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Recurrent Respiratory Papillomatosis

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Chapter 2

Age of onset of Recurrent Respiratory Papillomatosis: a distribution analysis

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Abstract

Background: Distribution of age of onset of Recurrent Respiratory Papillomatosis (RRP) is generally described to be bimodal, with peaks at approximately at 5 years and 30 years. This assumption has never been scientifically confirmed and authors tend to refer to an article which does not describe distribution. Knowledge of the distribution of age of onset is important for virological and epidemiological comprehension. Objective of this study was to determine the distribution of age of onset of RRP in a large international sample.

Design: Cross-sectional distribution analysis.

Participants: Laryngologists from twelve European hospitals provided information on date of birth and date of onset of all their RRP patients treated between 1998 and 2012. Centers which exclusively treated either juvenile onset or adult onset RRP patients, or were less accessible for one of these groups, were excluded to prevent skewness.

Main outcome measures: A mixture model was implemented to describe distribution of age of onset. The best fitting model was selected using the Bayesian Information Criterion.

Results: Six hundred and thirty-nine patients were included in the analysis. Age of onset was described by a three component mixture distribution with lognormally distributed components. RRP starts at three median ages 7, 35 and 64 years.

Conclusions: Distribution of age of onset of RRP shows three peaks. In addition to the already adopted idea of age peaks at pediatric and adult age, there is an additional peak around the age of 64.

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a disease mainly caused by Human Papillomaviruses (HPV) types 6 and 11.[1] HPV6 and 11 are also associated with 90% of anogenital warts.[2] RRP presents with recurrent growth of exophytic wart-like tumors throughout the airways, most commonly in the glottis.[3] Due to the recurring character of RRP, patients may require dozens of surgical interventions to assure good phonation and to avoid tracheotomy.[1] Multiple (adjuvant) therapies have been tried with variable success.[4]

Clinically two forms of RRP are recognized: Juvenile onset RRP (JoRRP) and Adult onset RRP (AoRRP). The maximum age of onset of JoRRP differs between articles, but is generally chosen at 18 years of age.[5] The reported incidence is 0.17-1.34 per 100,000 for JoRRP and 0.54 per 100,000 for AoRRP.[5-9] Higher estimations (up to 4 per 100,000) of both JoRRP and AoRRP incidence have been made, but these were based on less reliable estimation methods such as surveying otolaryngologists.[10, 11] The transmission of HPV6 and 11 in JoRRP is thought to be vertical from mother to baby during labor, as babies born to a mother with genital warts have a 200 times higher chance of acquiring RRP in comparison to children born to a mother without genital warts.[12] Firstborns and children of young mothers have the highest chance of being infected,[3, 13] conceivably due to a longer delivery time, implying prolonged exposition time to the virus.[12] It is not totally clear how HPV in AoRRP is transmitted, but orogenital sexual transmission might be a causative factor.[14] This is supported by the fact that AoRRP is associated with a higher lifetime number of sexual partners compared to healthy controls.[15]

Knowledge on disease transmission is essential for understanding disease biology. RRP is generally assumed to start around the age of 5, or between 30 and 40 years. Authors often refer to Cohn et al. (1981) to describe a bimodal distribution of age of onset of RRP.[16] Cohn et al. however do not discuss age of onset of RRP, but report a case series of JoRRP patients.[16] There is no scientific confirmation of the assumption of bimodality. Therefore an international multicenter evaluation of the age of onset of RRP was conducted to better understand the biology of HPV in RRP and to generate new ideas on the transmission of HPV.

Methods

Laryngologists from all 16 participating hospitals from 11 countries of the international multicenter study by Tjon Pian Gi et al. (2013) were invited to participate in this retrospective international multicenter study.[17]

All laryngologists were asked to provide date of birth and date of diagnosis of all their RRP patients treated between 1998 and 2012. Inclusion criteria for patients were: [1] RRP histologically confirmed by an experienced head and neck pathologist, [2] known date of first diagnosis, only when certain that this was the first episode and first histological diagnosis, [3] known date of birth, [4] diagnosis and treatment performed in a European hospital. To avoid selection bias, enquired hospitals were asked if they treated both children and adults with RRP. Patients treated at a department that only or preferentially accepted juvenile or adult patients with RRP, or were less accessible for one of both groups, were excluded from further analysis.

