TITLE

RECURRENT RESPIRATORY PAPILLOMATOSIS AT KENYATTA NATIONAL HOSPITAL, NAIROBI-KENYA

A TEN-YEAR RETROSPECTIVE STUDY BETWEEN JANUARY 1990-DECEMBER 1999.

A THESIS SUBMITTED IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE (ENT SURGERY) OF THE UNIVERSITY OF NAIROBI

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.

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ACKNOWLEDGEMENT

I would like to express my sincere appreciation to my supervisor Dr. Macharia for his guidance and valuable advice in the writing of this dissertation.

I am also grateful to the staff in the records department, KNH for their diligence in retrieving the case files and to Joyce who spent tedious hours typing the dissertation.

DEDICATION

This work is dedicated to my dear parents Mr. and Mrs. Christopher Muriithi Gichoya for their inspiration and constant encouragement.

ABBREVIATIONS

1.	HPV	-	Human Papilloma Virus
2.	RRP	-	Recurrent Respiratory Papillomatosis
3.	JLP	-	Juvenile Laryngeal Papillomatosis
4.	JORRP	-	Juvenile Onsent Recurrent Respiratory Papillomatosis
5.	AORRP	-	Adult Onset Recurrent Respiratory Papillomatosis
6.	KNH	-	Kenyatta National Hospital
7.	PDT	-	Photodynamic Therapy
8.	DHE	-	Dihematoporphyrin – Ether
9.	C/S	-	Caesarean Section
10.	D/L	-	Direct Laryngoscopy
11.	CO_2	-	Carbon Dioxide Laser
12.	ENT	-	Ear,Nose and Throat

LIST OF FIGURES AND TABLES

CONTENTS

SUMMARY

This is a retrospective study of 74 cases of Recurrent Respiratory Papillomatosis (RRP) treated at Kenyatta National Hospital (KNH) over a ten-year period (1990-1999). The peak age group at presentation was 2-3 years with a range from 4 months to 34 years. There was a slight male predominance at 54.1%.

Most of the patients came from Central (29.7%) and Nyanza (28.4%) provinces. The commonest presenting symptoms were hoarseness, stridor and dysnoea. The glottis was the commonest site involved (95.8%). Extra laryngeal site involvement was found in 13.5% of cases.

All cases were managed by direct laryngoscopic removal of papillomas with micro forceps. 50% of cases required more than one excision to control their recurrences. Tracheostomy was done on 20.3% of patients out of whom 53% were later successfully decannulated.

8.1% of patients developed complications, which was mainly laryngeal stenosis. There was no mortality recorded during the period under review.

INTRODUCTION

Recurrent Respiratory Papillomatosis (RRP) also called Juvenile Laryngeal Papillomatosis (JLP) is the most common benign neoplasm of the larynx in children [14]. RRP is a better term since the papillomas are seen in adults and may involve the entire respiratory tract. This disease is often frustrating and difficult to treat because of its tendency to recur and spread throughout the respiratory tract. There are currently no single or combination treatments that reliably eradicate the Human Papilloma Virus (HPV), the aetiologic agent of RRP.

Although histologically a benign neoplasm, by virtue of obstruction of the airway, RRP is a serious and potentially life threatening disease. The clinical course of RRP is unpredictable, the papillomas may respond to treatment, recur chronically or spontaneously regress.

Malignant transformation in RRP has been documented [17,37,67]. RRP has a world-wide distribution and involves all socio-economic groups. Papillomatosis may have its onset either during childhood (age<16 years) [3] or in adulthood (age>16 yrs) [2]. These disease entities are called Juvenile onset Respiratory Recurrent Papillomatosis (JORRP) and Adult onset RRP (AORRP) respectively.

The JORRP exhibits a female preponderance while the AORRP is commoner in males, and tends to be less aggressive and less severe. [16,68]. The toll of the disease relates to its recurrence and the deleterious consequences of its morbidity, the financial concerns attendant on multiple hospitalizations and the emotional strain associated with any chronic problem.

Kenyatta National Hospital (KNH) is the only public health institution with facilities for management of RRP hence the majority of patients with RRP in Kenya are cared for in KNH, being the country's main referral health institution.
This study is an investigation of the status of this disease as it presents at Kenyatta National Hospital.

LITERATURE REVIEW

HISTORICAL BACKGROUND

RPP was first recognized by Mackenzie in 1871 when he described papillomas in the larynx of a child, thus coining the term Juvenile Laryngeal Papilloma (JLP).[1]

In 1928, Ullman first suggested the viral aetiology of this condition when he reported the experimental transmission of warts to the vagina of a dog and to his own arm using an extract of human laryngeal papilloma [2]

In the 1960's, it became apparent that the disease is not confined to the laryngeal mucosa only and does occur in other areas of the respiratory tract. Also the disease was found to be notriously recurrent and that it may persist, upto adulthood or even initially present in adult life. Thus RRP was found to be a more descriptive term. [2,3]

AETIOLOGY

RRP is caused by the Human Papilloma Virus (HPV) which is a small double stranded DNA virus 50 nm in diameter and consisting of a circular genome of approximately 8 Kb [2].

The HPV is a species – specific epitheliotrophic DNA virus with 8000 base pairs in a double – stranded circular DNA genome. HPV types are identified according to sequence homology, such that when there is less than 50% cross hybridization in liquid phase reassociation tests, a different sub type is designated [4]. Currently, more than 90 sub-types of HPV have been identified from the skin and mucous membranes[5]. All are epitheliotrophic, over half are associated with cutaneous disorders and the remainder associated with mucosal disease [4]. Each type has predilection for particular sites. For example, types 1,2,4,5 and 8 affect non-genital areas of the skin. Genital areas are affected by types 6,11,16,18,30 etc. HPV results in condylomatous, dysplastic and neoplastic changes in the skin and mucosal surfaces.[6]

Tumorgenicity

HPV types have often been divided into "oncogenic" (or High risk types) and "non-oncogenic" (or low risk types) based on the relative association of the HPV type with malignant transformation. The "High risk" HPV types include types 16, 18, 31, 33, 35, 45, 51, 52 and 56. The "Low risk" HPV types are 6, 11, 42, 43 and 44.

HPV types 6 and 11 are the causal agents of RPP. The HPV type 6 has further been subtyped from A – F. According to Mounts and Kashima [7] HPV –6C is the most common subtype in RRP and tends to be associated with more severe and extensive disease. HPV types 6 and 11 also cause warts on the penis, vulva, cervix, perianal areas and Schneiderian papillomas. An association between cervical HPV infection in the mother and the incidence of RRP's has been established [7].

HPV types 6 and 11 have been found in cervical condylomata and laryngeal papillomas. Initial evidence for this association was established by electron microscopy, immunocytochemistry and Southern blot technique. More recently, in-situ hybridization and polymerase chain reaction (PCR) techniques have confirmed the presence of HPV types 6 and 11 in recurrent laryngeal papillomas. The virus may be present not only in the papillomas, but also in apparently normal adjacent epithelium [8].

After infection the viral particles may remain in the basal layer of the mucous membrane replicating by a process known as episomal maintenance. As the cells of the basal layer differentiate, changes in the host cell allow the viral genes to be switched on (transcribed) and viral particles can be identified in the stratum – granulosum/corneum [2]

MODE OF TRANSMISSION

The most likely mode of transmission for JORRP is believed to be ingestion of viral particles or infected cells from the birth canal. In AORRP, the primary mode of transmission is believed to be sexual contact [9].

Various clinical studies have tried to link JORRP to mothers with genital HPV infections [2,10,11]. Cook et al reported an association of JORRP with maternal Condyloma at time of delivery. Strong et al reported that 50% of patients with RRP younger than 5 yrs were born to mothers with genital warts at the time of delivery . Hallden and Majmudar reported 54% while Quick et al reported 67% of children with RRP were born to mothers with genital warts.[10]
Condylomas in the male sexual partners were not recorded in any of these studies and subclinical disease was not investigated for in these studies.

HPV types 6 and11 are the predominant isolates from both genital warts and RRP and that the papilloma viruses from the larynx and genital tract are indistinguishable when looking at DNA sequencing, while RRP is rare in babies delivered by caeserian section (1 RRP in 109 deliveries[11]) which bypasses the area of maternal infection. This therefore suggests a vertical mode of transmission of JORRP. It has been further documented prospectively that vertical transmission of HPV to the new born oropharynx can occur at delivery. [11]
A lack of higher rate of correlation between maternal condylomata acuminata and JORRP may be due to a lack of documentation of the papillomas and the finding that some 20% of normal cervix without overt exophytic lesions may harbour HPV [11].

Some authors have suggested cesarian section for women with active HPV lesions at delivery (Bennett RS et al) [11,12]. However, this is not absolutely protective. There has been a report of an infant who developed RRP after being delivered by ceasarian section before rupture of the amniotic membranes, and HPV had been isolated from amniotic fluid [11]

These reports suggest that there maybe more than one mode of transmission of JORRP. It has also been found that siblings of children with RRP do not seem to have an increased risk of developing RRP. Thus the risk of vertical transmission is fairly low and has been estimated to be about one in 400 vaginal births in mothers with active condylomata (Shah et al, 1986)[10,11].

Currently, it is not well understood why RRP develop in so few children whose mothers have condyloma. Other factors such as patient immunity and local trauma have been postulated. [10]. Several patients with RRP born by ceaserian section have been suggesting an intrauterine transmission of HPV that would not have been prevented with cesarean section. This mode of transmission may result from an infection of the maternal lower genital tract that reaches the fetus while still in the uterus, or through blood borne (haematogeneous) transplacental intrauterine transmission. Sedlacek et al and Tseng et al have shown that asymptomatic pregnant women transmit HPV despite having negative cervical swabs, suggesting a haematogeneous route of spread. In the study by Tseng et al, seven neonates had HPV – positive cord blood samples. However, RRP did not develop in any of the newborns with positive HPV blood samples in either of these prospective studies[11].

Therefore, although maternal genital HPV infection is undoubtedly the reservour for JORRP, it is unclear which mothers would benefit from elective caesarian section to prevent transmission. Shah et al [12] showed that young primiparous mothers with condylomas are at a higher risk of transmission of JORRP to their infants and hence advocate the options of a ceaserian section to such mothers. However, since the morbidity and mortality of a cesarean section are much higher than that of a vaginal delivery, a finer definition of the risk factors associated with RRP is needed before cesarean delivery can be advocated to decrease the incidence of this disease.[10,13]

CLINICAL TRIAD OF JORRP

The clinical triad of a first-born delivered vaginally to a young (teenage) mother has been noted in JORRP [12,68]. Schneider et al have reported that the amount of viral DNA maybe increased during pregnancy. Transmission of HPV infection is influenced by three main factors.

1. Dose of infecting agent
2. Close and prolonged contact favouring transmission of the infectious agent.
3. Recipient susceptibility

In genital tract lesions caused by viruses, the highest levels of viral shedding occurs from recently acquired primary infections. Thus, HPV in genital lesions may be at the highest levels during the later stages of pregnancy, particularly among those who have recently acquired infections. The vaginally delivered newborn is exposed to HPV-infected secretions in the birth canal. This exposure maybe greater in those mothers having a prolonged second stage labour, which is common at first delivery. These considerations may help to explain the clinical triad noted in JORRP – i.e. why being a first born by vaginal route to a teenage mother is a risk factor for JORRP.

The manner in which AORRP is acquired is speculative. It is possible that it represents reactivation of aquiscent virus acquired at birth or due to oral contact with HPV infected genitals [6].

However, the clinical triad associated with JORRP has not been proven in AORRP, thus suggesting a different mode of transmission. Instead, a larger number of sexual partners and the practice of oral sex (oral genital contact) are the risk factors for AORRP. Homosexual preference and history of sexually transmitted diseases (STD's) do not appear to be risk factors in transmission of AORRP [6,68].

