	Papillary	Same	I	Total Thyroidec.
LF	32 F	-	N	5.5 x 3.5	-	-	Papillary	Same	I	Total Thyroidec.
ZB	60F	-	N	5x 2.5 x 2	-	-	Papillary	Same	II	Total Thyroidec.

TABLE II

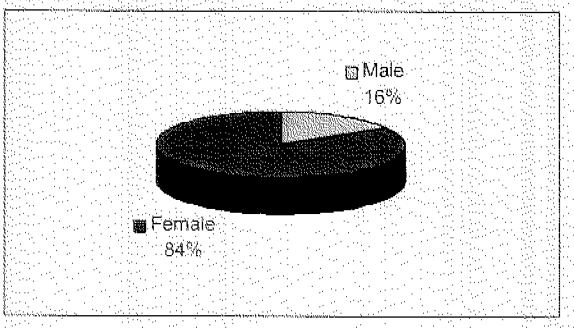
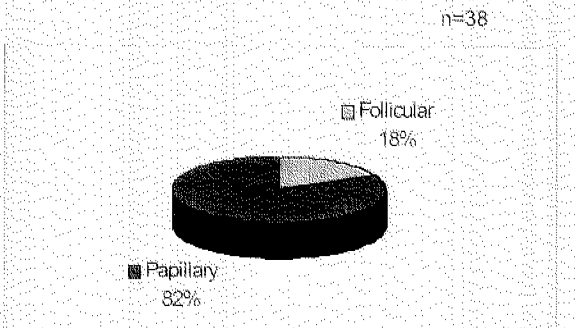


TABLE III
Distribution of Patients According to Age Groups

	No. of Patients	Percentage
Less Than 45 years old	21	55%
Equal or Greater Than 45 years old	17	45%

There were only two subtypes of differentiated thyroid carcinoma observed in the cases reviewed, these were the papillary and follicular carcinoma. Papillary carcinoma accounts for 31 out of the 38 cases reviewed (82%). Follicular carcinoma accounts for 7 which translates to a mere 18%. All of the 7 patients with the follicular type of carcinoma were females while of the 31 patients with papillary thyroid carcinoma, 6 were males and 25 were females.

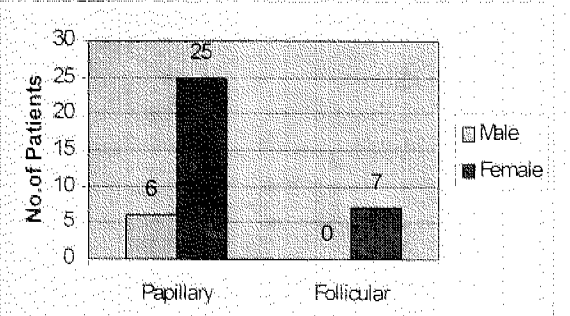
TABLE IV
Distribution of Patients According to Types of Thyroid Carcinoma (Papillary or Follicular)



Sex Distribution in Thyroid Malignancy Patients of STUH - ENT – CD 1995-2000

Age distribution ranged from 16 years old to 71 years old with a mean age of 41 years old. Mean age for females was at 38 years old while that for males was at 58 years old.

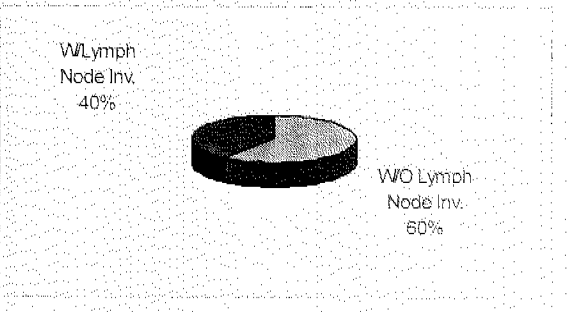
TABLE V
Distribution of Male and Female Patients in Papillary and Follicular Carcinoma



With regards to morphology, 92% of these cases presented as a nodular mass as compared to only 8% which presented as a multinodular mass. Incidentally, all of the cases which presented as a multinodular mass had papillary carcinoma.

Of the 38 cases reviewed, 15 (40%) of the cases presented with lymph node involvement at the time of admission. Also, all of these cases with lymph node involvement were of the papillary type and underwent prophylactic neck dissection. Of the 15 patients with positive lymph node involvement, 8 had modified radical neck dissection, 2 had posterolateral neck dissection, one had paratracheal neck dissection, two had selective neck dissection, one had extended neck dissection and one had a radical neck dissection.

TABLE VI
Distribution of Cases with Lymph Node Involvement



Tumor size in greatest diameter was assessed in each of the 38 cases reviewed and mean size was 5.45 cm. Mean size for the follicular variant was 5.67 cm while for the papillary variant 5.23 cm.