Gender of each patient was registered. Date of diagnosis was defined as the date of first histological confirmation of RRP, as this is the only objective measure of RRP and RRP is a disease which can only be diagnosed through histological confirmation. Date of birth and date of diagnosis were registered as month-year to avoid unnecessary exclusion of patients, due to the absence of the exact day of the month.

All data was collected and entered into a database (Microsoft Excel 2007). Approval of the Institutional Review Board is not required in The Netherlands for a retrospective case file study.

Statistics
A mixture model was implemented to describe the distribution of the age of onset. The assumption was made that all centers contributed to this model in a similar way, implying that the age of onset per country is the same. On the basis of Bayesian Information Criterion,[18] the best fitting mixture distribution was selected using either normally or lognormally distributed components and changing the number of components. Statistical analyses were executed with procedure FMM of SAS Institute, version 9.3.

Results

Of the 16 invited hospitals 13 (81%) provided their patient data. One of the hospitals (which accounted for 11 children) was not found to be eligible, because its preferred treatment of children and due to the non European patient group (Mexico). Therefore 12 hospitals from 8 European countries supplied the needed information of their patients. Information was provided on 659 patients. Twenty patients (3%) were excluded because the date of diagnosis was unavailable. Therefore 639 patients were included for further analysis.

The number of included patients per center is shown in table 1. The percentage of males was 71% (452/639). The youngest patient who presented with RRP was 29 days old, the oldest patient was 89 years. Eighteen percent (115/639) of patients had JoRRP (age<18 years) and 82% (524/639) of patients had AoRRP (age≥18 years).

Table 1. Number of included patients per participating center (name, city and country). Sorted on number of patients, from highest to lowest percentage.

Center	City, Country	Number of participants N (%)
Helsinki University Hospital	Helsinki, Finland	236 (36.9)
University Medical Center Groningen	Groningen, Netherlands	91 (14.2)
Poznan University of Medical Sciences	Poznan, Poland	52 (8.1)
Medical University of Graz	Graz, Austria	47 (7.4)
Klinikum Stuttgart	Stuttgart, Germany	43 (6.7)
Greater Poland Cancer Centre	Poznan, Poland	42 (6.6)
Iuliu Hatieganu University of Medicine and Pharmacy	Cluj-Napoca, Romania	35 (5.5)
Maastricht University Medical Center	Maastricht, Netherlands	27 (4.2)
University Hospital of Louvain de Mont-Godinne	Yvoir, Belgium	25 (3.9)
Erasmus Medical Center	Rotterdam, Netherlands	21 (3.3)
Medical University Innsbruck	Innsbruck, Austria	10 (1.6)
Hospital Gral de Catalunya Sant Cugat del Vallès	Barcelona, Spain	10 (1.6)

