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Recurrent respiratory papillomatosis – the Manchester experience, 1974–1992

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Abstract

A series of 59 patients of all ages with recurrent respiratory papillomatosis (RRP) treated over an 18-year period is presented. A number of these patients were initially diagnosed in childhood but required treatment throughout adult life. The frequency of laser treatment was not related to either disease duration or age at onset. In 28 patients, the HPV type was identified, showing that HPV type 11 was more common in children and ran a more protracted clinical course. The requirement for tracheostomy in this series was small, whereas the incidence of malignant change in adult patients was significant.

Key words: Papilloma; Laser; Laryngeal diseases

Introduction

Since the initial description of the condition 'Juvenile Laryngeal Papillomatosis' by MacKenzie (1880), it has become clear that the disease is not confined to children nor is the larynx the only affected site. Papillomata have been reported at all ages and throughout the upper aerodigestive tract, even within the lung parenchyma (Strong *et al.*, 1976; Schnadig *et al.*, 1986; Chaput *et al.*, 1989; Lindeberg *et al.*, 1989). This has prompted many authors to consider the condition as two distinct disease groups, one of juvenile and the other adult onset. Although the incidence and prevalence of the disease is hard to determine, it has been estimated that seven new cases per million per year occur in the USA (Strong *et al.*, 1976), with a similar reported incidence in Denmark (Bomholt, 1988). The viral aetiology of RRP has now been confirmed and extended to include DNA typing. Despite these scientific advances, a cure for the condition is still elusive.

We present our experience of RRP over the past two decades. The clinical course of the patients is analysed and a number of conclusions drawn relating to the natural history of the disease. In the light of our findings, current treatment methods are discussed.

Clinical subjects

Between 1974 and 1992, 59 patients with recurrent respiratory papillomatosis (RRP) were treated at both the Christie Hospital and the Manchester Royal Infirmary by the senior author (WTF). While some patients with RRP are treated within peripheral hospitals, many are referred to our unit for assessment and treatment, particularly when the disease has spread beyond the larynx. The population sampled is therefore skewed by this secondary referral pattern.

A retrospective analysis of various patient and treatment parameters was carried out and where available correlated with viral type.

Results

A total of 59 patients were treated over the 18-year period and all were followed-up on a regular basis until they became disease-free, as demonstrated by endoscopic examination. Whereas data is complete on 23 patients who have been discharged or have died, 36 individuals are still under regular review.

There were 41 males and 18 females in the group. At presentation to our unit 47 cases were adults (above 16 years) and 12 children. Although an age range of 18 months to 72 years was found at presentation, in many cases the patients had been symptomatic long before this time and some had received prior treatment for their condition. In all 59 patients, we were able to obtain reliable data from the referring centre showing that at disease onset, 20 were children and 39 adults (age range one month to 70 years). The average duration of symptoms prior to presentation to our unit was six years one month (range one month to 53 years). During this period, the patients had a mean of 6.33 (range 0 to 60) treatments. Whilst under our care they received a mean of 4.9 (range 0 to 21) further treatments over a period ranging from one month to 13.5 years (mean three years four months). The total duration of symptomatic disease and the treatment period for each patient at the referring centre and our unit is shown in Figure 1. It is clear that the eventual number of treatments required cannot be inferred from the disease duration, nor from the age at which the patient first develops symptoms (Figures 2 and 3). Patients still under review will probably require further treatments.

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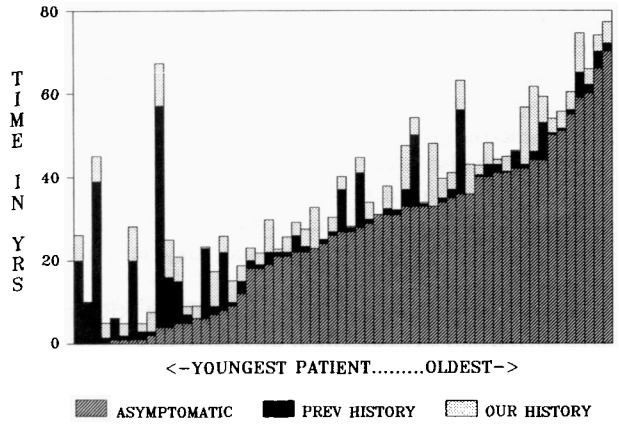

FIG. 1

Age at symptom onset and disease duration (y-axis) of 59 patients in ranked order (x-axis).

The HPV DNA type was assessed in 28 patients using standard techniques (Corbitt *et al.*, 1988). Sixteen cases were HPV type 6, 11 were HPV type 11 and in one case no viral type could be found. No other viral types were identified although all material was tested for HPV types 16 and 18. Analysis of the viral type by age demonstrates that HPV type 11 tends to occur in the younger patients (mean age of symptom onset 9.5 years) whereas HPV type 6 occurred throughout the age range (mean age of symptom onset 30 years) (see Figure 4). Patients with HPV type 6 required fewer treatments (mean 5.8; range two to 63) than those with HPV type 11 (mean 8.8 treatments; range one to 69). Due to the large range in each group, these differences do not reach statistical significance.