EPIDEMIOLOGY OF RRP

RRP is the most common benign neoplasm of the larynx in children and adults.[14] It has a worldwide distribution.

INCIDENCE

The incidence in the USA was stated as 7 per 100,000 per year by Strong et al 1976[2].In their 20 year (1965-1984) study of 2.8 million Danes, Elbrond et al calculated a 3.84 per 100,000 incidence rate. They further reported a juvenile onset rate of 3.62 per 100,000 and an adult onset rate of 3.94 per 100,000. In a study by Derkay, 1995 the incidence of paediatric RRP's was found to be 4.3 per 100,000 children younger than 14 years and the adult onset RRP to be about 1.8 per 100,000 of citizens older than 15 years in the USA. [10]

In a separate study by Derkay in the state of Virginia in USA an incidence of 4/100,000 for children and 1/100,000 for adults was found. Thus it is estimated that between 1500 to 2500 new cases occur in the USA each year (Strong et al 1976/Derkay, 1995)[2,10].

JORRP is commoner than AORPP with peaks at 2 and 11 years of age [15]. However, according to Woisard et al (1997) the incidence of AORRP seems to be increasing.

SEX INCIDENCE

In JORRP, there is a female preponderance. In AORRP, there is a male preponderance of about 3:1 [2,68].AORRP is usually first diagnosed in the fourth decade.[3]

GEOGRAPHICAL INCIDENCE

RPP is found worldwide. It affects all racial groups. It is found in all socioeconomic groups and is not confined to the disadvantaged as was previously claimed. [2,68]

CLINICAL FEATURES

In children, the symptoms of RRP can begin as early as 2 months of age with a majority (75%) being diagnosed by 5 years of age [11]. The initial symptom is hoarseness of voice, abnormal cry or voice change. Increasing stridor, wheezing and acute respiratory obstruction may occur but they are usually late manifestations of the disease process.

Papillomas usually form initially on the vocal cords, so interference with laryngeal function occurs early in the disease. Hence, hoarseness or wheezing not responsive to bronchodilators and steroids in a child should always be investigated.

The clinical presentation in AORRP is similar but is usually less aggressive, invasive and severe. [11,16]. In RRP, the larynx is affected in almost 100% of the cases, the majority involving the glottis, followed by supraglottis and subglottis. The trachea is the next most common site (Benjamin; Bent)[11]. Tracheal and pulmonary extension may be encountered. Distal spread of disease is particularly distressing owing to the difficulty in adequately removing the papillomas and ensuring a patent airway. Also the surgical trauma associated with excision leads to tumour implantation in distal sites, which may be beyond the reaches of endoscopy [17]. Reports show tracheal involvement to be as high as 17% to 26% of patients with RRP [11].

Tracheostomy greatly increases the chances of development of tracheal disease and seeding papillomas on the tracheostomy site. Hence, avoidance of tracheostomy is recommended if possible.

Lung parenchyma involvement is characterised by small homogeneous nodules and cavitary lesions of various thickness with a diameter of up to several centimetres. Pulmonary involvement leading to restrictive lung disease or pulmonary cystic disease carries significant morbidity but has fortunately been reported to occur in less than 1% (Kramer et al - 1985 Sadikot et al- 1997). [11]

Reports of oesophageal papillomas are rare, but in one series an 8% incidence of oesophageal papillomas was found (Benjamin - 1988) all of which resolved spontaneously. Irwin et al reported that in 78% of patients, papillomas had spread to regions separate from the original site of the lesion [11]. In more aggressive (or invasive) RRP, the papillomas may also extend upwards to invade the nasopharynx, tonsils, soft palate and oral cavity. [2,17].

Pneumothorax has been reported in RRP with extension to the lung parenchyma. It was noted that the multiple nodular and cystic lesions in the lung parenchyma resulted in the development of cystic pneumotoceles, presumably from the ball valve effect of a nodular lesion - this in turn resulting in the development of pneumothorax. (Anderson et al 1993). Other pulmonary lesions that have been found include:
Cystic pneumotoceles and abnormal air filled spaces reported by Kulman et al. 1993 on X-ray and CT scan. Kerley et al. 1989, have reported lung cavitation.
Thus, in the lungs, RRP produces cystic spaces that may be seen on X-ray. The cysts are lined with squamous epithelium and may be filled with fluid or air. The pulmonary spread is multicentric, relentlessly progressive and eventually fatal. [2,11,16].

DIAGNOSIS

1. High index of suspicion on basis of history.

2. Flexible fibre-optic endoscopy

3. Direct Laryngoscopy (D/L) with biopsy for definitive diagnosis.

Venturi jet systems of anaesthesia during D/L has been abandoned since it was found to blow viral particles and blood into the lower respiratory tract and hence increase risk of distal spread of RRP [18].

CHARACTERISTICS AND CLINICAL COURSE OF RRP

The papillomas of RRP are benign squamous papillomas that occur in clusters on the involved mucosa. The fronds of papillomas may be sessile and spread over a wide area of mucosa or they may be pedunculated and localised. Characteristically, the lesions are multiple however, occasionally at the onset of the disease or if the disease is about to become quiescent only a single lesion may manifest.

Thus grossly, papillomas appear as irregular, exophytic, pedunculated, nodular masses that may be single or multiple. They are pink to red, firm to palpation and may vary in size. They have a characteristic exophytic growth pattern with exuberant cauliflower like projections protruding into the laryngeal lumen. [19]

HISTOLOGY

Respiratory papillomas are projections of vascular connective tissue cores covered by stratified squamous epithelium and abnormal squamous keratinization is the norm. The histological lesions are classified as:

1. Condylomata - Papillary squamous lesions with squamous hyperplasia, koilocytosis and parakeratosis.

2. Squamous papillomata - Papillary squamous lesions with squamous hyperplasia and no koilocytosis.

SITES OF PREDILECTION IN RRP

Studies of sites of predilection for RRP have revealed that they tend to occur at the squamociliary junction (i.e. anatomic sites in which ciliated and squamous epithelia are juxtaposed.)

Thus the predominant sites of disease in RRP are the limen vestibuli, nasopharyngeal surface of the soft palate, mid zone of the laryngeal surface to the epiglottis, the upper and lower margins of the ventricle, the under surface of the vocal cords, the carina and bronchial spurs. These are sites that have the common histologic feature of a squamociliary junction.

Traumatized ciliated epithelium usually heals by becoming non-ciliated epithelium due to squamous metaplasia, resulting in an latrogenic squamociliary junction. This explains the recognised propensity of papillomas to recur in sites of previous excision or epithelial injury. Similarly, tracheostomy causes squamociliary junctions. This results in the commonly observed development of tracheal papillomas after tracheostomy.

The apparent preferential localisation of papilloma at squamociliary junctions has the following implications:

1. Detection of occult asymptomatic papillomata is enhanced by careful examination of squamociliary junctions.
2. Iatrogenic papilloma "implantation" is preventable by avoiding injury to non-diseased squamous and ciliated epithelia.
3. Tracheostomy should be avoided where possible. [20]

RECURRENCE

The lesions of RRP are notoriously recurrent even after the most radical extirpation. Recurrence may cause airway obstruction within 2 weeks of remission [21].

HPV DNA has been demonstrated in macroscopically normal laryngeal mucosa both in patients who are in remission (Steinberg et al – 1983) and in patients with active papillomatosis [22,23].

The actual infected tissue extends far beyond the clinically apparent laryngeal papillomas. According to Smith et al, HPV infection is present in clinically normal respiratory tract tissue and that the reservoir site of re-infection is commonly in the lower airway – trachea and bronchi [22].
Complete clinical remission of RRP does not require total eradication of viral DNA. Like Herpes simplex virus DNA, HPV DNA may remain silent during clinical remission, but it retains the potential to cause relapse in an immunocompromised host or after epithelial trauma. [20,24]

Sometimes, it appears that removal of the papillomas has an enhancing effect on the growth rate of the lesions, so that the recurrence may be larger than the original lesion. [2]. It has been presumed that there is some hormonal influence in the disease process of RRP. This is based on the observation that there is an increase in the growth rate of genital condylomata in association with pregnancy, (Bennett et al – 1987) and some cases of spontaneous regression are observed during puberty. However, most authors do not believe that there is any relationship between the rate of control or recurrence with the onset of puberty. [3,11,13]

REMISSION

Remission of RRP can take place at any age and at any time, whether remission occurs or not appears to be unrelated to the thoroughness of the removal or to the method of removal of the disease. The chance of remission is greatest if the disease presents between the ages of 6 and 10 years. The overall chance of achieving remission in patients less than 16 years of age at the time of presentation is 46% if they are followed for one year and treated by appropriate endoscopy and laser surgery. While for AORRP the overall chance of remission is 26%. The disease is more likely to undergo remission in the larynx (48%) than in the tracheobronchial tree (27%) or in the lungs (0%). [2]
The duration of remission varies from 2 years to lifelong. Relapses may occur at any time and for no apparent reason. Since a relapse may occur in any patient at any time, the best that can be hoped for at present is prolonged remission rather than a cure [2].

Unfortunately, RRP has the potential to spread in a small number of cases from the larynx to involve the tracheobronchial tree. This occurs in 11% of cases with the lung parenchyma involved in 3% of cases. [2].

PREDICTORS OF PROGNOSIS IN RRP

Characteristically, the clinical course in RRP is unpredictable. Some patients have a solitary lesion that responds to a few treatments while other patients have a more aggressive or invasive form characterised by frequent chronic recurrence, involvement of anatomical multiple sites, distal spread to the tracheobronchial tree and need for multiple surgical procedure [25].

Various studies have been done in attempts to link the clinical course and prognosis of RRP with the initial endoscopic findings [16]; Histological findings [24,26,27]; the Human papillomavirus subtype [7,28] and viral co-infections [29].

However, none of these studies were able to clearly identify those patients at risk for aggressive disease. According to Doyle et al [13] and Gabbott et al [15], early age at diagnosis (less than 4 years) and subglottic involvement may be independent predictors of aggressive disease.

Stern et al, [25] used flow cytometry to analyse nuclear DNA and determine S-phase fraction in RRP biopsy specimens obtained at presentation. They found that the S-Phase fraction was significantly higher in the initial biopsy specimen from patients who had an aggressive clinical course. Hence concluding that S-phase fraction may be predictive of aggressive disease but they need to do prospective studies to confirm this.

CLINICAL STAGING SYSTEM FOR RRP

Currently, there is no universally accepted staging system for RRP; several scoring and staging systems have been proposed. A staging system is beneficial since it would provide the clinician and RRP researcher with the following advantages:

1. Give an accurate evaluation of disease severity at any single observation.
2. Help to assess disease course/progression over time i.e. document the natural course of the disease and its prognosis.
3. Help to compare clinical data from different sources.
4. Help to accurately report the results of adjuvant therapies

The various proposed staging/grading systems include:

a) Kashima et al [30] staging system as part of the "papilloma study group" multi-institutional interferon study.

b) Lusk et al [31] proposed a staging system for estimating the volume of laryngeal papilloma occluding the glottis by dividing the right and left halves of the glottis into three equal parts.

c) Waitrak has proposed a RRP scoring scale, which is a modification of the Kahima method that incorporates more anatomical sites and a subjective severity rate. [33].

d) Zalzal and others have used an intraoperative laryngeal diagram to serially record disease involvement in their RRP patients. [33].

However, most of the above staging systems fail to consider disease outside the larynx, suffer from a high degree of potential subjectivity among observers and give little information about the clinical status of the patient.

The current and most reliable staging/severity scale is that proposed by Derkay et al [33] (June 1998): -

The surgeon assigns a score of 0 to 3 (0 = absent, 1 = surface lesion, 2 = raised lesion and 3 = bulky lesion) to each side of the aerodigestive tract. Summing the scores at each involved site generates a composite score. In addition, the surgeon denotes the laryngeal lesions on a standardized diagram - indicating sites of biopsy, laser /microforceps treatment, documents site in which adjuvant drug therapy has been administered and finally answers six questions regarding the patients clinical course (i.e. interval of surgery, total number of recent surgeries, urgency of this surgery, quality of voice, degree of stridor at time of surgery and degree of respiratory distress).

