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REVIEW PAPER

Juvenile-onset recurrent respiratory papillomatosis

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ABSTRACT

Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare disease caused by an infection of human papillomavirus (HPV) – most commonly types 6 and 11. These types of HPV are vaccine-preventable. The virus is transmitted vertically. Human papillomavirus can alter immune response by reducing interferon-γ and interleukin-2 expression. Most JORRP patients develop symptoms before the age of 5 years. In severe cases this disease can lead to airway obstruction or malignant transformation. The treatment primarily consists of surgery as well as intralesional or systemic bevacizumab therapy or adjuvant therapy. Patients who develop symptoms at a younger age usually need more surgeries than older patients with JORRP. To reduce the incidence rate of JORRP, HPV vaccination is recommended.

KEY WORDS:

recurrent respiratory papillomatosis, HPV, papilloma, paediatric disease, juvenile-onset recurrent respiratory papillomatosis.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) can affect adults and children. The most frequently affected organ is the larynx [1]. Squamous papillomas are formed by human papillomavirus (HPV), mostly types 6 and 11 [2, 3]. Additionally, cases of infections with high-risk oncogenic HPV strains, such as HPV 16, 31, 33, 35, and 39, have also been reported [3]. Recurrent respiratory papillomatosis is divided into juvenile-onset RRP (JORRP) and adult-onset RRP (AORRP). Juvenile-onset recurrent respiratory papillomatosis is usually more aggressive and recurs more often than AORRP, but an aggressive form of the disease can also occur in AORRP [4]. Juvenile-onset recurrent respiratory papillomatosis is the most prevalent benign, laryngeal tumour in children, but it is considered to be a rare disease. It is a recurrent disease [5]. The age of diagnosis is often 2–3 years [6]. While AORRP is transmitted by sexual activity, JORRP is transmitted vertically [4]. A 'JORRP triad' has been described with 3 risk factors associated with JORRP- a firstborn, vaginal delivery, and a young mother. However, birth by caesarean section does not prevent vertical transmission of the virus. Most JORRP cases could be prevented if patients' mothers were prophylactically vaccinated with HPV vaccine before exposure to HPV during sexual activities, because almost all JORRP patients are infected by vaccine-preventable HPV types 6 and 11 [7]. There is a decreased incidence reported in countries with recommended HPV vaccination [3].

PATHOGENESIS

In adults, HPV infection is primarily transmitted through sexual activity [8]. In the context of JORRP, infection most commonly occurs through vertical transmission of the virus from mother to child during vaginal delivery. Newborns can contract the virus while passing through the birth canal, particularly if the mother has active papillomatous lesions in the genital area [9]. Following HPV infection, the virus enters the basal layer of the laryngeal epithelium through microabrasions in the mucosal

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membrane [10]. The virus encodes the viral proteins E6 and E7, which modulate cell cycle regulation and disrupt proliferation control mechanisms [11]. Specifically, the E6 protein promotes ubiquitination and proteasome-dependent degradation of the tumour suppressor protein p53 by forming a trimeric complex with E6, p53, and the E6-associated protein. This interaction compromises p53's role in apoptosis regulation and cell cycle arrest. Consequently, the loss of the p53 function facilitates uncontrolled cellular proliferation [12]. Meanwhile, the E7 protein inhibits the activity of the retinoblastoma protein, leading to unregulated proliferation of infected epithelial cells [13]. The combined effects of E6 and E7 drive extensive epithelial cell proliferation, resulting in the formation of exophytic papillomas on the vocal folds and other laryngeal structures [14]. These lesions are highly vascularised and prone to rapid recurrence following surgical removal [1].

Human papillomavirus has the ability to modulate the host immune response, facilitating the persistence of infection and the development of papillomas. Studies have shown that patients with JORRP exhibit reduced expression of interferon-γ and interleukin-2, leading to insufficient maturation of cytotoxic T lymphocytes (CD8+). Additionally, an increased presence of immunosuppressive FoxP3+ cells has been observed within papillomatous tissues, further inhibiting the immune response [15].