A total of five patients required tracheostomy for airway management (of which four were carried out before referral to our unit). All seven patients with distal spread beyond the larynx were children at disease onset and required an average of 3.5 (range one to 14) laser-bronchoscopies to control the disease, in addition to a total of 66 laryngeal treatments (range two–20). Among the adult onset population, although some of the papillomata were single, the majority were multiple lesions (65 per cent). Laryngeal malignancy occurred in three of the adults treated but in none of the children. Two of these cases had HPV type 6, the other being untyped. One individual developed a squamous cell carcinoma of the bronchus 21 years after the onset of laryngeal papillomata without distal disease. This patient had also suffered from sarcoidosis for a number of years. Only one patient had received radiotherapy which was carried out soon after disease onset in childhood following failure of suction diathermy. This patient also had pulmonary tuberculosis and for almost 20 years had a tracheostomy. Sixty-three years after her first treatment, she still requires periodic laser laryngoscopy.

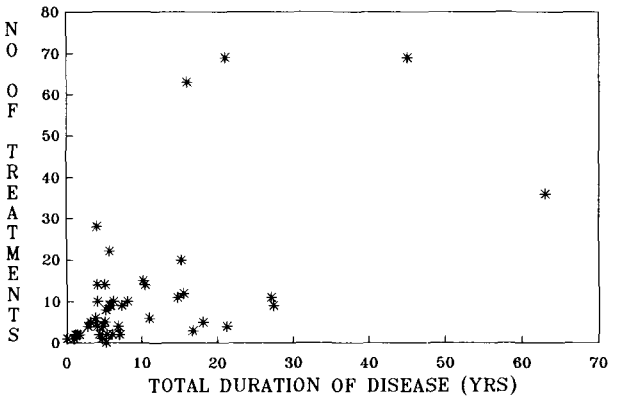

FIG. 2

Treatment frequency *versus* total disease duration.

Discussion

As the earliest accounts of recurrent respiratory papillomatosis were in children, it is not surprising that the condition was named juvenile laryngeal papillomatosis (JLP). Although papillomata were subsequently described in adults, authors still report cases as being of either juvenile or adult onset, implying that these represent different clinical conditions (Bomholt, 1988; Quiney *et al.*, 1989). In the younger age group, papillomata tend to be multiple, and patients present with the laryngeal symptoms of hoarseness, a poor cry, or with stridor (Irwin *et al.*, 1986). Given the larger diameter of the airway in adults, presentation with stridor is less common and hoarseness is usually the presenting complaint (Clements and Gravelle, 1986). Although adult lesions are often solitary (Quiney *et al.*, 1989), in our study, the majority of adult onset cases had multiple lesions. Lindeberg *et al.* (1986) suggested retaining the distinction between adult and juvenile forms of the disease, but further subdivided each of these according to whether papillomata were multiple or solitary. A number of recent studies however, suggest that RRP is a single clinical entity (Capper *et al.*, 1983). Our study supports this view as no age group was exempt from developing the disease.

There is no doubt that papillomata are of viral origin, with the epithelial cells within the airway being infected by human papilloma virus (HPV), in particular types 6 and 11 (Abramson *et al.*, 1987). We found that the latter is more prevalent in the younger age group and is associated with a more protracted clinical course requiring a greater number of treatments. This agrees with work by Mounts *et al.* (1984) who felt that individuals with HPV type 11 had a worse prognosis.

Whilst the viral aetiology of this condition is certain, doubt exists as to the source of the infection. Many individuals have a maternal history of genital condylomata, suggesting transmission at birth and HPV 6 and 11 are the most common types found in genital warts, adding further weight to this argument (Abramson *et al.*, 1987). How-

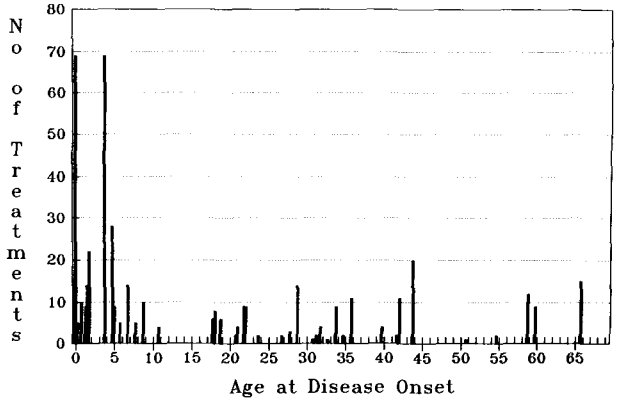

FIG. 3

Treatment frequency *versus* age at disease onset.