We also staged the cases reviewed based on the TNM system proposed by the American Joint Committee on Cancer Staging for papillary, follicular and medullary thyroid carcinoma. From this we found out that, of the 38 cases reviewed, 22 (58%) belong to stage I, 8 (21%) belong to stage II and 8 (21%) belong to

stage III. There was no case of stage IV thyroid carcinoma reported. Thirty one cases of papillary thyroid carcinoma showed that 19 (61%) are in stage I, 4 (13%) are stage II and 8 (26%) are stage III. The follicular type which has 7 reviewed cases had 3 (43%) cases in stage I and 4 (57%) cases in stage II.

TABLE VII
Distribution of Different Stages of Carcinoma Between Papillary and Follicular Subtypes

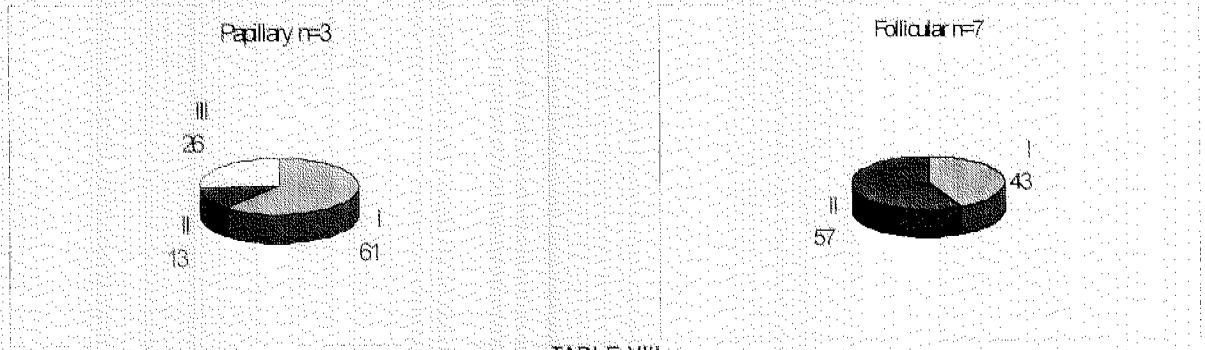


TABLE VIII
Distribution of Thyroid Carcinoma Patients by Stage on Admission

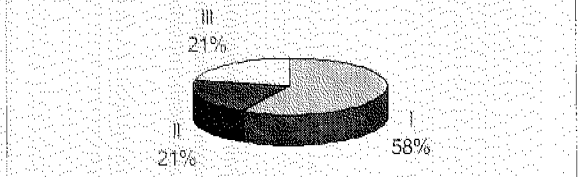


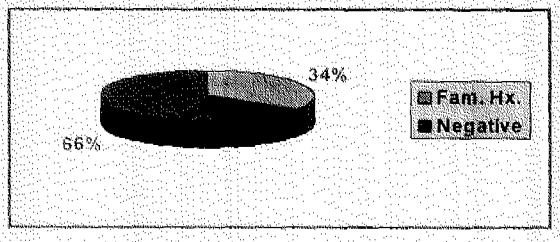
TABLE IX
TNM Classification by the American Joint Committee on Cancer Staging for Papillary, Follicular and Medullary Thyroid Carcinoma

	Papillary or Follicular	
	Age < 45 yrs	Age 45 or Older
Stage I	Any T, any N, M0	Any T1, any NO, M0
Stage II	Any T, any N, M1	T2 or 3, N0, M0
Stage III		T4, N0, M0 or T, N1, M0
Stage IV		Any T, any N, M1
	Medullary:	
Stage I	T1, N0, M0	
Stage II	T2-4, N0, M0	
Stage III	Any T, N1, M0	
Stage IV	Any T, any N, M1	
	Undifferentiated:	
Stage IV (all cases)	Any T, any N, any M	
Definition of TNM		
Primary Tumor (T)	T0=No evidence of primary tumor T1=Tumor 1 cm or less in greatest dimension limited to the thyroid T2=Tumor more than 1 cm but not more than 4cm in greatest dimension limited to the thyroid T3= Tumor more than 4 cm in greatest dimension limited to the thyroid T4= Tumor of any size extending beyond the thyroid capsule	
Regional Lymph Nodes	N0= No regional lymph node metastasis N1= Regional lymph node metastasis N1a= Metastasis in ipsilateral cervical lymph node(s) N1b= Metastasis in bilateral, midline, or contralateral cervical or mediastinal lymph node (s)	
Distant Metastasis (M)	M0= No distant metastasis M1= Distant metastasis	

Taken from AJCC Cancer Staging Handbook, 5th Edition 1997

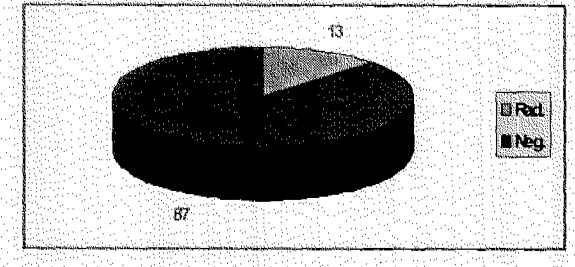
Family history (thyroid disease or Ca) was positive in 13 cases (34%) for which, 3 were follicular Ca while the rest were of the papillary type.

