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Review Article

Risk factors for the development and severity of juvenile-onset recurrent respiratory papillomatosis: A systematic review

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ABSTRACT

Objectives: Juvenile-onset recurrent respiratory papillomatosis (JoRRP) is a rare yet aggressive disease caused by human papillomavirus (HPV). Although many newborns are likely exposed to HPV, few develop JoRRP and the clinical course of the disease varies from one child to another. This systematic review seeks to provide an up-to-date understanding of the risk factors for acquisition and severity.
Methods: We conducted a comprehensive literature search in EMBASE, MEDLINE and EBMR databases using various combinations of keywords related to JoRRP etiology, risk factors and severity. We also searched Google Scholar and the reference lists of eligible studies. Our search was limited to original studies published in French or English between 1995 and July 2012 and to patients under 20 years of age.
Results: Of 1362 citations, we retrieved 102 articles and found 14 additional studies. We retained 32 studies meeting inclusion criteria. All were observational and together included 2296 JoRRP cases. Risk factors could be classified mainly as maternal and birth history, viral genotype, and host factors. A history of genital warts during pregnancy and delivery was strongly linked to the development of JoRRP. Depending on ethnicity, specific human leukocyte antigen class II alleles and immune response factors were important determinants of JoRRP acquisition and severity. HPV-11 genotype and younger age at onset of JoRRP were important predictors of severity.
Conclusions: Genetic and immunological profiles underlying the acquisition and clinical course are not readily modifiable. Thus, preventing condylomas in women of childbearing age could reduce the burden of this life-threatening disease.

Contents

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1. Introduction

Juvenile-onset recurrent respiratory papillomatosis (JoRRP) is a rare yet aggressive disease caused by the human papillomavirus (HPV). The wart-like growths in the upper airway are mostly due to HPV genotypes 6 and 11 [1,2]. Several observational studies have associated the JoRRP to maternal vaginal condylomas [3–6].

The incidence and prevalence of JoRRP vary from one country to another. The incidence has been estimated at 0.24–4.3 per 100,000 children, the prevalence at 1.11–2.59 per 100,000 children [7–10]. Although the disease is rare, morbidity is notoriously high. Recurrent proliferative lesions in the respiratory tract can spread to the trachea, bronchi or pulmonary parenchyma and compromise local function such as vocalization, breathing and swallowing [11–15].

The course of the disease can vary from mild to severe. Some children experience minor symptoms with spontaneous and complete remission at puberty, while others require multiple surgeries throughout childhood [13] at great physical, emotional, and financial burden to the individual, the family, and society [16,17]. In rare yet severe progression, the disease may transform into malignant lesions [14], or in 1–3% of cases, may spread to the lower respiratory tract, entailing high mortality [11].

Individual studies have analyzed the risk factors associated with the occurrence and severity of JoRRP but findings have not been consistently replicable. Various published reviews have described the clinical manifestations and treatment options [12,16,18–26]. None, however, has focused systematically on etiology and prognosis. This systematic review, by summarizing recently published data, seeks to provide an up-to-date understanding of the risk factors for acquisition and severity.

2. Methods

2.1. Search strategy

We conducted a comprehensive systematic review of studies investigating risk factors associated with the acquisition and severity of JoRRP. We searched EMBASE, MEDLINE and Evidence-Based Medicine Reviews (EBMR) databases using the OvidSP interface with the following combinations of keywords and Boolean operators: (Laryn$ OR respiratory) AND (HPV OR papilloma or Papillomaviridae OR Papillomavirus Infections) AND (Disease* OR lesion* OR infection*) OR (Juvenile onset recurrent papillomatosis OR JORRP OR Juvenile laryngeal papilloma) AND (cause* OR sever* OR acquisition OR etiology OR Risk factor OR Risk Factors OR agress$). Given the use of new techniques for HPV genotyping since the late 1990s, we limited our search to studies published between 1995 and July 2012. We also limited it to studies investigating patients under 20 years of age, a cut-off proposed by Lindeberg et al. [27]. Only studies published in French or English were retained. We conducted an additional search using Google scholar, conference proceedings, and the reference lists of all eligible studies and any previous reviews on JoRRP, again eliminating studies of adults only (age $\geq$ 20). In all cases, we excluded studies analyzing tissues outside the respiratory tract or investigating less than 5 patients. Case reports, editorials and opinion pieces were not considered eligible.

2.2. Study screening, data collection and quality assessment

Two of the authors (MW and CR) screened the identified titles after removal of duplicates. The same authors then screened the abstracts and selected which full-text manuscripts to retrieve for evaluation. Studies conforming to inclusion and exclusion criteria were then classified according to study objective: acquisition, severity of disease, or both. Each of these steps was performed independently and in duplicate. Any discrepancies were resolved by consensus, with referral to a third author (JN or HT) where necessary.

We collected research data on demographics (country, year of publication, study population, age of participants), study design, and results of HPV genotyping. For all variables analyzed as potential determinants of JoRRP acquisition or severity, we noted relative risks (odds ratio or risk ratio) and confidence intervals (CI) when applicable and available. Where the authors provided only *p*-values for statistical test results, we reported the *p*-value and direction of the association. We assessed each study for quality, according to levels of evidence determined by study design and potential bias [28]. Given the design variability and insufficient similarities in outcome measures of the included studies, we did not deem it appropriate to extend this review to a meta-analysis [29].

3. Results

3.1. Description of included studies

Our initial search identified 1362 citations. Of these, we retrieved 102 unduplicated full-text articles that conformed to eligibility criteria (Fig. 1). We found 14 additional studies from the reference lists. We retained 32 studies altogether, of which three [30–32] focused on risk factors for both acquisition and severity of disease.

All 32 studies were observational and together reported on a total of 2287 JoRRP cases. Seven studies included both JoRRP and adult-onset recurrent respiratory papillomatosis (AoRRP) cases [30,31,33–36,38] (Table 1). Analyzed variables included socio-demographics, maternal pregnancy history, immune response characteristics and genetic profile. Sixteen studies examined HPV genotypes [2,7,13,33,35–46], particularly HPV-6.

3.2. Socioeconomic status

Only 4 publications [13,17,44,47] examined the link between JoRRP and socioeconomic factors (Fig. 2). Medicaid coverage (a proxy for a low socioeconomic status in the US, as opposed to private insurance coverage) was significantly associated with JoRRP severity in a 10-year prospective study in Alabama, US [13], but not in a study of 603 cases in 22 tertiary pediatric care centers (also in the US) [17]. It was thus unclear whether or not the availability of medical health insurance played a role as a facilitating factor for timely access to care and better prognosis. Leung et al. confirmed that, in a universal health care setting (Canada), socioeconomic status was not significantly associated with JoRRP severity [47]. Similarly, in a multicentre study of 118 JoRRP cases in the US and Canada, neither maternal education level nor gross household income was indicative of disease progression