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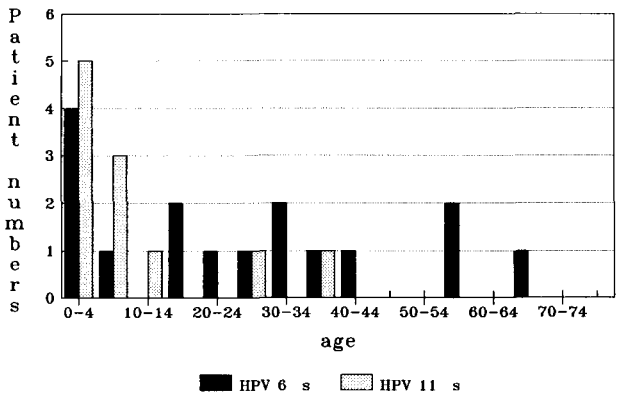

FIG. 4

Distribution of viral types by age at symptom onset.

ever, this is unlikely to be the sole explanation as some individuals have no such history, whilst others develop the disease many decades later. In addition, not all individuals born to mothers with genital warts develop the disease. In many viral infections, such as herpes simplex or Epstein Barr virus, infected individuals may develop a recognized disease or remain asymptomatic (Irwin *et al.*, 1986). Why this should be the case is unknown, although variations in cell mediated immunity may be responsible. Perrick *et al.* (1990) demonstrated subnormal natural killer cell activity in individuals with papillomatosis, whilst Jakubikova *et al.* (1992) found a decreased T-lymphocyte count in children with the disease.

In RRP, apparently normal cells within the upper airway harbour latent papilloma virus particles explaining the tendency of papillomata to recur after macroscopic elimination of all disease (Abramson *et al.*, 1987). Affected individuals may eventually develop immunity to the virus resulting in clinical remission which often occurs around puberty. This may be due to a hormonally induced alteration in immune function (Corbitt *et al.*, 1988). Many of our patients with juvenile onset disease have continued to require treatment well into, and sometimes throughout, adult life. Some of these individuals experienced remission during early adult life only to relapse many years later, a feature noted by other authors (Bomholt, 1988; Corbitt *et al.*, 1988). Abramson *et al.* (1987) felt that pregnancy may lead to an acceleration of papillomata growth, again possibly related to altered immune status. Activation of latent virus may also offer an explanation for late onset disease, although the trigger for the activation in such cases is unknown.

Until remission occurs, treatment is based on the maintenance of a clear airway, usually by microlaryngoscopy and laser treatment to the papillomata. Adjuvant treatment with acyclovir, interferon or other immunostimulants has been used with some success (Aguado *et al.*, 1991; Leventhal *et al.*, 1991), albeit often temporary (Irwin *et al.*, 1986; Abramson *et al.*, 1988; Perrick *et al.*, 1990).

The complications of the condition are related to both the treatment and the disease. Anterior and more rarely posterior webbing within the larynx may occur with laser treatment, along with a variable degree of scarring within the airway (Wetmore *et al.*, 1985). On occasions, particularly in the younger age group, a tracheostomy may be required for airway management. Irwin *et al.* (1986) commented that over 60 per cent of children at Great Ormond Street had required tracheostomy, whereas in our series only five patients (25 per cent of the total children) received such treatment. Unfortunately after tracheostomy the papillomata have a tendency to develop at the stoma site, possibly due to trauma-induced metaplasia at the tracheostomy site (Abramson *et al.*, 1987). Distal disease may also occur which is amenable to laser treatment when confined to the trachea and larger bronchi. Invasion of lung parenchyma is almost impossible to control and the relentless progression may lead to death (Lindeberg *et al.*, 1989).

Malignant transformation in adult onset RRP is well recognized and an association with HPV type 11 has been found, (Mounts and Kashima, 1984; Lindeberg *et al.*, 1989). Amongst a series of such adult onset cases, Strong *et al.* (1976) found an incidence of just over seven per cent with laryngeal malignancy. This is almost identical with the incidence of laryngeal tumours in our series (7.5 per cent of adult onset cases), although we found a predominance of HPV 6 (two cases). In the younger age group, such malignancy has also been recognized. Pulmonary malignancy has been reported in cases with parenchymal involvement with papillomata (Schnadig *et al.*, 1986) and laryngeal carcinoma following irradiation (Irwin *et al.*, 1986).

Conclusions

Common usage dictates that authors will still refer to childhood and adult forms of RRP. We believe that this distinction is an arbitrary one, the age at disease onset being determined by host immunological factors and the viral type. Treatment at presentation is based upon the maintenance of the patients' airway by the use of laser, although techniques of immune enhancement hold promise for the future. Tracheostomy should be avoided if at all possible, due to the risk of papilloma seeding and distal spread. The risk of malignant change is significant, particularly in the older patient.

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