TABLE X
Distribution of Thyroid Ca patients with regards to a Positive Familial Predisposition



History of prior radiation exposure was seen in 5 patients (13 %). Only 1 case of follicular Ca was positive for radiation exposure while the rest were also of the papillary variant.

TABLE XI
Distribution of Thyroid Ca Patients with regards to prior Radiation Exposure



With regards to surgical treatment of these thyroid carcinomas, two of the papillary variant underwent ipsilateral lobectomy with isthmusectomy. Thirteen underwent total thyroidectomy. Four underwent completion thyroidectomy for recurrence, two underwent subtotal thyroidectomy, and nine underwent near total thyroidectomy. Of the follicular type of thyroid carcinoma, six underwent total thyroidectomy while only two underwent near total thyroidectomy with preservation of only the parathyroids. (Table I)

Fine needle aspiration biopsy was very accurate in diagnosing papillary thyroid carcinoma (100%) while it fell to only 62% with regards to the follicular variant. (Table I)

DISCUSSION

Thyroid carcinomas consist of a wide array of morphologic subgroups. Among the follicular cell derived tumors are: differentiated thyroid carcinomas which include the papillary and the follicular type and the undifferentiated (anaplastic) thyroid carcinomas. Medullary thyroid carcinomas are derived from the parafollicular or C cells. Different subgroups represent different characteristics and manifestations.

Of the 38 cases we reviewed in a span of 6 years, we noted an increase in the incidence of thyroid malignancy as compared to the 11 cases reviewed by Zantua.[2]

The incidence of thyroid cancer in the Philippines is three times more in females. [4] This was confirmed by this study which has a slightly higher preponderance for females with a ratio of 1:5. Mean age taken from all cases gives us a figure of 41 years old with a distribution range of 16 years old to 71 years old. This only shows us that we may have a lower age bracket for defining high risk groups in our own local setting as confirmed by the study of Cuasay et al which has a mean age of 39 years old[5]. This is in comparison with foreign studies in staging systems like that of the American Joint Committee on Cancer which uses 45 years old in defining high risk groups.(Refer to Table VIII).

Almost 95% of thyroid cancer in the Philippines are well-differentiated carcinoma, and are highly curable by appropriate surgery alone[6]. Papillary carcinoma is the most common malignant tumor of the thyroid gland and is generally associated with a good prognosis.[7] This study confirms these findings of papillary carcinoma being the most prevalent of all thyroid malignancies with an 82% distribution among the cases reviewed.

Thyroid carcinoma occurs more often in solitary than in multinodular goiters[8]. This study confirmed this finding by giving a 92% incidence of nodular presentation with regards to tumor morphology among the cases reviewed.

Papillary thyroid carcinoma tends to metastasize via the lymphatic system, with cervical metastasis occurring in 40% to 60% of the patients at diagnosis[9]. This may explain the incidence of lymph node involvement involving only papillary type of thyroid carcinoma for which prophylactic neck dissection was instituted. Incidentally there was one case of follicular cancer by fine needle aspiration biopsy with lymph node involvement turned out to be papillary carcinoma on final histopath which may give us an idea that papillary carcinoma has a predilection for lymph node involvement.

It was also observed that most of the patients with papillary thyroid carcinoma belong to stage I while those with the follicular type belong to stage II which creates a picture of greater aggressiveness on the part of the follicular subtype.

There was also positive family history in 34% of the cases in conjunction with what Gagel et al observed when they stated that there is an increasing evidence that genetic factors may play a role in a small percentage of papillary and follicular thyroid carcinoma[10]

Prior exposure to radiation is a major risk factor in thyroid carcinoma according to Laudico.[6] This was even confirmed by many foreign studies which have documented the increased risk of thyroid carcinoma in individuals exposed to low level radiation.[11]

Fine needle aspiration biopsy has emerged as the most sensitive and specific procedure for cytologic diagnosis for thyroid carcinoma as confirmed by both foreign and local studies. Incidentally, this study also confirmed the sensitivity and specificity of FNAB in diagnosing follicular carcinoma (62%) as compared to papillary carcinoma (100%) as stated by Zantua[2] and the AACE[11].That is why it has been our treatment protocol for cases that are found to have follicular adenoma or carcinoma by FNAB to request for rush frozen section (RFS) intra-operatively for confirmation which may turn out to be carcinoma or of another variant (ie. Papillary).

Finally, surgical treatment for each of the case was properly instituted following guidelines of the AACE.