Age of onset was described best by a three component mixture distribution with lognormally distributed components. The distribution is presented in figure 1.
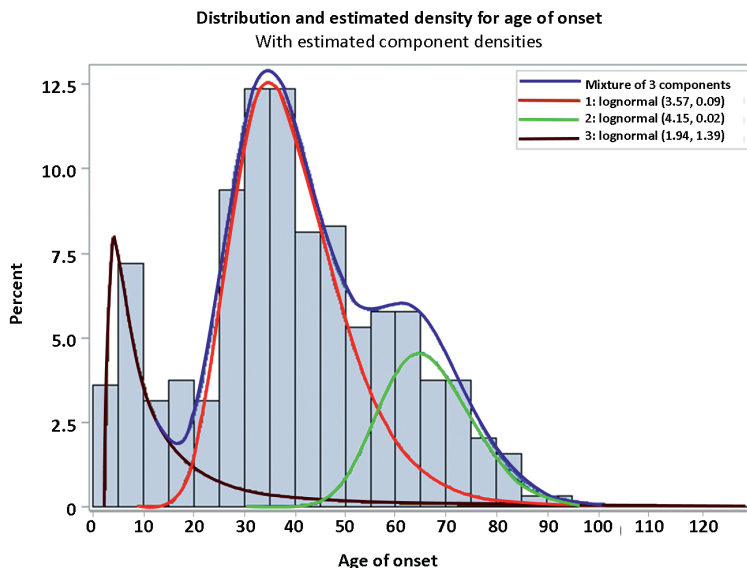
Figure 1. Distribution of age of onset of Recurrent Respiratory Papillomatosis. Included are the lines for the model of the total group and the three best fitting distributions (components) which determine this distribution. N = 639. Horizontal axis: age of onset. Vertical axis: percentage of included patients. Component densities are shown as lognormal (mean, variance).

Table 2 presents median age of onset, mean age of onset, standard deviation of the three distributions, and distribution of the three age groups per sex. Data show that HPV infection starts around three different ages: approximately 7, 35 and 64 years. Due to skewness of the lognormal distribution the average age lies higher, even substantially higher in the youngest group. This skewness also explains the high standard deviation in this age group.

Components	Median age	Mean age	St. dev.	Distribution of gender per component	
				Male	Female
1	6.9	13.9	24.1	33.7%	66.3%
2	35.5	37.1	11.3	53.3%	46.7%
3	63.6	64.2	9.4	71.7%	38.3%

Table 2. The three components of the total distribution of age of onset of Recurrent Respiratory Papillomatosis. The proportion of gender per component is shown. Note that the proportion of females is higher for the first component. St. dev. = standard deviation.

HPV status was not determined in 470 patients (74%). In 169 (26%) patients HPV status was positive for HPV6 or HPV11. This number was too small for a subgroup analysis of age distribution.

Discussion

Synopsis of key findings
This article is the first to analyze the distribution of age of onset. This distribution has three peaks. These incidence peaks are situated around the age of 7, 35 and 64 years. Most patients, regardless of gender, will acquire the disease around the middle age group (35 years). The distribution of age of onset of RRP has many times been cited after Cohn et al. (1981) as bimodal,[16] with peaks of incidence around the age of 5 and between the ages of 30 and 40. The distribution of age of onset was never mentioned in that article, nor statistically substantiated elsewhere.

Although many articles have reported mean age of onset in AoRRP and JoRRP, this article is the first to analyze actual distribution of age of onset of both JoRRP and AoRRP patients. Knowledge of the distribution of age of onset may have great impact on our thinking of HPV spread and prevention strategies.

Strengths of the study
Bayesian statistics are state of the art and an exceptionally suitable technique to analyze hypotheses on distribution.[19] Although Bayesian statistics have been around for more than a century, current computer power enables us to make maximum use of it.[20] Bayesian statistics are extremely suitable to model distributions and will probably be used more often in future medical research.[18-20] Due to these characteristics this statistical technique was used to answer the research question.

Comparison with other studies
Analysis of the incidence of RRP shows a trimodal distribution. RRP is divided in JoRRP and AoRRP. Histologically both entities are considered as one entity.[21] Therefore differentiation between these two entities is artificial. The first peak of incidence of RRP is around the age of 7. Other researchers showed a peak at 4 years of age.[5, 7] This difference in median ages can be explained by two aspects. Firstly, the three component mixture distribution (Figure 1) demonstrates that the three groups are not perfectly separated by specific ages. This implies that we cannot use perfect discrete cutoffs to identify the groups, as is artificially done between JoRRP and AoRRP. Children below the age of 15 years hardly ever