Although JORRP is a benign disease, it has the potential to progress toward malignant transformation, particularly in patients with prolonged and intense exposure to HPV-11 [16]. This process is typically associated with additional risk factors, such as exposure to tobacco smoke, immunosuppression, or co-infection with oncogenic HPV strains (e.g. HPV 16 and 18). The key mechanisms underlying malignant transformation involve mutations in the *TP53* gene and the persistent activation of proliferative pathways driven by viral proteins E6 and E7 [17].

SYMPTOMS AND DIAGNOSIS

Papillomas in children grow at a faster rate than in adults [18]. Seventy-five per cent of paediatric patients with JORRP experience the first symptoms before the age of 5 years. The first affected site is usually the vocal cords. Typically, the first symptoms include hoarseness and a weak cry. When advanced, JORRP may lead to airway obstruction manifesting with stridor and difficulty in breathing [19]. A study found that in the first year after diagnosis, patients with airway manifestations have symptoms at a younger age and require more surgeries than patients with voice manifestations [18]. Complications of JORRP may include malignant transformation and the spread to the trachea and lung parenchyma. The progression to the trachea refers to 8% of cases, bronchi 3%, and lung parenchyma fewer than 1% of cases [20]. A study on 82 paediatric patients revealed that being diagnosed with JORRP prior to the age of 5 years and having a tracheostomy contributes to extralaryngeal spread of JORRP. This study also found an association between HPV type 11 infection and the extralaryngeal spread [19].

Juvenile-onset recurrent respiratory papillomatosis caused by HPV type 11 is linked to a younger age of diagnosis, higher risk of malignant transformation, and an elevated number of surgical treatments needed [21].

Pulmonary involvement in JORRP patients is associated with an increased number of surgeries needed, higher mortality rate, and greater occurrence of tracheotomy, which cannot be decannulated [22].

The diagnosis is based on fibreoptic examination and laryngoscopy with sampling. Laryngotracheal endoscopy is considered to be the most valid diagnostic measure [3].

The severity of the disease is usually graded using the Derkay staging system. It uses the anatomical disease distribution and the impact of symptoms on daily functioning.

One limitation of this staging system is that, although it accurately identifies the presence of disease, the number of affected sites, and the bulkiness of each lesion, it fails to differentiate the varying severity levels within a single site [23]. Molecular biology techniques, such as polymerase chain reaction (PCR) combined with restriction fragment length polymorphism, allow for the detection of specific HPV types in samples. This method helps stratify patients based on their cancer risk level, i.e. no risk, low risk, or high risk [24]. Droplet Digital PCR divides a nucleic acid sample into up to 20,000 nanolitre-sized droplets, where each undergoes PCR amplification and analysis. Results are reported digitally, ensuring highly accurate, reproducible quantification with sensitivity far exceeding traditional PCR [25].

TREATMENT

The primary treatment consists of surgery [2]. The aim of the surgical treatment is to decrease the disease burden, prevent airway obstruction, and reduce voice symptoms [18]. But the recurrence rate in RRP is not lowered by a broad resection of papillomas if the excision is not made to reduce voice symptoms or prevent airway obstruction, because HPV can remain latent in epithelial cells of the larynx even when the papilloma is not visible. In proximate HPV infected cells an injury of the mucosa can increase the HPV expression [26].

A connection between the age of presentation and the number of surgical treatments needed was found; patients under the age of 3 years are at over 5 times the risk of needing more than 4 surgeries in the first year after developing signs and symptoms, compared to older patients [18]. A study on 50 JORRP patients who did not have a recurrence of the disease in at least 5 years showed the possibility of progression to self-healing at the age of around 9 years. However, the number of patients with self-healing is low – 50% have a recurrent disease and

need surgery after the age of 14 years. Herein, 41.3% of patients did not have a recurrence of JORRP for at least 5 years, emphasising the importance of non-surgical treatment [27].