CONCLUSION AND RECOMMENDATION

Our experience with thyroid malignancy supports both local and foreign findings. Most of our patients with thyroid malignancy have a female preponderance with a mean age of 41 years old. Majority presented with a nodular mass, the size of which is greater than 4 cm in greatest diameter. They were diagnosed accurately with fine needle aspiration biopsy especially of the papillary type, forty percent of which had lymph node involvement and most belonged to stage I. Among the male subgroups it was also observed that patients typically present with an age bracket of 50-60 years old and with a nodular mass greater than 4 cm. in greatest diameter. This is mostly of the papillary type and usually belong to stage III. Added to this was a significant observation revealing a younger age group especially among females with thyroid malignancies in our review. Clinical prognostic factors reviewed and relationships observed may help us in the future with regard to improved patient care and treatment. Thus, it is also recommended that multi-center networking be done and active participation in the Tumor Board to improve the sampling size and therefore arrive at more significant findings.

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NASOPHARYNGEAL ANGIOFIBROMA: A FIVE-YEAR EXPERIENCE*

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Abstract

Objectives: 1. Determine the demographic data of the patients diagnosed with angiofibroma; 2. Determine the tumor stage of the angiofibroma in each patient through computerized tomography; 3. Determine the procedures performed for the excision of the angiofibroma; 4. Determine the blood loss for the excision of the angiofibroma.
Design: Case series.
Setting: Tertiary hospital.
Patients: Six patients admitted and operated on for nasopharyngeal angiofibroma from September 1996 to September 2001.
Results: Six patients were admitted and operated on for nasopharyngeal angiofibroma with five males and one female. The mean age of the male patients upon admission is 18.6 years and 53 in the female. The patients included in this study presented mainly with massive epistaxis and nasal obstruction. All patients underwent preoperative computed tomography (CT) scanning of the nasopharynx. Based on Sessions' staging system, the five male patients belong to stage IA (1 patient), IB (3 patients), and IIA (1 patient). The female patient started at IIB but later progressed to IIC. Using Chandler's system, four patients had stage II tumor while the rest, including the female, had stage III. A total of nine operations were done on the six patients (Table 3). The female underwent four operations, the last three for residual tumor. Surgical intervention in all patients consisted of excision of the mass. All the males underwent a transpalatal approach. The female patient underwent tracheostomy, radical maxillectomy right, and orbital excenteration right. Blood loss in all the procedures ranges from 1.2 to 3.0 L. (mean of 2.0 L).
Conclusion: Patients are mostly males, with an age ranging from adolescence to early adulthood, and presents with nasal obstruction and massive epistaxis. Females, though rarely, can be afflicted by the tumor. She was on her fifth decade of life but her presenting signs and symptoms are similar with the males. Most patients operated on belong to the low-grade tumors based on the Session's and Chandler's staging of nasopharyngeal angiofibroma. Surgical removal of the tumor remains as the treatment of choice. Transpalatal removal of the tumor in its early stages is advisable. However, extensions to the pterygomaxillary and orbital areas require a more radical transmaxillary approach. The average blood loss is 2.0 L among all the cases studied. It was observed that the higher the staging of the tumor, the more radical is the operation, and the more blood is lost during its excision.

INTRODUCTION

Nasopharyngeal angiofibroma is a highly vascular tumor commonly found in the nasopharynx. Its name, juvenile nasopharyngeal angiofibroma, reflects the fact that the primary manifestations of the tumor occur during adolescence. It is histologically benign but clinically malignant in that it has the capacity for local destructive growth and fatal hemorrhage.

It is fairly uncommon, accounting for only 0.5% of all head and neck neoplasms. It generally presents with massive bouts of frequent epistaxis and nasal obstruction, at 73 and 71%, respectively.[1] The occurrence of the tumor ranges from 9 to 29 years, mean of 15 years,[2] while others would cite 7 to 21 years, with a peak between 14 and 18 years. Only rarely has this lesion been identified with females.

The site of origin of the angiofibroma has been the subject of speculation. It appears to originate in the posterior nasal cavity rather than

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in the nasopharynx, specifically on the posterolateral and superior nasal cavity at the point where the sphenoidal process of the palatine bone meets the horizontal ala of the vomer and the root of the pterygoid process of the sphenoid bone, near the upper margins of the sphenopalatine foramen.[3]

The exact nature of the tumor has been very much debated. Though immunohistochemical markers and electron microscopy have documented the vascular origins of the tumor, the factors that contribute to its growth are still unknown. Its associations with polyposis, hormones, and other genetic abnormalities are currently being studied.

Surgical removal of the tumor remains as the treatment of choice. However, this carries a potential for extensive morbidity and mortality due to hemorrhage. Despite its vascular nature, piecemeal excision of the tumor through the external nares was advocated until 1834. Advances in the technology, diagnosis and management of this tumor has decreased the morbidity and mortality associated with its excision. It was later observed that less bleeding was noted when the tumor was extracted with its pedicle. This led to surgical techniques that provided adequate exposure of the tumor and allowed its complete excision.