Summing the scores for each of the subjective assessments generates a clinical score. The severity rating (score) can also be automatically tabulated for the surgeon in the computerised version.

This staging/severity scale is fast, creates a record that accurately reflects disease status, assures complete data collection that is suitable for data analyses, and is sensitive enough to detect subtle changes over time in the patient's clinical status.

MALIGNANT TRANSFORMATION

Spontaneous malignant transformation of RRP to either squamous cell or verrucous carcinoma has been reported in the larynx and lung. [17]

Smoking and bleomycin administration are claimed to increase the risk of malignancy, while previous radiotherapy might increase this rate by up to 16 folds [34,35]. Survival after malignant transformation is reported to be very short.

There have been reports of malignant degeneration in RRP patients who have not received radiotherapy and do not smoke [11]. Carcinoma developing from pre-existing papilloma arises much earlier in irradiated patients (average duration of disease of 10yrs)

when compared with non-irradiated patients (average of 30yrs) .The irradiated patients have a much worse prognosis with the disease being fatal in most cases whereas most non-irradiated patients survive. Thus radiotherapy is contradicted in RRP. [36]

Cocarcinogens, host immunocompetence and duration of infection all play a role in malignant degeneration of RRP, but the exact understanding of the interaction of these factors is still limited. Malignant transformation is commoner in adults and higher in solitary lesions [37].

The risk of malignant transformation is very low especially in non-irradiated patients. It has been estimated by various researchers to be between 2% - 7% [34,35,37,38].
According to Lie et al [35] the average interval between the onset of papillomas and diagnosis of carcinoma is 24yrs. The precise mechanism of malignant transformation of RRP is still unknown.

The mechanism suggested to account for HPV oncogenesis has been the synthesis of an E6 viral oncoprotein, which binds to the wild type p53 (tumour suppressor gene) via an adenoside triphosphate (ATP) dependent step leading to p53 degradation and inactivity. Modulation of transcriptional regulatory function occurs with subsequent genomic instability or even elimination of p53 by proteolytic degradation.
The mutant p53 promotes tumour formation through loss of growth suppression. [39]

The p53 protein is a key element in cell cycle regulation and initiation of programmed cell death (apoptosis). The absence of a functional p53 protein leads to unregulated cell growth. The gene that encodes the p53 protein contains 11 exons and cancer associated mutations have been reported to occur in all but exon 1. The exons most commonly involved are 5,6,7 and 8. [40]

MANAGEMENT OF RRP

Currently there is no therapeutic regime that completely cures RRP. The current therapeutic modalities of RRP stress for the maintenance of a patent airway and acceptable voice while preventing complications.

The mainstay of treatment for RRP is surgical extirpation, but various medical treatment regimes have also been tried.

SURGICAL THERAPY

The following surgical treatments have been used in the removal of RRP:-

1. Thermal cautery
2. Cryosurgery
3. Ultrasound
4. Cold instrument surgery using microlaryngoscopy and cupped forceps for the removal of papillomas.
5. Laser surgery

Surgical therapy should be based on the principle of preservation of non-diseased tissue to prevent the complication of laryngeal stenosis while attempting total removal of papillomas. Presently the procedure of choice is microsuspension laryngoscopy with CO_2 laser and /or microforceps to remove papillomas.

The advantage of laser is its superior precision and greater expediency of removal of disease and the inherent haemostatic properties of the laser. This allows vapourization of the papillomas while preserving normal tissue architecture. Microforceps are used for the biopsy and for removing the bulk of the disease.

A thorough knowledge of laser application has resulted in fewer complications associated with laser use such as airway fires, pneumothorax and anaesthetic complications. An additional hazard to theatre personnel maybe the inhalation of smoke generated by the laser, which contains HPV DNA. [41]

However, there have been reports of delayed local tissue damage associated with laser use. One animal study showed that the CO_2 laser ablation caused longer healing and denser fibrosis in comparison with microforceps. [41]. Most of the problems involve the delayed formation of laryngeal webs. Both Crockett et al [42] and Wetmore et al [43], report delayed tissue complications in about 35% of cases. The most common area affected is the anterior commissure followed by posterior commissure webs, vocal cord scarring and inter-arytenoid bands. The data of Crockett et al suggest that the number of laser surgeries and the severity of disease had a linear relationship to the frequency and severity of complications.

In order to reduce the scarring and complications of latrogenic airway stenosis to a minimum, great care should be taken by the endoscopist to try to avoid damage to the underlying and adjacent mucous membranes, with the avoidance of exposure to the vocalis muscle. [2]

Papillomas at the anterior commissure are particularly prone to produce scarring, so treatments should be separated by a month and only one cord treated at a time. Low power settings (1-3 watts) with the laser in intermittent mode or the newer microspot (0.3mm) laser also help to reduce scarring and web formation [44,45]. Presently, the 585-nanometer pulsed dye laser (PDL) has been shown to treat RRP with less tissue damage than the CO_2 laser [46].

The treatment of lower airway RRP is extremely difficult. Bergler et al [47] report the use of argon plasma coagulation (APC) with flexible endoscopy to treat lower airway RRP. The APC is said to give controlled limited penetration into the tissues and good control of bleeding with no carbonization or vapourization, which is essential in the treatment of lower airway RRP.

Pierce et al [48] have reported treatment of tracheal papillomatosis by endobronchial resection using a Neodymium Yag laser. Matt et al [18] have reported the use of a modified Healy Jako subglottoscope with CO_2 laser for treating tracheal disease. They claim that this system provides for easier access to the carina and main-stem bronchi than a laser bronchoscope.

However, even with the removal of all clinically evident papillomas, latent viral tissue may remain which explains the recurrent nature of RRP. Therefore, the aim of therapy in extensive disease should be to reduce the tumour burden, decrease the spread of disease, create a safe and patent airway, improve voice quality and increase time interval between surgical procedures. Future curative therapy of RRP will probably include the laser for management of the airway coupled with effective forms of adjuvant medical therapy.

MEDICAL TREATMENT OF RRP

The variety of attempts at medical control of this disease reflects the difficulty in determining its definitive curative therapy. Therapeutic trials to control the underlying viral infection have included radiation therapy, anti-viral and immunomodulating agents, Indole-3-carbinol, interferons and photodynamic therapy.

Radiation Therapy

It is no longer used due to the risk of inducing malignant disease. [34,35,49]
Radiotherapy may increase this rate by up to 16 folds.

Indole -3- carbinol therapy

Indole - 3 - carbinol is a chemical found in high concentrations in cruciferous vegetables. It has been shown to alter the growth pattern of RRP cell cultures and to be effective in an in vivo animal model of RRP.

According to Rosen et al, 66% of patients in their study responded favourably to indole 3-carbinol therapy with no significant complications noted. [50]

Indole-3-carbinol affects the ratio of hydroxylation of estradiol. Changes in the ratios of urinary 2-hydroxylation and 16-Hydroxylation of estradiol caused by indole-3- carbinol correlated well with clinical response. However, more studies are needed for further evaluation of the efficacy of Indole-3-carbinol therapy in RRP. [50]

Antiviral Agents

After a report of an apparent success with acyclovir in three RRP patients by Aguado et al [51], Morrison et al [52] tried acyclovir in four patients and concluded that acyclovir does not influence the RRP disease process. They stated that Papilloma viruses lack the key enzyme, Thymine Kinase that is necessary for the acyclovir activity. They therefore, do not recommend use of acyclovir in RRP.

Another antiviral agent, Ribavirin in an aerosol form, was used to treat a child with RRP involving the tracheobronchial tree, and it resulted in a significant reduction in the frequency of therapeutic endoscopies.

Other immunomodulating agents and anti-viral agents tried in the therapy of RRP are Inosine Pranobex [53], Adenine arabenoside [54], 5-Fluorouracil [22], Methotrexate and lysozyme Chlorhydrate [62].

While some of these drugs may have had a beneficial adjuvant effect, none has been established as having a major role in the treatment of RRP. Hence the use of antiviral and Immunomodulating agents in RRP requires more investigation.

Interferons

Human leukocyte interferon-alpha has been used most often in RRP. Preliminary reports in the early 1980's were quite encouraging [56,57,58]. Several prospective studies using interferon in association with the carbon dioxide laser found a mixed response. Those patients who benefited experienced either complete eradication of the disease or a decrease in tumour growth and a resultant reduction in the number of surgical procedures necessary to control the disease. [59,60]

Healy reported results from a multi-institutional study that showed that human leukocyte interferon helps to control disease in the first 3 to 6 months of treatment but that the effectiveness is questionable after 6 months of treatment. A different study group using lymphoblastoid interferon found that the response lasts beyond the 6 months and the response can be re-introduced after a period of non-treatment with interferon. [61,62]

The difference in the response was attributed to the three-times higher dosages of interferon. Mullooly and associates [63] also observed the dose related response of RRP to interferons. It is still not clear which mechanism of action interferons have against RRP. Recent data showed that HPV and DNA are not inhibited by interferon in those patients having recurrence during therapy [23]. Also, latent infection is not eliminated by interferon.

Toxicities associated with interferon include acute reactions - fever, chills, headache, myalgia and nausea that decrease with prolonged therapy. Chronic effect of decreased child growth rate is abolished once therapy is ceased. Other reactions include leukopenia, thrombocytopenia, skin rashes, alopecia, pruritus, systemic lupus erythematous and fatigue, which appear to be dose related. [64]
Therefore, the response to interferon is variable but it retards growth of papillomas in some patients especially in the first 6 months. Its role is in the treatment of recalcitrant RRP as an adjuvant to the surgical therapy.

Photodynamic Therapy (PDT)

Photodynamic therapy (PDT) using Dihematoporphyrin ether (DHE) was originally developed as a cancer treatment. The photosensitizer (DHE) is selectively localized and retained in hyperplastic and neoplastic tissues. When activated by laser light at the appropriate wavelength (630nm), DHE produces cytotoxic agents that selectively destroy cells containing the substance.

Utilizing a rabbit model, Shikowitz et al [65] were the first to demonstrate the effect of PDT on viral induced papilloma lesions. Basheda and associates reported on a 13-year-old patient with endobronchial and parenchymal disease and found that PDT was effective in regressing the endobronchial lesions but not the parenchymal lesions.
In studying 33 RRP patients treated with PDT, Abramson et al [24] found that there was a significant reduction in the average rate of papillomatous growth, especially in those with the worst disease. However, latent infection with HPV was noted to persist in clinically normal tissue after the PDT.

Mullooly et al [63] found that the only side effect of PDT in 26 patients who received DHE was photosensitivity, which usually occurred within 2 weeks of therapy but can occur as long as 8 weeks after therapy. Other reported side effects of PDT are hypersensitive skin reactions, local oedema, nausea, a metallic taste, liver toxicity, anaphylaxis and clinical exacerbation of systemic lupus erythematous. [66]

Shikowitz et al [65] demonstrated that PDT-DHE is a promising treatment of RRP. Using Laser light dose of 50J at 630nm from an Argon pump dye laser and DHE at an optimized dose of 4.25 mg/kg, they obtained a reduction in recurrence rate of 50%. However, the biological basis for the change in recurrence rate of RRP after PDT is not yet known. The parameters that determine whether an individual patient will respond are unclear. Studies of PDT for RRP using a new photosensitizer, meso-tetra (hydroxyphenyl) Chlorine (MTHPC) has shown great potential.

JUSTIFICATION OF THE STUDY

Recurrent respiratory papillomatosis is one of the commonest causes of upper airway obstruction in children seen in the ENT department at KNH and often requiring emergency surgical intervention. Also due to its recurrent nature and causation of hoarseness of voice, it gives significant morbidity and distress to the patient. There has been no clinical study of this condition at the KNH that would help in formulating an appropriate management protocol. This study aims to fill that void.