The tumour is resected with the use of cold steel, laryngeal microdebrider, laser, or radiofrequency ablation. The use of pulsed dye laser is not recommended due to a shortage of availability in many hospitals [2]. A study compared CO_2 laser and microdebrider in the treatment of 39 paediatric patients and found the microdebrider to be more efficacious [28].

Bevacizumab vascular endothelial growth factor inhibitor can be administered locally by intralesional or sublesional injections [29, 30]. A case report of multiple tracheal pyogenic granulomas following an intra-epithelial bevacizumab therapy in a 2-year-old child has been reported [29]. For severe RPR systemic administration of bevacizumab is efficacious and safe. For a better outcome, long-term therapy of bevacizumab is advised [5]. Rogers *et al.* reported that an adjuvant intralesional injection of bevacizumab after the use of microdebrider and KTP laser in 10 paediatric patients with severe RRP lowered the Derkay staging, raised the paediatric voice-related quality of life score, and lengthened the time between surgeries [31].

Side effects for systemic bevacizumab treatment include hypertension, thrombosis, electrolyte imbalances, and renal damage [30].

Adjuvant therapy is considered in patients with more than 4 surgeries annually, fast resurgence of papillomas with airway obstruction, or when more than one site is affected [20, 30]. Adjuvant therapy may reduce the risk of extralaryngeal spread of RPR [19]. Adjuvant treatment might consist of oral indole-3-carbinol, mumps vaccine, heat shock protein E7, interferon, celecoxib, and intralesional cidofovir [30]. Cidofovir in adjuvant therapy for RRP is used off-label [2]. Intralesional cidofovir is considered for patients with severe disease. This drug was found to extend the period between surgeries [3].

Adjuvant therapy with a measles mumps rubella (MMR) vaccine can notably decrease the HPV viral load, but more research is needed to confirm the inhibitory character on the HPV DNA replication [32].

Tracheotomy should be limited to severe cases with airway obstruction, but decannulation should be performed without delay because tracheotomy is associated with an increased risk of lower colonisation [30].

HUMAN PAPILLOMAVIRUS VACCINATION

Human papillomavirus was detected in papilloma biopsy specimens from nearly all children with JORRP, with HPV 6 found in 83.9% of cases and HPV 11 in 16.0%. Human papillomavirus vaccination is highly effective in preventing infections caused by vaccine-targeted HPV types [7]. A study conducted in northern Sweden demonstrated that, in patients with RRP, the number of surgical procedures required per year decreased from 2.0 to 0.8 following HPV vaccination. This suggests a potential role of the vaccine in reducing the need for surgical interventions [33]. Research also indicates that maternal vaccination before childbirth may reduce vertical transmission of HPV, a key route of JORRP infection [7, 34]. Additionally, the administration of the MMR vaccine has been suggested as an adjuvant therapy for JORRP [32]. Previous perspectives have suggested that HPV vaccines lack therapeutic efficacy because their primary mechanism of action is the prevention of infection rather than the treatment of existing infections. However, recent findings propose that vaccination may help limit disease progression [35]. While evidence supports the efficacy of HPV vaccines (such as Gardasil®) in reducing the need for surgical interventions, large, multi-centre randomised clinical trials are still needed to confirm the true effectiveness of this approach [36–38].

CONCLUSIONS

In conclusion, JORRP is a chronic viral disease caused by HPV, primarily genotypes 6 and 11, and is transmitted vertically during childbirth. The virus infects the laryngeal epithelium, where the viral proteins E6 and E7 disrupt cellular proliferation control, leading to the formation of papillomas. The disease is characterised by an impaired immune response and frequent recurrences following surgical treatment, with a potential risk of malignant transformation in some cases. Symptoms include hoarseness, a weak cry, and in severe cases airway obstruction. The treatment consists of surgery, bevacizumab, and adjuvant therapy, but no treatment was found to be a cure for JORRP. Human papillomavirus vaccination may help limit JORRP progression and reduce the need for surgical interventions, although further research is required to confirm its effectiveness.

DISCLOSURES

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