Advances in technology has endowed the surgeon several approach options in dealing with angiofibroma. The most recent of these is the endoscopic removal of these tumors. Though initial reports showed high recurrence rates with this method, mainly due to poor exposure, several recent researches has showed great promise for the approach.

Other technological breakthroughs, such as accurate imaging techniques afforded by computed tomography, angiography and magnetic resonance imaging, embolization of feeding vessels, electron microscopy to determine the nature of the tumor, and endoscopy, have contributed in understanding the tumor. This has equipped the present-day otolaryngologist with an armamentarium of choices for its treatment. Radiation and immunotherapy are currently being tapped to combat this tumor.

Nasopharyngeal angiofibroma remains a challenge for otolaryngologists, due to its intraoperative blood loss, recurrences, and the destructive nature of its extensions. This research aims to provide knowledge on this tumor based on the clinical and surgical experiences gathered at a tertiary hospital from September 1996 to September 2001. Such knowledge may guide other practitioners as they encounter this unique vascular tumor.

This study aims to present the clinical and surgical experience of Ospital ng Maynila Medical Center, a tertiary hospital, on juvenile nasopharyngeal angiofibroma from September 1996 to September 2001.

The specific objectives of this research are to:

(1) determine the demographic data of the patients diagnosed with angiofibroma;
(2) determine the tumor stage of the angiofibroma in each patient through computerized tomography;
(3) determine the procedures performed for the excision of the angiofibroma; and
(4) determine the blood loss for the excision of the angiofibroma.

MATERIALS AND METHODS

All patients admitted and operated on for nasopharyngeal angiofibroma at the Ospital ng Maynila Medical Center from September 1996 to September 2001 were determined and their charts were retrieved from the Medical Records Section.

Data gathered were from the charts and their operating room records. Efforts were made to contact patients to assess their current status.

Patients seen or admitted who were suspected to be afflicted by the same vascular tumor but were not operated on were excluded from the study.

RESULTS

The Ospital ng Maynila Medical Center admitted 6 individuals who were diagnosed and operated on for nasopharyngeal angiofibroma from September 1996 to September 2001, five males and one female. The age of the patients upon admission ranges from 14 to 22 (mean of 18.6) among the males and 53 in the female. (Table 1)

During this period, there was another male patient admitted who was highly suspicious for juvenile nasopharyngeal angiofibroma. He was 23 years old and presented with massive epistaxis. However, computed tomography of the head and neck revealed a vascularized tumor with intracranial extensions which necessitated transfer to another hospital. Also, since no biopsy or surgery was done, there was no histopathological confirmation of the diagnosis.

The patients included in this study presented mainly with massive epistaxis and nasal obstruction. Massive epistaxis estimated at a third to a half of a cup is the chief complaint among the males. The history of epistaxis

TABLE 1
Demographic Data and Signs and Symptoms of Patients Diagnosed with Nasopharyngeal Angiofibroma Ospital ng Maynila Medical Center September 1996 to September 2001

Patient	Age	Sex	Signs and Symptoms
1	19	male	Epistaxis for 6 months
			Nasal obstruction for 6 months
			No bulging palate, otitis
2	17	male	Epistaxis for 7 months
			Nasal obstruction for 4 months
			(+) Bulging palate, otitis
3	22	male	S/P excision 1 year ago
			Epistaxis for 6 months
			Nasal obstruction for 6 months
			Previous excision 1 year ago
			No bulging palate, otitis
4	53	female	Maxillary swelling for 4 months
			Nasal obstruction for 4 months
			No epistaxis except on biopsy taking
			(+) Proptosis, bulging palate, otitis
			(+) Dyspnea, dysphagia
5	21	male	Epistaxis for 24 months
			Nasal obstruction for 12 months
			(+) Bulging palate, otitis
6	14	male	Epistaxis for 7 months
			Nasal obstruction for 7 months
			No bulging palate, otitis

ranges from 6 months to 24 months (mean of 10 months). The female presented with chief complaint of a swelling on the right maxillary area of 4 months duration.

Nasal obstruction was observed in all patients. The duration of the symptom ranged from 4 to 12 months (mean of 6.5 months). The obstruction was observed to be initially on and off and later became persistent. It was observed to be associated with hyponasal speech and anosmia.

The male patients experienced mainly epistaxis, nasal obstruction, hyponasal speech and anosmia. The female patient experienced no epistaxis except during punch biopsy. A total of 4 biopsies were done all revealing chronic inflammation. She also had numbness of the right maxillary area. No preoperative biopsy was done on the four of the five males in lieu of the possible bleeding problems expected of the tumor. One male had a previous excision of an angiofibroma at another institution a year before.