AIMS AND OBJECTIVES

OVERALL AIM

This study is intended to provide information about recurrent respiratory papillomatosis at the Kenyatta National Hospital as a retrospective survey of all recorded cases from January 1990 to December 1999.

OBJECTIVES

1. To determine the epidemiological data of patients with RRP namely:
   a) Age of onset
   b) Sex
   c) Geographical distribution
   d) Birth rank
2. To determine the presenting signs and symptoms of the disease and their duration.
3. To determine the number and frequency of recurrences and average remission time.
4. To determine the sites involved by the papillomas in the respiratory tract.
5. To determine the number and frequency of operations needed to control the disease and treatment mode.
6. To determine the complications of RRP and the complications arising from the treatment of this disease.
7. To compare all the above information with that of other institutions worldwide.

MATERIALS AND METHODS

Study Design

This is a retrospective study of all available clinical records of patients with recurrent respiratory papillomatosis at the Kenyatta National Hospital from January 1990 to December 1999.

Data collection was from clinical records as follows:

1. Patients files from the KNH medical records department.
2. Operating theatre records
3. Admission records in the ENT wards
4. Pathology records.

The following information was extracted from the clinical records:

1. All personal data
2. Presenting signs and symptoms and their duration.
3. Past medical and relevant family history.
4. Sites involved
5. Investigations done and results.
6. Management and number of operations done.
7. Complications

The information so obtained was entered into a proforma form to facilitate easier analysis of data. (Appendix)

Ethical Consideration

Permission to carry out the study was obtained from the ethical and research committee of Kenyatta National Hospital. Information collected in the course of this study will be handled confidentially.

Sample Size

The entire population of patients with a diagnosis of RRP over the study period (1990-1999) was included in the study so no special sampling methods were used.

Inclusion and Exclusion Criteria

Patients with a positive histological diagnosis or suggestive case history and D/L findings of RRP were included in the study.

Other causes of hoarseness or respiratory obstruction like malignant tumours of the larynx, laryngomalacia, vocal cord paralysis et cetera were excluded from the study.

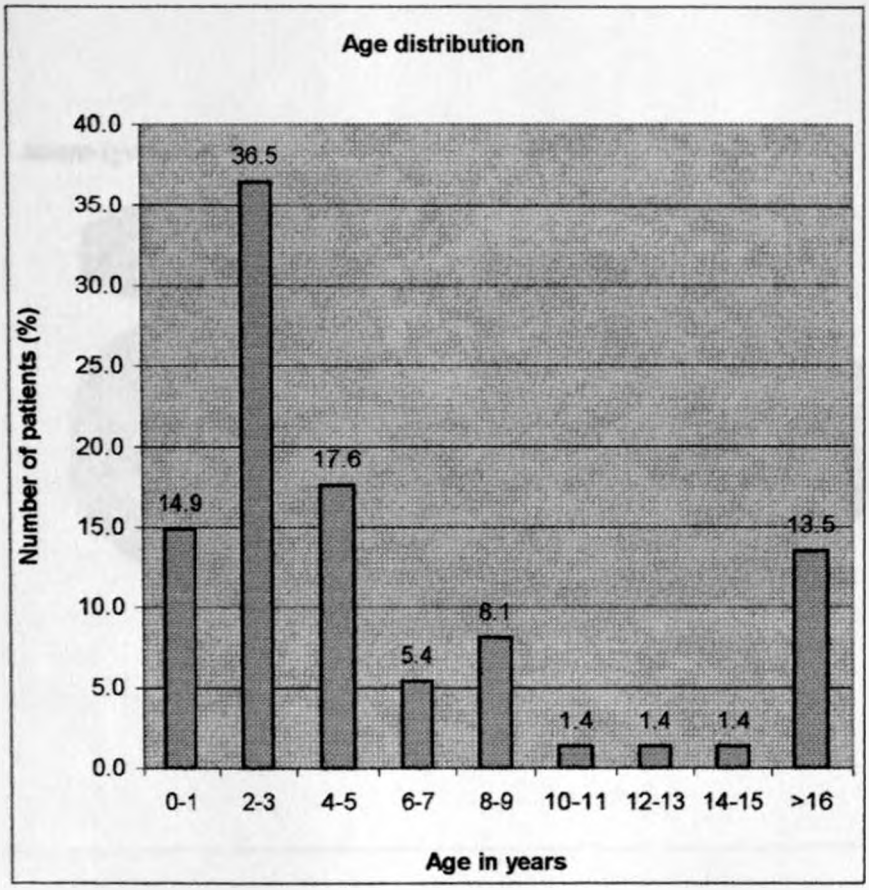
RESULTS

Table 1: Distribution of patients according to year of first presentation

Year	Number of Patients	Percent
1990	9	12.2
1991	4	5.4
1992	5	6.8
1993	6	8.1
1994	6	8.1
1995	7	9.5
1996	8	10.8
1997	7	9.5
1998	13	17.6
1999	9	12.2
Total	**74**	**100.0**

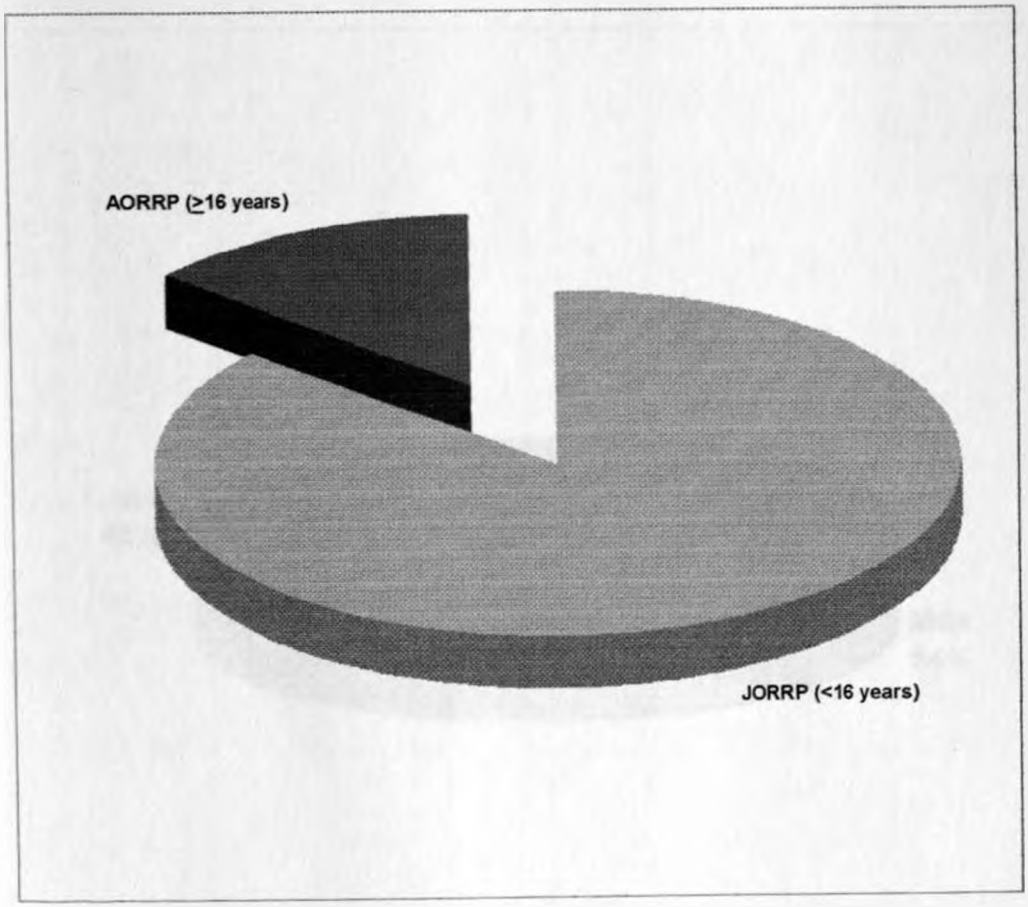
The distribution of RRP patients according to year of first presentation is as shown. 1998 recorded the highest number of new patients at 17.6% while 1991 the least at 5.4%. On average seven new patients are seen per year.

Figure 1: Age distribution



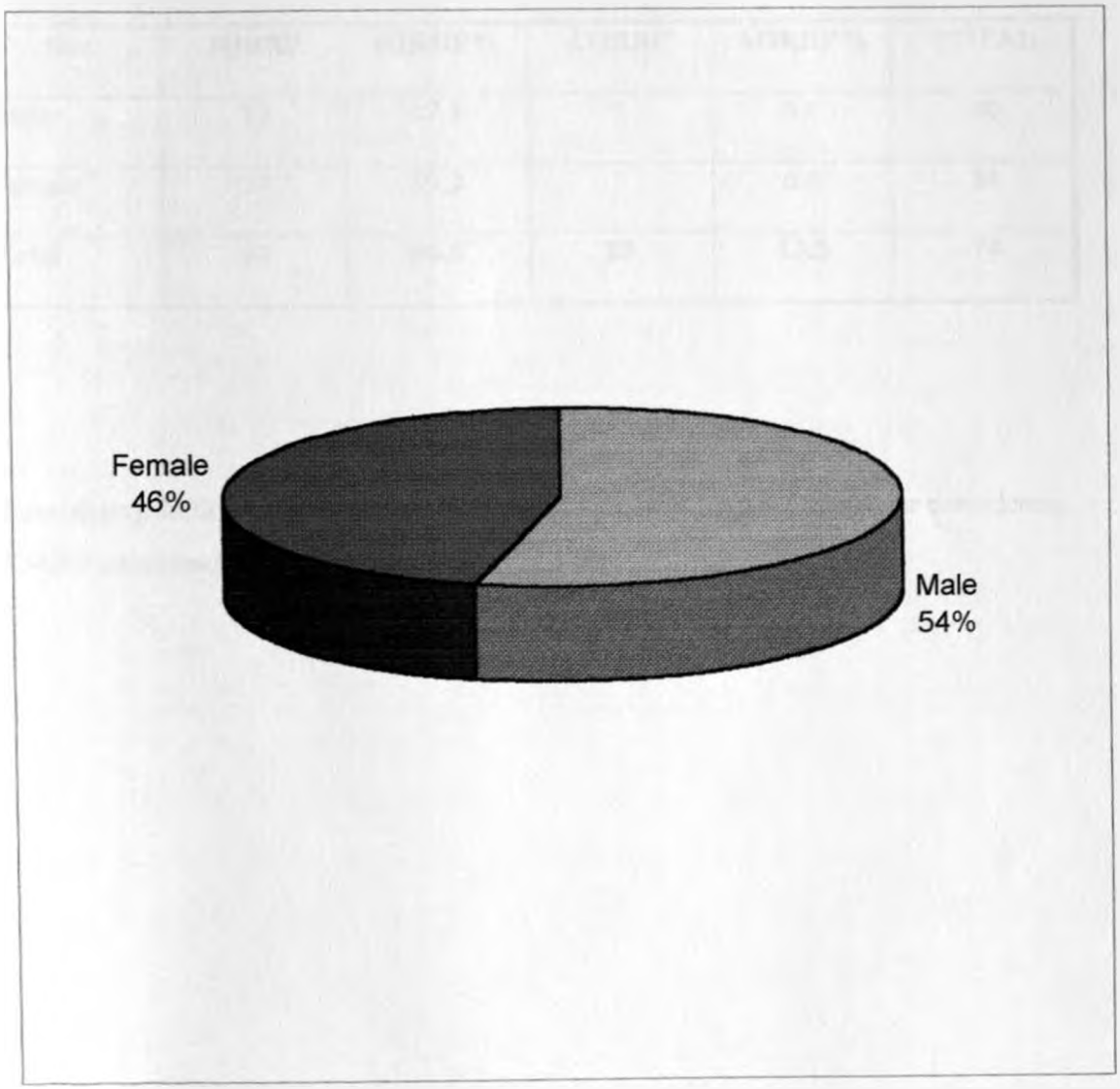
The patient's ages of onset ranged from 4 months to 34 years. Most patients (36.5%) presented within the 2-3 years age group. Majority of patients (69%) presented before six years of age.