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belong to the second group. Only 0.19% of all people in the second group is younger than 15 years old. However, 25.6% of all people belonging to the first group are more than 15 years old. The additional 25.6% in our group 1, which is typically ignored in traditional JoRRP, increases the median age compared to literature. Secondly, this study describes the age of diagnosis, as this is the most objective measure of disease onset. Especially in children, age of diagnosis can differ up to one year from start of symptoms, mostly due to misdiagnosis.[22, 23] Other articles on JoRRP did not describe their definition of age of onset.[5-9] It is possible that age of start of symptoms is used to describe age of onset in these articles; this can even further explain the relative high median age of onset of the first peak in this study. The second peak of incidence is approximately at the age of 35, which is in agreement with other researchers.[5, 24] We are first to describe a third peak of incidence of RRP, which is found around the age of 64.

Our results show two peaks of age of onset in adults. Data obtained in our series show a remarkably comparable age distribution to that found by Gillison et al., who performed an extensive cross-sectional study with 5579 participants who were older than 14.[25] They showed a bimodal age distribution of oral HPV infection with peaks in persons aged 30 to 34 as well as in persons aged 60 to 64.[25] Those peaks, however, were mostly caused by high-risk HPV types.[25] Two large cohort studies on cervical HPV also describe a second peak of incidence of low-risk HPV above the age of 55.[26, 27] Therefore the peaks of incidence seen in AoRRP patients in our study are probably at least partly related to the incidence of HPV in the population. HPV infection in the juvenile group (first peak) is most probably caused by vertical transmission.[14] The peak between 30 and 34 years is explained by sexual behavior and smoking, which impairs immune response.[25, 28] The peak at the age of 64 cannot explained by these factors. Activation of latent viral infection as a result of age-associated loss of immunity has been suggested.[25, 29] Our data provides the opportunity to investigate a trend in the incidence of HPV infection in older adults, say over 45 years old. For older adults the year of onset does not seem to affect the age of onset substantially (linear regression: P=0.383). Thus the mean age at onset for older adults seems homogeneous over time, which implies that there is no clear trend. It should be noted that our data already contains HPV infection in older adults from 1984.

The division between JoRRP and AoRRP is made on the basis of age of onset; it is justifiable that the third peak represents the median of a third onset type of RRP.

This study shows a gender distribution in RRP of 71% men versus 29% women. This distribution is comparable with distribution shown by other researchers.[5, 30, 31] In addition, this distribution is comparable to the gender distribution of oral HPV infections.[25] It might therefore be related to incidence of oral HPV infection.

Limitations of the study

A limitation of this study is that it was not designed to analyze exact incidence and prevalence numbers of RRP in the population. However, in our study a higher number of patients had AoRRP compared to the number of patients with JoRRP. This is in agreement with the results of Omland et al. who showed an incidence of 0.17 per 100.000 for JoRRP and 0.54 per 100.000 for AoRRP in a European group.[5] Regarding age of onset, the presented sample therefore seems well comparable with that population. Two cities had children's hospitals in their region which treated some local JoRRP patients, leaving them out of our study population. Investigation of these centers showed that exactly 6 JoRRP patients were missed due to referral to a children's hospital. Inclusion of these patients would have had very limited influence on the results considering the presented sample size of 639 patients. A distribution analysis per HPV type was not performed due to absence of this information for too many patients.

Explanation of exclusion criteria

This study was performed in a very large European sample of RRP patients and results can therefore be considered to be representative for Europeans. One could argue that exclusion of hospitals which exclusively treat either children or adults could lead to underrepresentation of one of these groups. In the design of the study it was chosen to exclude these hospitals because overrepresentation of JoRRP or AoRRP patients could lead to unintentional skewness. Exclusion applied to only one participating hospital with 11 children in this study, as they preferably did not treat adults (this center was also excluded due to its non-European settlement). Inclusion would not have changed the trimodal distribution at all and it would have changed the exact numbers very little.

Conclusion

The age of onset of RRP has a trimodal distribution. Peaks in incidence are situated around the ages of 7, 35 and 64.

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