All patients underwent preoperative computed tomography (CT) scanning of the nasopharynx (Table 2). All male patients presented with a vascular nasopharyngeal tumor that enhances with contrast. The tumor would obscure the bilateral nasopharyngeal areas and would extend superiorly to the base or into the sphenoid and inferiorly to the oropharynx. Pterygomaxillary area involvement is uncommon, with only 2 patients afflicted. Haziness of the different sinuses was seen in all patients.

The female patient presented initially with an enhancing osteolytic tumor that involves the right maxillary antrum and orbit, the nasopharynx, the sphenoid sinuses, pterygopalatine area, and extends to the hypopharyngeal area. No intracranial involvement was seen among all the patients. Succeeding CT scans of the patient showed extensions to the zygomatic and temporal area.

A total of nine operations were done on the six patients (Table 3). Four male underwent excision of the tumor for the first time. The female underwent four operations, the last three for residual/recurrent tumor. Surgical intervention in all patients consisted of excision of the mass. All the males underwent a transpalatal approach. One of them underwent additional medial maxillectomy and tracheostomy. Ligation of the external carotid artery was performed in three male patients. The female patient underwent tracheostomy, radical maxillectomy right, and orbital excenteration right.

Blood loss in all the procedures ranges from 1.2 to 3.0 L (mean of 2.0 L). The greatest blood loss was observed in the male patient who underwent medial maxillectomy followed by the female patient. The least blood loss was noted in the patient who had an excision of a recurrent tumor after external carotid ligation. Intra and postoperative blood transfusions were carried out in all patients. It consisted of a volume-by-volume replacement of the blood losses.

TABLE 2
CT Scan Findings in Patients Diagnosed with Nasopharyngeal Angiofibroma
Ospital ng Maynila Medical Center, September 1996 to September 2001

Patient	Age	Sex	CT scan findings	Staging Classification	
				Session	Chandler
1	19	male	Enhancing nasopharyngeal mass No pterygomaxillary area involvement No sphenoid sinus involvement No polysinusitis; No intracranial involvement	IA	II
2	17	male	Enhancing nasopharyngeal mass Pterygomaxillary area involved Sphenoid sinus involved Polysinusitis; No intracranial involvement	IIA	III
3	22	male	Enhancing nasopharyngeal mass No pterygomaxillary area involvement Sphenoid sinus involved Polysinusitis; No intracranial involvement Palatal defect present	IB	II
4	53	female	Enhancing nasopharyngeal mass Pterygomaxillary area involved Involved maxillary antrum, orbit and hypopharynx Polysinusitis; No intracranial involvement Sphenoid sinus involved	IIB-IIC	III
5	21	male	Mildly enhancing nasopharyngeal mass No pterygomaxillary area involvement Polysinusitis; No intracranial involvement No sphenoid sinus involvement	IB	II
6	14	male	Mildly enhancing nasopharyngeal mass No pterygomaxillary area involvement Polysinusitis; No intracranial involvement Sphenoid sinus involved	IB	II

TABLE 3
Operation Performed in the Excision of Nasopharyngeal Angiofibromas
Ospital ng Maynila Medical Center, September 1996 to September 2001

Patient	Age	Sex	Operation Done	Blood Loss	Duration of
				(liters)	OR (hours)
1	19	male	24-Feb-98 Ligation of External Carotid Artery Excision via Transpalatal Approach	1.5	3
2	17	male	29-Sep-98 Tracheostomy Ligation of External Carotid Artery Excision via Combined Transpalatal and Denker's Approach with Medial Maxillectomy	3	6
3	22	male	5-Jan-99 Ligation of External Carotid Artery Excision via Transpalatal Approach	1.2	3.5
4	53	female	6-Sep-99 Tracheostomy Radical Maxillectomy Orbital Excenteration	2.9	4.3
			22-Feb-00 Excision	1.85	3
			15-Aug-00 Excision	2.4	5
			21-Nov-00 Excision	1.3	2
5	21	male	29-Aug-00 Excision via Transpalatal Approach	2.2	4
6	14	male	19-Jun-01 Excision viaTranspalatal Approach	1.35	4.25

Preoperative transfusion was only necessary in three male patients.

Follow-up of the male patients ranges from 3 to 6 months. There is no evidence of any residual or recurrent disease upon follow-up. The female patient died of pulmonary disease 5 months after the last operation. She still presented with a residual/recurrence of the tumor.