Figure 2: Types of RRP



The majority of cases are of JORRP (< 16 years) at 86.5% while AORRP (>=16 years) cases comprised 13.5%.

Figure 3: Sex Distribution



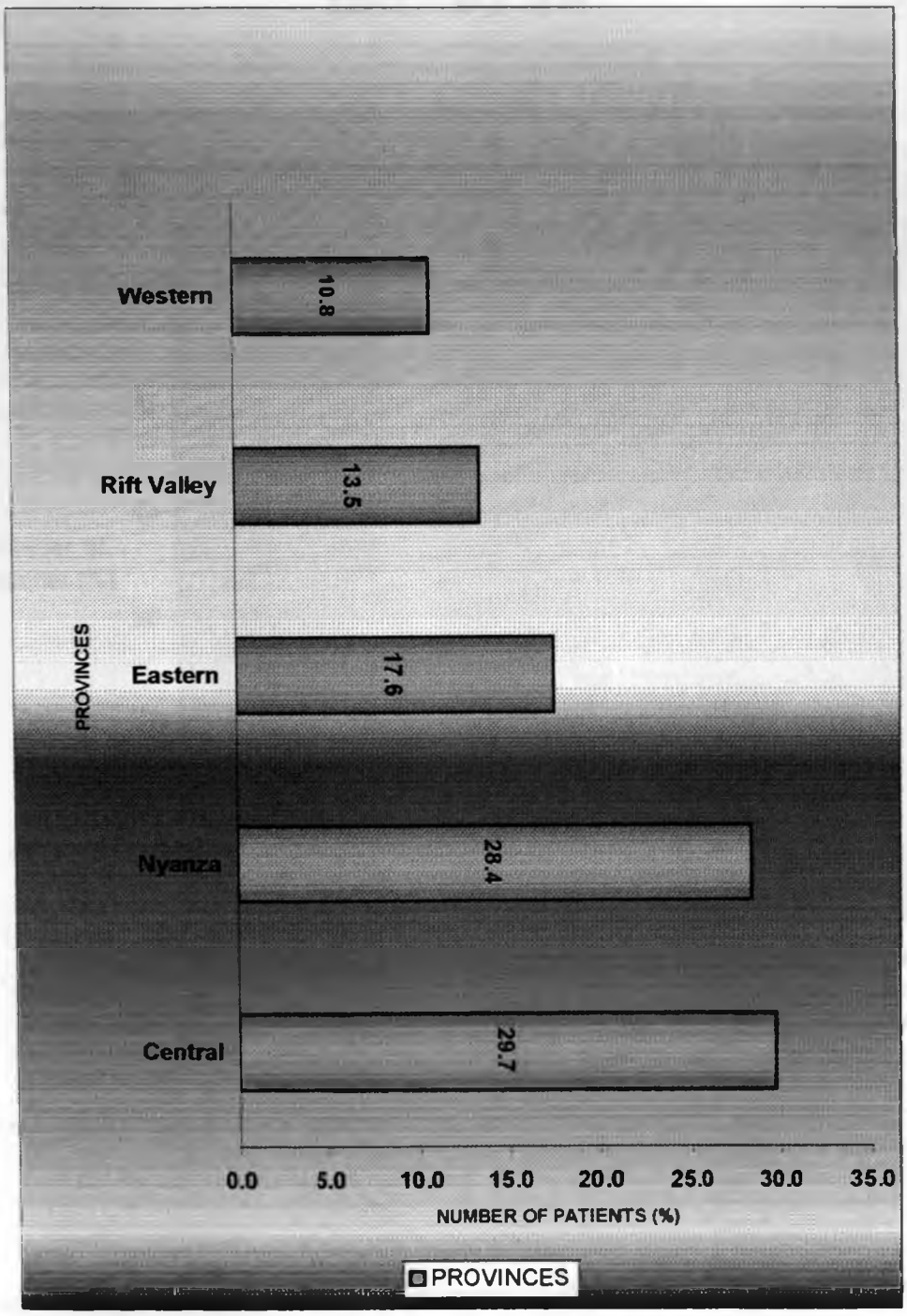
Sex distribution shows a male prepondence at 1.2:1 ratio.

Table 2: Age of Onset and Sex Distribution

Sex	JORRP	JORRP%	AORRP	AORRP%	TOTAL
Male	35	47.3	5	6.8	40
Female	29	39.2	5	6.8	34
Total	**64**	**86.5**	**10**	**13.5**	**74**

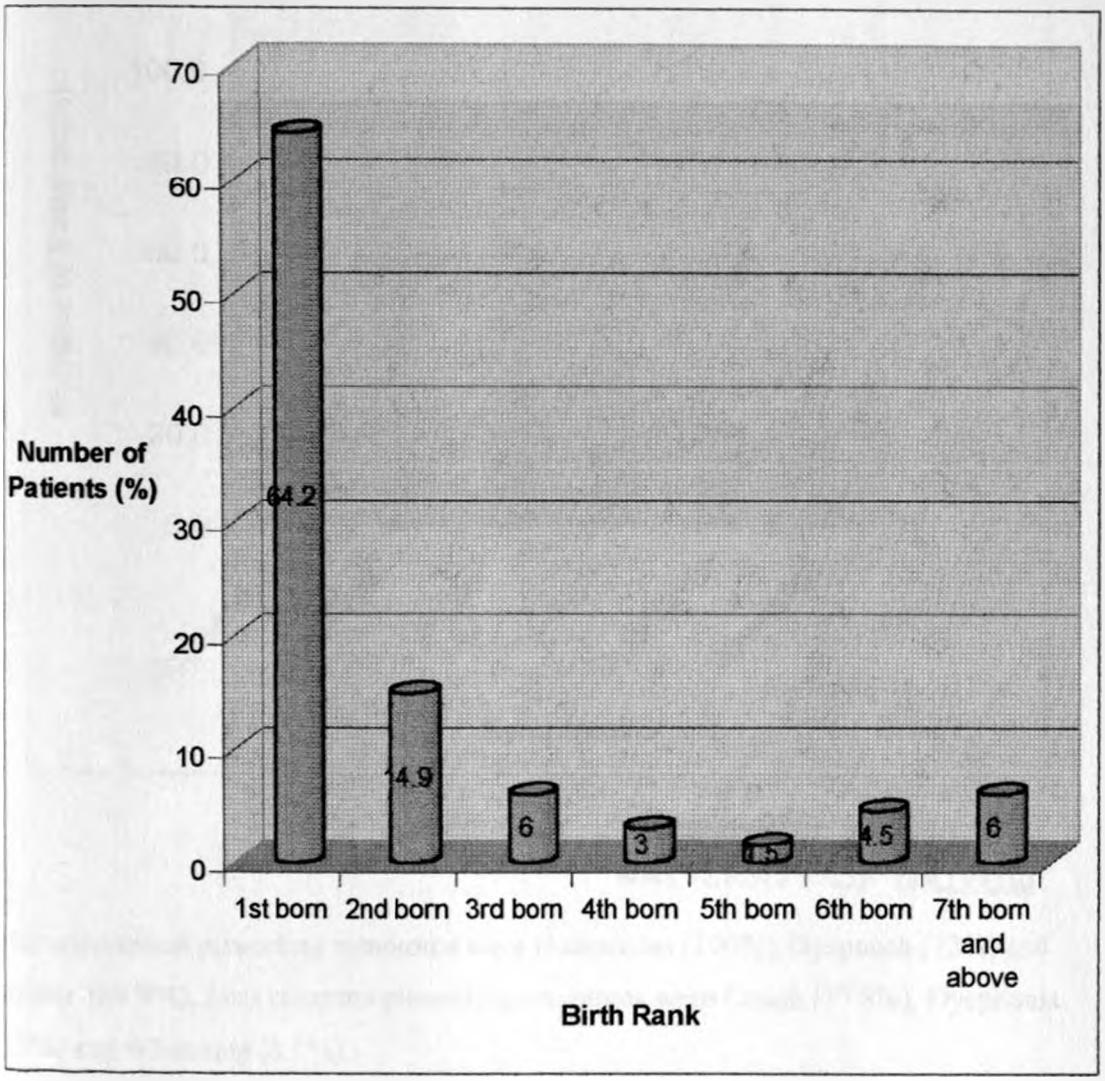
Considering AORRP alone, the sex distribution ratio of M: F is 1:1. However considering JORRP alone sex distribution ratio of M: F is 1.2:1.

Figure 4:Geographical Distribution (Provinces)



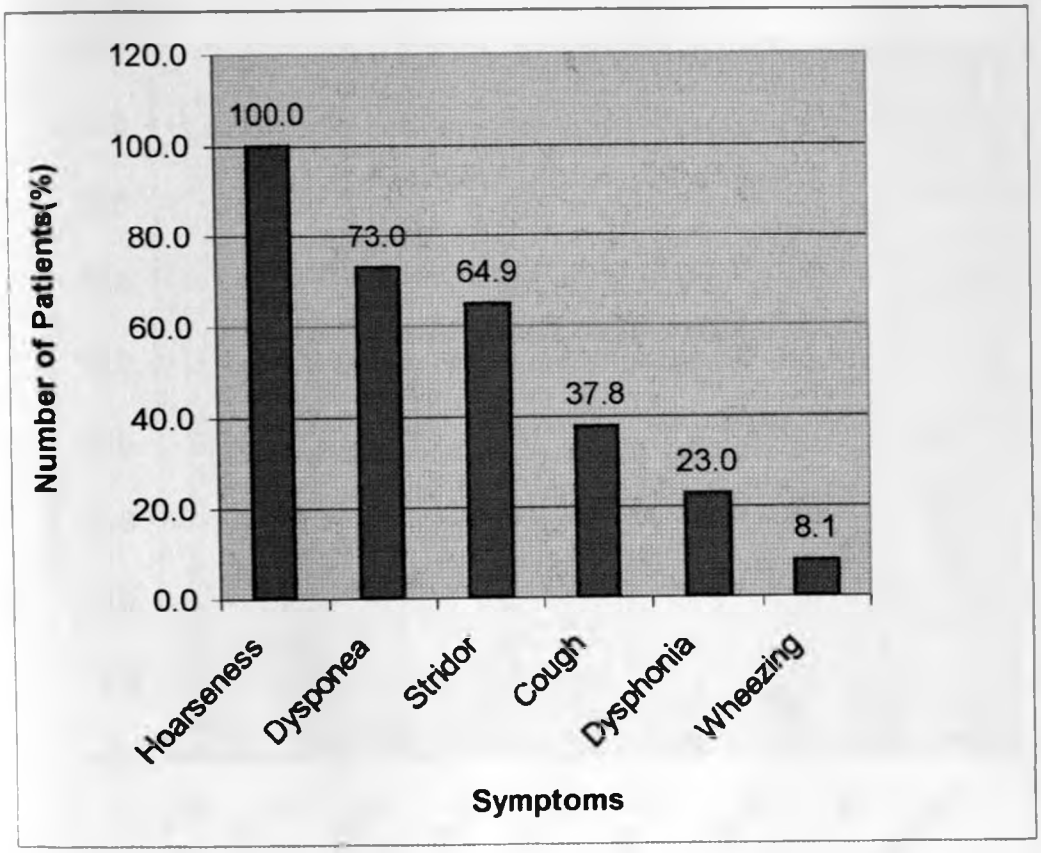
The provinces with the highest number of cases are Central (29.7%) and Nyanza (28.4%). Western province has the lowest number of cases at 10.8%.