DISCUSSION

Demography

The age of occurrence of nasopharyngeal angiofibroma among the male patients is not far from that in literature.[2,4] As for the female patient, due to its rarity, no comparison for the age is available. Out of a total of 2490 otorhinolaryngology admissions for the same period, admissions for nasopharyngeal angiofibroma numbers 9 (0.36% of total admissions) with the female patient being readmitted and operated on for four times. This would translate to an incidence of 18 per 5000 admissions. This is lower than the figures from the Department of Otolaryngology of the Philippine General Hospital that has seen and treated a total of 50 cases in a 6-year period (1973-1978), at an average of 8 cases annually to comprise 1.4% of the total annual admissions.[5] However, it is relatively high compared to figures from Taipei Veterans General Hospital at 1 per 5000 admissions, with a female to male ratio of 1:10.[6]

The presenting signs and symptoms of the disease are also identical with those published. According to a study of 30 patients gathered from 1972 to 1983, the most common signs and symptoms of angiofibroma are epistaxis, nasal obstruction, facial deformity, proptosis, bulging palate, deafness, otitis and nasal drainage.[7] Nasal obstruction, which presented at an average of 6.5 months prior to admission, is the most common symptom followed by epistaxis. Only three patients presented with bulging soft palate and otitis while only the female patient had proptosis and facial deformity.

Staging of nasopharyngeal angiofibroma

Staging systems have been proposed based on tumor location and extension. It was proposed that computed tomographic findings should be used for the standardized reporting and staging of patients with angiofibroma after a clinical investigation in which angiofibroma is suspected.[3] A staging system was proposed by Sessions *et al.*[8] due to a lack of standardization of tumor data in both individual series and international reports. The various stages reflect the number of anatomic sites occupied by the tumor rather than its actual size. The "simpler" or low-grade tumors are confined to the medial part of the skull base and are entirely extracranial. As a tumor extends laterally and/or intracranially, the staging description, and therefore the treatment plan, changes accordingly. A description of the stages is shown in Table 4.

Chandler *et al*[9] described an angiofibroma staging system similar to that proposed for cancer by the American Joint Committee. It is also a system based on clinical evaluation and computerized tomography. It is a four-stage system as shown in Table 5. Tandon *et al*[10] made his own modifications from the two previous systems based on the regions affected by the tumor. For the purpose of the present study, the former two staging systems will be used.

Based on Sessions' staging system, the five male patients belong to stage IA (1 patient), IB (3 patients), and IIA (1 patient). The female patient started at IIB due to the antral and orbital involvements but later progressed to IIC as the residual/recurrent tumor encroached to the cheek and temporal area. Using Chandler's system, four patients had stage II tumor while the rest, including the female, had stage III.

Operative procedures performed for the excision of the angiofibroma

Although radiation therapy and chemotherapy have met with some success in the treatment of nasopharyngeal angiofibroma tumors, the current consensus for optimal treatment of these benign vascular tumors remain surgical resection with the former modalities of therapy being reserved for unresectable disease.[11]

Selection of the surgical procedure for removal of the tumor is based on its location and extent. Based on a nine-year period of 50 cases of nasopharyngeal angiofibromas, the following approaches were recommended[10]. Angiofibromas that were limited to the nasopharynx and those with superior spread into the ethmoid or sphenoid sinuses had their tumors removed by transpalatal route, alone or in combination with other approaches. Tumors with lateral extensions into the pterygopalatine or infratemporal fossa or the cheek, and those with simultaneous superior and lateral spread underwent a transmaxillary excision. Those with intracranial extensions were addressed from below.

TABLE 4
Session's Staging of Angiofibroma and Incidence of Recurrence in 30 Patients
(Bremer et al, 1986)

Stage	Description	Patients (n)	Recurrence
IA	Tumor limited to posterior nares or nasopharyngeal vault	1	0
IB	Extension into one or more sinuses	2	0
IIA	Minimal lateral extension through sphenopalatine foramen into medial pterygomaxillary fossa	10	0
IIB	Full occupation of pterygomaxillary displacing posterior w all of antrum forw ard; superior	6	1
IIC	extension eroding orbital bones Extension through cheek, pterygomaxillary fossa into cheek and temporal bone	3	0
III	Intracranial extension	8	4

TABLE 5
Chandler's Staging of Juvenile
Nasopharyngeal Angiofibroma

Stage	Description
I	Tumor confined in the nasopharynx
II	Tumor extending into nasal cavity and/or sphenoid sinus
III	Tumor extending into one or more of the following: antrum, ethmoid sinus, pterygomaxillary and infratemporal fossae, orbit, and/or cheek
IV	Tumor extending into cranial cavity

Generally speaking, nearly all nasopharyngeal angiofibromas can be removed through some combination of the transpalatal, transantral-retromolar trigone (extended sublabial incision), and frontoethmoid approaches.[12] Various surgical approaches have been described recently: the facial degloving procedure and the extensive intracranial and extracranial approaches. The approach will be affected by the surgeon's experience with the technique.[3]

The preoperative staging classification based on clinicoradiological data of each case was the most important criteria in selecting the most adequate surgical approach. The operations performed for the removal of the tumors in this study ranged from excision via transpalatal approach, with or without ligation of the external carotid artery, to radical maxillectomy with orbital excenteration. All cases under stage I of Session's classification or stage II under Chandler's grouping underwent excision by transpalatal route alone. All cases under stage II of Session's classification or under stage III of Chandler's grouping underwent transmaxillary excision.