Figure 5: Birth Rank



Sixty-seven patients had their birth rank indicated of which the majority were first born at 64.2%.

Figure 6: Presenting symptoms

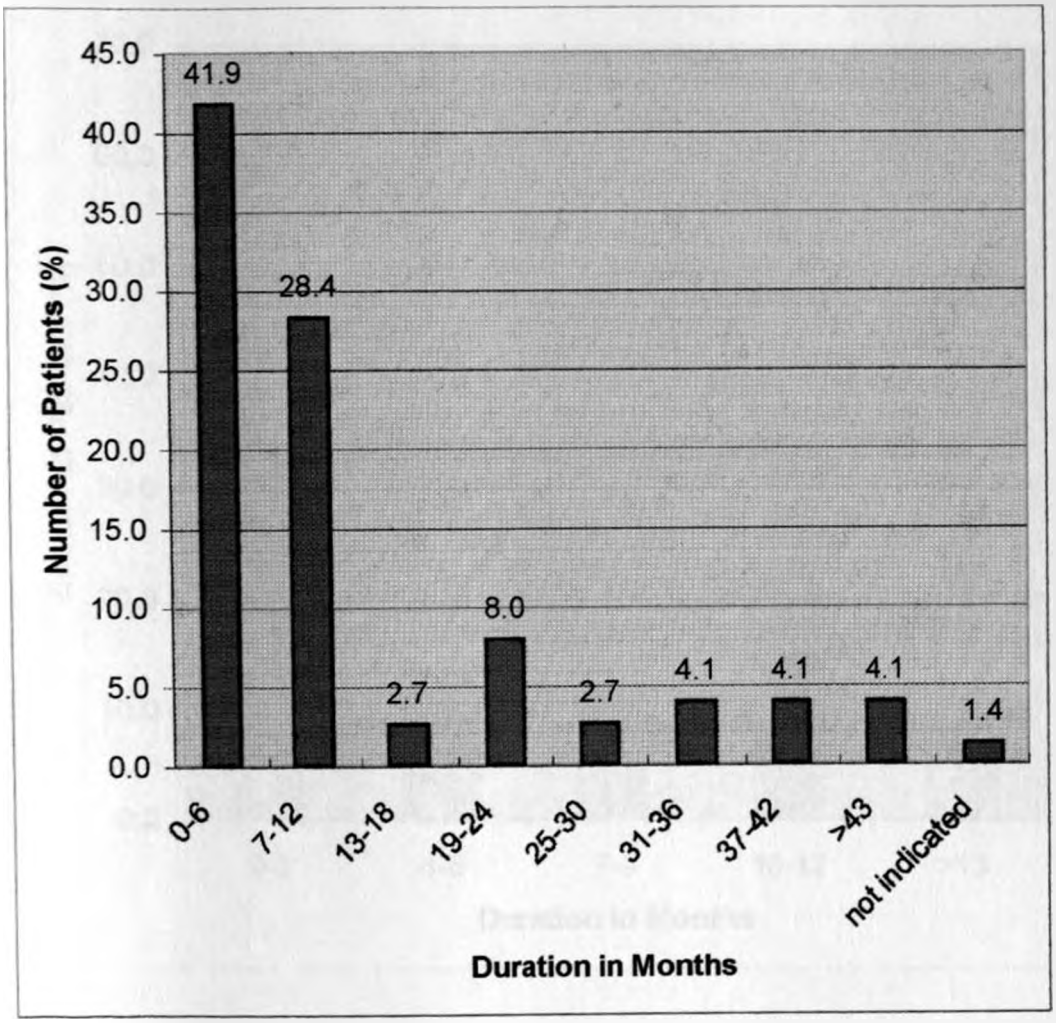


The commonest presenting symptoms were Hoarseness (100%), Dyspnoea (73%) and Stridor (64.9%). Less common presenting symptoms were Cough (37.8%), Dysphonia (23%) and Wheezing (8.1%).

Dysphonia included descriptions such as intermittent loss of voice, abnormal cry or voice change as recorded in the case files.

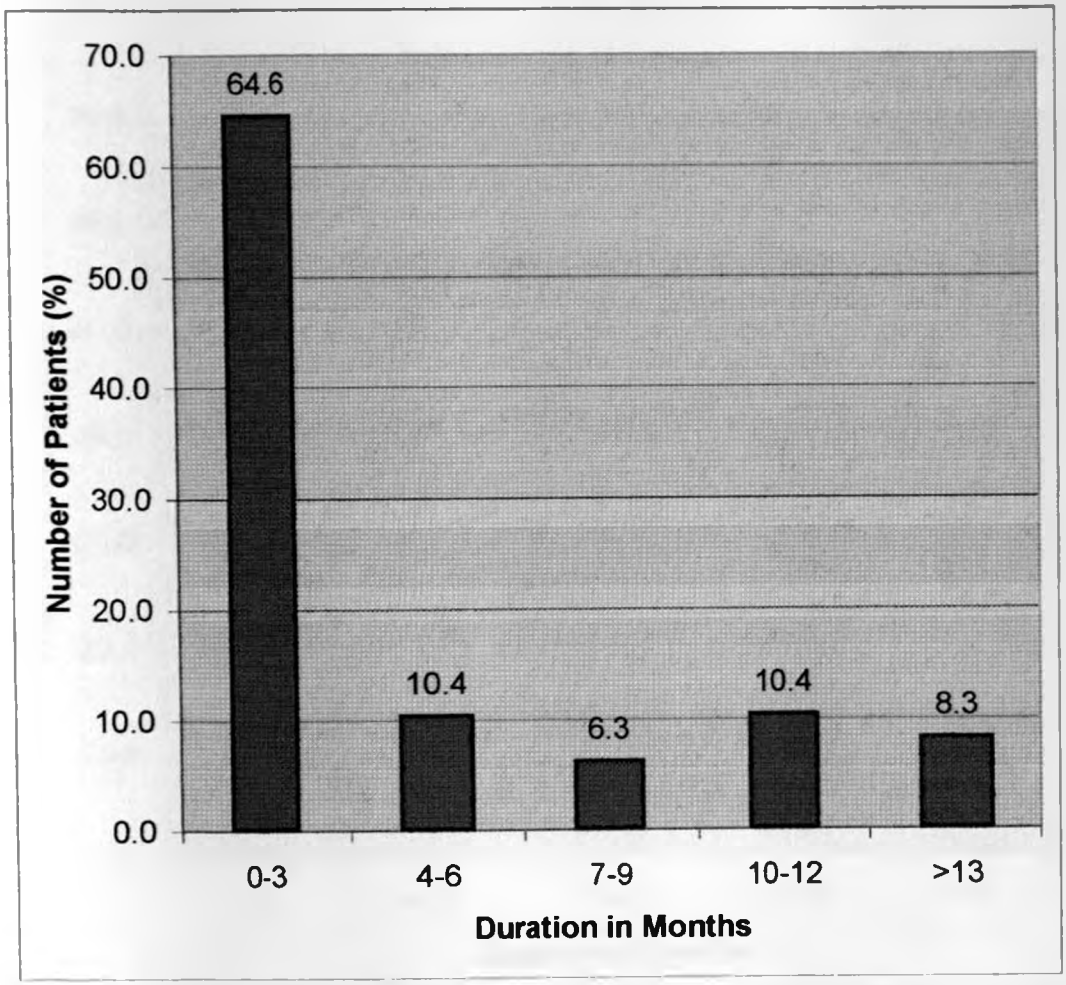
All patients with stridor also presented with difficulty in breathing (dyspnoea).

Figure 7: Duration of Hoarseness



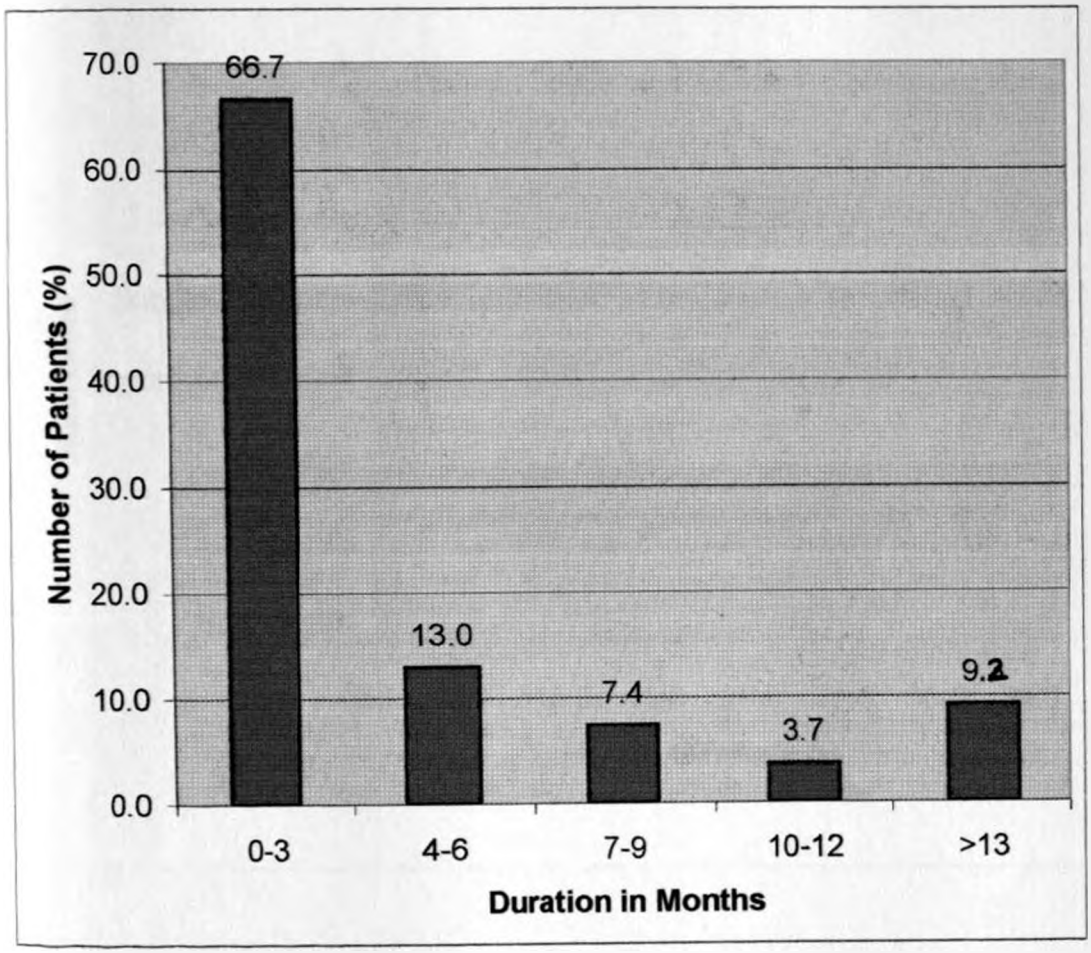
All patients with RRP presented with hoarseness of varying duration. 70% of patients presented with hoarseness of less than one-year duration before seeking treatment. In one patient (1.4%) duration of hoarseness was not indicated.