Ligation of the external carotid artery was undertaken in three cases as an alternative to an

TABLE 6
Operative Blood Loss in Embolized and Non-embolized
Cases of Juvenile Nasopharyngeal Angiofibroma
(Tuazon et al, 1986)

Source and Year	No. of Cases	Average blood loss (liters)
Embolized cases		
Fletcher et al, 1975	7	1.18
Roberson et al, 1979	12	0.8
Waldman et al, 1981	10	0.8
Tuazon et al, 1984	1	1.7
Non-embolized cases		
Conley et al, 1968	34	1.85
Jafek et al, 1973	34	2.7
Christiansen et al, 1974	29	1.7
Ward et al, 1974	12	1.3
Fletcher et al, 1975	16	2.39
Roberson et al, 1979	2	2.4
Tuazon et al, 1979-1983	11	3.5

TABLE 7
Operative Blood Loss in Embolized and Non-embolized
Cases of Juvenile Nasopharyngeal Angiofibroma
1995-2001

Source and Year	No. of Cases	Average Blood Loss (liters)
Embolized cases		
Moulin et al, 1995	16	1.04
Li et al, 1998	11	0.68
Yang et al, 1998	15	0.4
Wang et al, 2001	7	0.81
Non-embolized cases		
Moulin et al, 1995	10	5.38
Li et al, 1998	10	1.14
Wang et al, 2001	5	0.59

embolization technique. Angiography with identification and ligation of the tumor's feeding vessels would have been ideal, but financial constraints have made the option inappropriate. A combined transpalatal and Denker's approach was used in one case to address the pterygomaxillary extension.

Radical maxillectomy with orbital exenteration was done in one case due to a suspiciously malignant tumor, which has invaded the orbit and pterygomaxillary area. This is the female patient wherein several previous punch biopsies were incongruent with the clinical picture.

Blood loss for the excision of the angiofibroma

Blood loss in all the procedures ranges from 1.2 to 3.0 L (mean of 2.0 L). Of the nine operations done, three underwent external carotid ligation. The mean blood loss in the cases that had carotid ligation is 1.9 L. The mean blood loss in the 6 cases that didn't have any carotid ligation is 2.0 L.

The perioperative use of intra-arterial embolization to reduce vascularity of nasopharyngeal angiofibroma has received considerable attention through the years. Several studies have been made to determine the differences in blood losses between embolized and non-embolized patients.

There have been conflicting results in this field and its application to nasopharyngeal angiofibroma. A tabulation of the blood losses in embolized and non-embolized cases is presented in Table 6.[13] This shows various results during the early years of the technique. Another tabulation is presented in Table 7 that shows the more recent studies.

The significant role of embolization in reducing the blood loss, morbidity, recurrence, and intraoperative complications in dealing with this tumor has been well documented.[14,15,16,17] However, it is still questioned when statistical analysis fail to show a significant difference between the embolized and non-embolized cases.[18,19,6]

This has led to much debate on the importance of embolization for nasopharyngeal angiofibroma. It is interesting to note though, that most of these studies failed to classify the cases according to any staging system. The importance of the stage of the tumor to the blood loss incurred during its removal was explained by Moulin *et al.*[19] Preoperative embolization of the branches of the external carotid appears to facilitate removal of high-grade tumors. The benefit of embolization in low-grade tumors is less clear cut, probably because there is less vascularity in them and so removal is easier.

CONCLUSION

Based on the data gathered from the charts and operative records of patients at Ospital ng Maynila Medical Center who were diagnosed and operated on for nasopharyngeal angiofibroma from September 1996 to September 2001, the following conclusions were drawn:

- Patients are mostly males, with an age ranging from adolescence to early adulthood, and presents with nasal obstruction and massive epistaxis.
- Females, though rarely, can be afflicted by the tumor. She is on her fifth decade of life but her presenting signs and symptoms are similar with the males.
- Most patients operated on belong to the low-grade tumors based on the Session's and Chandler's staging of nasopharyngeal angiofibroma.
- Surgical removal of the tumor remains as the treatment of choice. Transpalatal removal of the tumor in its early stages is advisable. However, extensions to the pterygomaxillary and orbital areas require a more radical transmaxillary approach.
- The average blood loss is 2.0 L among all the cases studied. It was observed that the higher the staging of the tumor, the more radical is the operation, and the more blood is lost during its excision.

RECOMMENDATIONS

A lot can still be learned of this unique and uncommon tumor. Future studies on nasopharyngeal angiofibromas should keep the following things in mind:

This study cannot emphasize more the need for a standardized staging of nasopharyngeal angiofibromas. Most of the available literature on the tumor fail to stage the neoplasm. As such, the data they incur cannot be used maximally.

Further studies should be done on the effectiveness on preoperative embolization in reducing intraoperative blood loss in nasopharyngeal angiofibroma of both the low-grade and high-grade stages.

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