Figure 8: Duration of Stridor



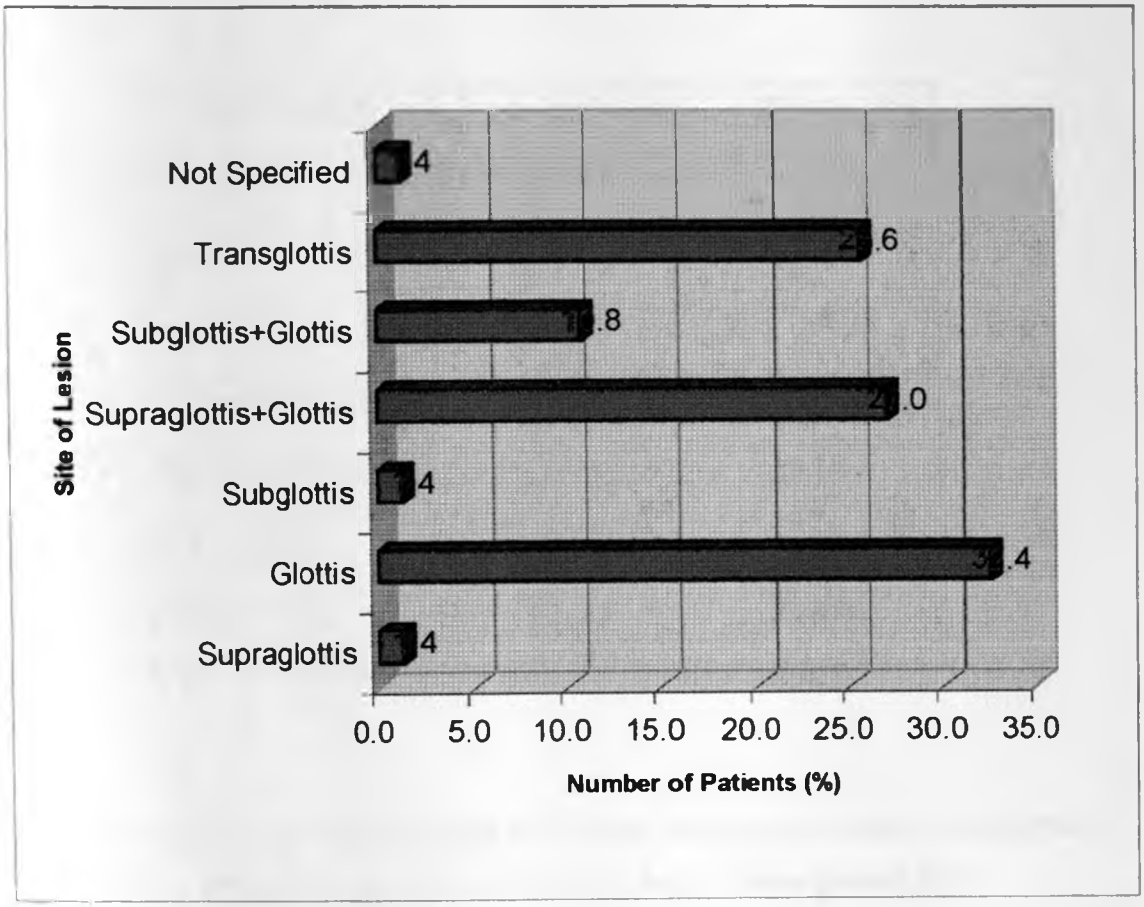
A total of 48 patients (65%) presented with stridor. A majority (75%) of these patients presented with stridor of up to six-months duration. Four patients (8.3%) presented with stridor of more than one-year duration before coming for treatment.

Figure 9: Duration of Dyspnoea



A total of 54 patients (73%) were noted to have difficulty in breathing of varying severity. Of these 80% presented within six-months duration. Five patients (9.2%) presented with dyspnoea after one year. These were patients who had previously been misdiagnosed as having asthma and had been on various bronchodilators before presenting to the ENT unit.

Figure 10: Site of Papillomas in the Larynx at first D/L assessment



The glottis was the commonest site of involvement by the papillomas in the larynx with 32.4% having involvement of the glottis alone. The total involvement of the glottis including other laryngeal sites was 95.8%. Involvement of the supraglottis and subglottis by the papillomas alone without involvement of glottis was rare at 1.4% each. Glottic and supraglottic involvement was the second commonest at 27%. This was followed by transglottic involvement at 25.6%. Glottic and subglottic involvement was 10.8%. In one patient (1.4%) the site of papillomas were not specified and no diagram shown. In the glottis most of the papillomas were found at the anterior commissure with less involvement of the posterior commissure and arytenoids. There was no right or left predilection of the papillomas in the larynx.

Table 3: Site of Papillomas in the Larynx at subsequent D/L assessment

Site of Lesion	No. of Patients	Percent (%)
Supraglottis	Nil	0.0
Glottis	4	10.8
Subglottis	Nil	0.0
Supraglottis + Glottis	12	32.5
Glottis + Subglottis	5	13.5
Transglottis	15	43.2
TOTAL	**37**	**100.0**

Thirty seven patients required more than one D/L assessment and excision of papillomas done mainly to manage the respiratory obstruction. Most of these patients had transglottic involvement at 43.2% . Glottic involvement alone was the least at 10.8%. No involvement of the Supraglottis and Subglottis alone was noted at subsequent D/L assessment.

Table 4: Other Sites of Papillomas in the Respiratory Tract

Site of Lesion	Number of Patients	Percent
Nose	1	1.35
Palate	2	2.7
Pharynx	2	2.7
Tracheostomy Stoma	1	1.35
Hypopharynx	1	1.35
Trachea	1	1.35
Uvula & Hypopharynx	1	1.35
Tracheostomy Stoma, Uvula & Oesophagus	1	1.35
TOTAL	**10**	**13.5**

13.5% of patients were noted to have papillomas in other extra laryngeal sites as shown above. One patient (1.35%) was found to have florid papillomas involving the tracheostomy stoma, uvula and oesophagus. Two patients (2.7%) had involvement of more than one extra-laryngeal site.

Table 5: Histological Diagnosis

Histological Diagnosis	Number of Patients	Percent
Histology report of RRP	64	86.5
Squamous cell carcinoma	1	1.4
Not indicated	9	12.1
TOTAL	**74**	**100.0**

Specimens with histology reports were mainly reported as:

- Simple papillomatosis
- Juvenile laryngeal papillomas
- Multiple papillomata
- Squamous laryngeal papillomas

One patient (1.4%) was noted to have an initial positive report for RRP but later underwent malignant transformation to squamous cell carcinoma of the larynx after a duration of one year. Sixty-four patients (86.5%) had histology reports in their case files. For nine patients (12.1%) the histology report could not be traced in the files although the whole case history and D/L findings confirmed RRP. In most repeated cases of papilloma excision, repeat biopsies for histology were not undertaken.

Family History of Similar Disease

Seventy-two patients (97.3%) had no positive family history of RRP among the siblings or in any other close relatives. For two patients (2.7%) this information was not indicated in the case files.

Table 6: Number of D/L+Papilloma excisions done

Number of Papilloma excisions	Number of patients	Percent
1	37	50.0
2	20	27.0
3	6	8.1
4	2	2.7
5	3	4.1
6	1	1.4
7	1	1.4
9	1	1.4
11	1	1.4
13	1	1.4
16	1	1.4
Total	**74**	**100**

Thirty-seven patients (50%) had one D/L and papilloma excision over the study period. The remaining 50% of patients required various numbers of papilloma excisions to treat the respiratory obstruction due to recurrent papillomas, with a maximum of 16 Direct Laryngoscopies and papilloma excisions performed over the study period. The average number of D/L and papilloma excisions required to manage the airway were between 2-3 excisions.

Table 7: Age of presentation versus average number of papilloma excisions done

Age of Presentation (years)	Number of patients	Total number of excisions done	Average number of excisions done
0-3	23	73	3.2
4-6	27	60	2.2
7-9	10	18	1.8
10-12	2	3	1.5
13-15	2	2	1
>16	10	13	1.3

Average number of papilloma excisions for JORRP was 2.4 while for AORRP was 1.3. The age group between 0-3 years had the highest average number of papilloma excisions at 3.2. There was a gradual decline in the average number of papilloma excisions done with increasing age of presentation as shown above.

Table 8: Duration between consecutive Papilloma excisions

Duration between consecutive papilloma excisions	Shortest duration (days)	Longest duration (months)	Average duration (months)
1st - 2nd surgery	19	72	10.7
2nd-3rd surgery	20	58	7.8
3rd - 4th surgery	16	9	2.8
4th - 5th surgery	5	7	2.5
5th - 6th surgery	15	8	3.1
6th - 7th surgery	26	6	3.5
7th - 8th surgery	54	5.7	3.8
8th - 9th surgery	24	3.3	2.1

The longest remission time between consecutive surgeries was found to be 72 months. This was between the first and second papilloma excision. The shortest duration between consecutive surgeries (4th-5th) was found to be five days, probably due to residual papillomas. On average, the duration between consecutive surgeries tends to be longer in patients with less active disease i.e. those requiring less than 3 papillomas excisions. Patients with more florid and active disease have shorter remission times and require more papilloma excisions to keep the airway patent.

Table 9: Number of Tracheostomies done

Place of tracheostomy	Number of Patients	Percent
KNH (ENT Unit)	9	12.2
Nyanza (PGH)	5	6.7
Maua Hospital	1	1.4
Total	**15**	**20.3**

Tracheostomy was done on 15 patients (20.3%). Six patients had their tracheostomy done in the referring institution as shown above. Of the patients done tracheostomy, eight patients (53%) underwent successful tracheostomy decannulation while seven patients (47%) were not yet decannulated during the study period.

The shortest period before decannulation was 27 days while the longest was found to be 60 months. An average of 10.8 months was found as the duration between tracheostomy and decannulation in those patients where it was possible.

Table 10: Complications

Complication	Number of Patients	Percent
Persistent tracheostomy stoma	1	1.4
Pulmonary hypertension	1	1.4
Glottis stenosis	2	2.7
Subglottic stenosis	1	1.4
Malignant transformation	1	1.4
Total	**6**	**8.1**

Six patients (8.1%) developed complications as shown in table 10.

Three patients (4.1%) developed laryngeal stenosis after many repeated papilloma excisions. They are all on tracheostomies and have not yet been decannulated. One patient (1.4%) a 19-year-old male patient underwent malignant transformation of the laryngeal papillomas to moderately differentiated squamous cell carcinoma of the larynx after a duration of one year.

DISCUSSION

On average 7 to 8 new patients with RRP are seen at KNH per year with a range of four to thirteen. Over the study period, there was no definite trend in the number of cases of RRP seen per year. However, a local study by Bal et al [32] over a fifteen-year period (1973-1987) found 113 cases of RRP. This similarly gives an average of 7-8 patients who were seen per year over their study period.

The age of onset varied from 4 months to 34 years with a peak age group of 2-3 years. This compares well with other studies by Gabbot et al [15] and Armstrong et al [69] where they found the peak age at diagnosis to be 2 years and 3.8 years respectively. The study by Bal et al [32] found the peak age group to be between 3-8 years. In this study the majority of cases (70%) presented before six years. This compares well with a study by Benjamin et al where 75% of patients were diagnosed by five years [11]. Most cases in this series were JORRP (86.5%) while AORRP was found to be 13.5%. Most authors find a prepondence of JORRP [10,11,14].

In this study, male patients accounted for 54.1% and female patients 45.9% with a M: F ratio of 1.2:1. However, considering AORRP alone the sex distribution ratio of M: F is 1:1 while for JORRP is 1.2:1. Therefore, there is an overall male prepondence. This is similar to other studies that have noted a higher incidence in males [32,69] while the series of Irwin et al showed a higher incidence in females [70]. In JORRP there is usually a female preponderance in contrast with AORRP where the reverse is true [2,16,68].
Most studies find a male prepondence in AORRP of about 3:1 [2,68]. However, in this study there was an equal sex distribution for AORRP.

The highest number of cases were found in Central 29.7% and Nyanza 28.4% provinces. Western province had the lowest number of cases at 10.8%.
No patients were found to come from North Eastern, Coast and Nairobi Province.
The fact that Central province had the highest incidence could be attributed to its proximity to KNH. The absence of patients from North Eastern province may be attributed to a lower population, greater distance from KNH and poor road infrastructure.

The absence of cases from Nairobi province could be explained on the basis that it's not considered as a home district by most patients as they give their medical history.
Coast province had a functioning ENT unit where papilloma excisions could be done, hence probably the absence of cases from that region.

90.5% of patients had their birth rank indicated out of which 62.4% were first bornes.
Other studies [12,68] have also found RRP to be commoner in first bornes who have been delivered vaginally to a young teenage mother. However, in this study the age of the mother at the time of birth could not be obtained.

The commonest presenting symptoms were hoarseness of voice (100%), difficulty in breathing (73%) and stridor (64.9%). Less common presenting symptoms were cough (37.8%), dysphonia (23%) and wheezing (8.1%). In most series, the main presenting clinical features are hoarseness, abnormal cry or voice change. Increasing stridor, wheezing and acute respiratory obstruction may occur but as late manifestations of the disease. [11]

The duration of hoarseness ranged from one week to 12 years. This wide variation in duration depended on whether the hoarseness was associated with other symptoms or not. Most patients with hoarseness and other symptoms suggestive of respiratory obstruction like stridor and dyspnoea tend to present earlier for treatment. Majority of patients (70.4%) presented with hoarseness of less than one-year duration.
Patients with stridor and dyspnoea presented earlier with a majority of 75% and 80% respectively presenting before six months. All patients with stridor also presented with dyspnoea. In most cases the degree of respiratory obstruction was not indicated in the medical records.

In 97.3% of patients there was no family history of any of the other siblings being similarly affected by RRP. In 2.7% of cases, this information was not indicated in the medical records. Hence, from this series elective caesarean section would not have been preventive against development of RRP in other siblings. Other studies show that siblings of children with RRP do not seem to have an increased risk of developing RRP [11].

Most studies show that caesarean section is not preventive against development of RRP; there is a need to fully determine the risk factors before advocating for elective caesarean section [10,13]

In all cases in this study, direct laryngoscopy (D/L) was the mode of diagnosis followed by a histological assessment of the biopsy specimen in most cases.

In this series, the first D/L assessment found the glottis to be the commonest site of involvement by the papillomas with 32.4% having glottic involvement alone. The total involvement of the glottis including other laryngeal sites was 95.8%. Involvement of the supraglottis and subglottis alone by the papillomas without involvement of the glottis was rare at 1.4% each.

Glottic and supraglottic involvement was the second commonest at 27%. This was followed by transglottic involvement at 25.6%. In the glottis most of the papillomas were found at the anterior commissure with less involvement of the posterior commissure and arytenoids. There was no right or left predilection of the papillomas in the larynx. Other researchers have found that the larynx is affected in 100% of cases of RRP with the majority involving the glottis followed by supraglottis and subglottis. [11,32].

At subsequent D/L assessment, glottic involvement alone was the least at 10.8% while transglottic involvement was the most at 43.2% of the patients performed more than one D/L and papillomas excision during the study period. This implies that the more aggressive form of RRP tends to involve multiple sites. There is also the possibility of reimplantation of the papillomas from the glottis to other multiple sites during the previous D/L and papillomas excisions done. This is clearly evidenced and supported by the fact that sometimes papillomas are reimplanted in the trachea and tracheostomy stoma after a tracheostomy has been performed [20,70,71]

13.5% of patients were noted to have papillomas in other extra laryngeal sites, namely the nose, palate, pharynx, hypopharynx, tracheostomy stoma and trachea. Pulmonary extension, reported to be less than 1% was not found in this study. [11]

Other authors have shown that the trachea and tracheostomy stoma to be the commonest extra-laryngeal sites affected by papillomas. These reports show tracheal involvement to

be as high as 17-26% of patients with RRP [11]. In this study trachea and tracheostomy stoma involvement was found to be 4.2%.

Oesophageal papillomas are rare, but in a study by Benjamin et al 1988, an incidence of 8% was found [11]. In this study only one patient (1.4%) was found to have florid papillomas involving the oesophagus, uvula and tracheostomy stoma.

Other series have shown papilloma spread to the nasopharynx, tonsil, soft palate and oral cavity [2,17].

Direct laryngoscopy and surgical extirpation of the papillomatous lesions by the use of laryngeal cup forceps treated all the patients in this series. Other treatment modalities like laser surgery and medical therapies of RRP were not used.

In this series 50% of the patients required only one papilloma excision to manage the airway during the study period. The remaining 50% required a various number of papilloma excisions to treat the respiratory obstruction due to recurrent papillomas, with a maximum of 16 papilloma excisions. The average number of D/L and papilloma excisions required to manage the respiratory obstruction were between 2-3 excisions.

The aggressive form of RRP is characterized by involvement of multiple sites, spread to the distal tracheobronchial tree, frequent recurrences, short remission times and subsequent need for frequent papilloma excisions or tracheostomy to control the airway [11,25,71].

Other researchers have shown aggressive RRP to be associated with JORRP, earlier age of onset and subglottic involvement [13,21,69]. In this study a comparison between age of presentation versus average number of papilloma excisions showed that children whose RRP was diagnosed at younger ages (< 3.0 years) tend to have more aggressive disease, with an average of 3.2 papilloma excisions for that age group.

Armstrong et al [69] have also found that RRP diagnosed before three years of age was more likely to have more severe disease as measured by the mean number of surgical procedures performed and by the number of anatomical sites affected. AORRP was found to be less aggressive than JORRP by requiring less papilloma excisions to control the airway with an average of 1.3 papilloma excisions for AORRP as compared to 2.4 for JORRP.

In this series, the longest remission time in between surgeries was found to be 72 months. This was between the first and second papilloma excisions. On average, the remission time in between surgeries tends to be longer in patients with less active disease i.e. those requiring less than three papilloma excisions.
Erisen et al [21] have recorded late recurrences of laryngeal papillomatosis in 2 patients after 44 and 47 years of remission respectively. This underscores the fact that while surgical treatment of RRP may maintain the airway, improve voice and in some cases control clinically overt disease; it does not address the sub-clinical mucosal HPV infection that may lead to recurrences many years after surgery.

Tracheostomy was performed on 15 patients (20.3%). Six patients (8.1%) had their tracheostomies done in the referring institutions due to acute respiratory obstruction. Tracheostomy was also performed on those patients who presented with aggressive disease requiring very frequent papilloma excisions and developing the complication of laryngeal stenosis due to scarring. Irwin et al [70] reported tracheostomies in 61% of cases of which 57% had developed spread of papillomas to the tracheobronchial tree. Shapiro et al [71] in a study of 35 patients between 1984 and 1994 found 13 patients (37%) required tracheostomy of which 50% of these patients had distal spread mainly limited to the tracheostomy site. Bal et al [32] reported tracheostomies in 23.3% of cases.

In this study two patients (2.7%) had involvement of the tracheostomy stoma. Fortunately no patients were found to have distal spread involving the lower airway and lung parenchyma. In order to avoid the complications of distal spread associated with tracheostomy, decannulation was done successfully on eight patients (53.3% of patients done tracheostomy). The shortest period before tracheostomy decannulation was 27 days while the longest was found to be 60 months with an average duration of 10.8 months. Tracheostomy decannulation was not possible in patients having complications of laryngeal stenosis or very aggressive RRP.

Complications were found in six patients (8.1%). Three were noted to have developed laryngeal stenosis after many repeated papilloma excisions. They are all on tracheostomies and have not yet been decannulated.

One patient, a 19-year-old male patient underwent malignant transformation of the laryngeal papillomas to moderately differentiated squamous cell carcinoma of the larynx. The duration between malignant transformation and first histological diagnosis of RRP was one year. There was no history of smoking, alcohol consumption or previous irradiation. The patient was done a tracheostomy and received both radiotherapy and chemotherapy. The remaining two patients were found to have persistent tracheostomy stoma and pulmonary hypertension respectively as complications.

Crockett et al [42] and Wetmore et al [43] have reported incidence of complications of about 35% in their series. The most common were anterior and posterior commissure webs, vocal cord scarring and interarytenoid bands. Bal et al [32] reported complications in 10.4% of patients, which were all cases of laryngeal and tracheal stenosis.
In order to reduce complications of latrogenic airway stenosis, the endoscopist should avoid damaging the underlying and adjacent mucous membranes and also avoid exposing the vocalis muscle. Since papillomas at the anterior commissure are particularly prone to producing scarring with formation of laryngeal webs, then treatments should be separated by a month and only one cord treated at a time [2].

Many authors [11,17,37] have reported malignant degeneration in RRP and it has been found to be commoner in AORRP and higher in solitary lesions [37]. Irradiation increases the risk of malignant degeneration. Therefore radiotherapy is contradicted in RRP [36]. The risk of malignant transformation is very low especially in non-irradiated patients. It has been estimated by various researchers to be between 2%-7% [34,35,37,38]. This is comparable with this study where an incidence of 1.4% was found. In this series, no mortality was reported compared to 3.5% mortality reported by Bal et al [32] in the same institution from 1973-1987. This could be attributed to improved anaesthetic care and surgical skills.

CONCLUSION AND RECOMMENDATIONS

1) Prospective studies should be done to fully determine the risk factors for JORRP and AORRP as well as determining the HPV viral type common in our set-up.

2) A clinical staging system should be adopted to provide uniformity in comparison of various modalities of treatment.

3) Use of intra-operative standard rubber stamp diagrams to allow uniform recording of the laryngeal lesions.

4) Improve on record keeping and the taking of a more detailed history by medical personnel.

5) Tracheostomy should be avoided where possible and early decannulation encouraged. This reduces the risk of the papillomas spreading into the trachea and distal airway.

6) Children with RRP before three years of age have a high risk of developing the more aggressive form of the disease. Therefore, education for parents and close follow-up is recommended to prevent complications and life threatening upper airway obstruction.

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APPENDIX

PROFORMA FORM

A. PERSONAL DATA

1. Name _____
2. Unit Number _____
3. Age of patient _____
4. Sex _____
5. Location: District _____ Province _____
6. Age (of onset) _____
7. Date of (1st) Presentation (at clinic or ward) _____
8. Date(s) of (1st) Admission _____
9. Date(s) of (1st) Surgery _____
10. Date(s) of (1st) Discharge _____
11. Referring Institution _____

B. HISTORY

1. SYMPTOMS	ABSENT	PRESENT	DURATION
Hoarseness			
Stridor			
Wheezing			
Respiratory obstruction			
Other			

2. Family History of similar disease	ABSENT	PRESENT	RELATION TO PATIENT

3. Birth rank-

C. SITES OF PAPILLOMAS

1. Larynx:

- Epiglottis surface — Lingual surface _____ Laryngeal _____

	Right	Left
• Aryepiglottic folds:	_____	_____
• False vocal cords :	_____	_____
• True vocal cords :	_____	_____
• Aryterioids:	_____	_____

- Anterior Commissure: _____
- Posterior Commissure: _____
- Subglottis: _____

2. Trachea

- Upper one-third _____
- Middle one-third _____
- Lower one-third _____

	Right	Left
• Bronchi	_____	_____

- Tracheostomy stoma _____

3. **Other sites**

- Nose _____
- Palate _____
- Pharynx _____
- Oesophagus _____
- Lungs _____
- Other _____

D. INVESTIGATIVE FINDINGS

1. HAEMATOLOGICAL/BIOCHEMICAL

Normal	Abnormal (describe)

2. RADIOLOGY Describe any done

3. HISTOLOGY/PATHOLOGY Reports (Date/Report)

E. SURGICAL THERAPY

1. Data of D/L + Papilloma excision

D/L and Papilloma excision	Date	Duration (Between operation in months)
1st operation		
2nd operation		
3rd operation		
4th operation		
5th operation		
6th operation		
7th operation		
8th operation		
9th operation		
10th operation		

Total number of D/L + Papilloma excisions done during study period _____

Follow up period in months _____

Longest remission time in between subsequent operations in months _____

Average number of operations/year _____

2. **Other operations done:**

i) Tracheostomy - give date done _____

Decannulation- date if done _____

ii) Any other related surgical procedures done _____

F. ANY MEDICAL OR OTHER MODES OF TREATMENT OFFERED:

_____

_____

G. COMPLICATIONS: **Describe**

_____

_____