RECURRENT RESPIRATORY PAPILLOMATOSIS

CLINICAL COURSE AND PSYCHOSOCIAL ASPECTS

M.R.M. SAN GIORGI

Recurrent Respiratory Papillomatosis

Clinical course and psychosocial aspects

Michel R.M. San Giorgi

Recurrent Respiratory Papillomatosis
Clinical course and psychosocial aspects
Thesis, Rijksuniversiteit Groningen, The Netherlands

This thesis was written with the guidance of the research institute DARE of the Cancer Research Center Groningen.

Cover: Eric San Giorgi, superdik.com, The Netherlands
Design/ layout: Ferdinand van Nispen, *my*-thesis.nl, The Netherlands
Print: W.M. Veenstra, Groningen, The Netherlands
ISBN: 978-90-367-9814-3

The publication of this thesis was financially supported by:

ALK-Albelló BV, Allergy Therapeutics, Atos Medical, ChipSoft, Daleco Pharma, Dos Medical, Laservision Instruments BV, Mardeno Services BV, Meda Pharma, MediTop, Phonak, Prof. dr. Eelco Huizinga Stichting, Soluvos Medical BV, ZEISS

university of groningen

Recurrent Respiratory Papillomatosis

Clinical course and psychosocial aspects

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. E. Sterken
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

woensdag 5 juli 2017 om 16.15 uur

door

Michel San Giorgi
geboren op 29 juli 1987
te Nijmegen

Promotores
Prof. dr. B.F.A.M. van der Laan
Prof. dr. E.M.D. Schuuring
Prof. dr. F.G. Dikkers

Copromotor
Dr. J.E.H.M. Hoekstra-Weebers

Beoordelingscommissie
Prof. dr. H.A.M. Marres
Prof. dr. C.A.H.H. Daemen
Prof. dr. H. Hollema

Content

Chapter 1

General introduction

Introduction

Recurrent Respiratory Papillomatosis is a disabling disease that is characterized by recurrent growth of exophytic wart-like lesions throughout the airways.[1] The disease is mainly associated with Human Papilloma Virus (HPV) 6 and 11.[2] Patients generally present with speech problems.[3] Without treatment they eventually develop a compromised airway.[3] Although many therapies have been tried, there is no curative treatment for RRP. Due to the recurrent character of RRP, patients depend on repetitive surgical removal of the lesions or papillomas.[3]

1. Human papillomavirus

The Human Papillomavirus (HPV) is a highly prevalent virus, which has a great specificity for tissues and species.[4] It is a small double-stranded non-enveloped DNA virus, which infects merely stem cells in the basal layer of mucosa or skin.[5] Since it was firstly described, 120 HPV types have been found.[4] These HPV types are generally categorized as 'low risk' HPV or 'high risk' HPV, which describes the ability of the virus to transform healthy cells into malignant cells.[6]

The genome of HPV consists of nine multifunctional genes.[6] Seven of these genes are early expressing (E prefix) and two are late expressing (L prefix) in the viral life cycle.[6] The pathologic properties of the virus are caused by the E-genes. These are responsible for the replication of the virus, but more importantly the interaction with the host cell proteins.[6] The L-genes are important for the structural outlay of the virus.[6]

It is thought that the HPV virus enters tissue by invading stem cells of the basal layer through micro-lesions of the epithelium.[7] Due to very low gene expression, the HPV virus induces immune regression and latency.[7] HPV can therefore evade the immune response for years.[8] During cell division HPV DNA is multiplied and distributed into the new cells.[6] Newly formed host cells with HPV DNA then migrate to the upper epithelial layers, while differentiating.[6] Differentiation leads to high levels of amplification of the viral genome.[6] The differentiation of the host cells can lead to the recurrent formation of epithelial lesions.[8]

High-risk HPV types can cause precursor lesions of anogenital cancer, precursor lesions of head and neck cancer, anogenital cancer and head and neck cancer.[9] It is even thought that HPV causes more than 5% of all cancers worldwide.[9] Low-risk HPV types can cause cutaneous warts, anogenital warts, low-grade cervical intraepithelial neoplasm and RRP.[2, 9]

2. Recurrent Respiratory Papillomatosis

2.1 Etiology

Clinically two forms of RRP are recognized; the juvenile onset type (JoRRP, age <18 years) and the adult onset type (AoRRP, age ≥18 years).[10] HPV in JoRRP is vertically transmitted during labor.[11] Newborns born to a mother with condylomata have a more than 200 times higher chance of acquiring RRP compared to children born to a mother without condylomata.[12, 13] In a small number of patients in utero transmission is suspected, as they were born by caesarian section.[14, 15] Firstborns and children of young mothers have a higher chance of acquiring RRP.[11, 14] This is conceivably due to a longer delivery time and therefore a prolonged exposition time to the virus.[13] It is not clear how HPV in AoRRP is transmitted, but an association with orogenital sexual transmission might be a co-factor.[11]

Most of the cellular and immunological pathways that cause RRP are still to be unraveled. It was shown that HPV prevents an effective immune response in RRP patients, although most patients did not show any other immunological problems.[16] The balance between the necessary T helper cell 1 response and the less effective T helper cell 2 [T(h)2] response is shifted towards the T(h)2 side in RRP patients.[16] This effect seems to be site specific and only comprised to the airways.[16] The shift to T(h)2-like chemokines quantitatively predicts disease severity.[17]

2.2 Histology

RRP is histologically recognizable by pedunculated masses with fingerlike projections of non-keratinized stratified squamous epithelium with a central core of fibrovascularized connective tissue (figure 1).[18] Furthermore, a papilloma is histopathologically typified by basal cell hyperplasia, increased mitoses in

the basal layers of the epithelium, koilocytotic changes, nucleomegaly, and dyskeratotic cells.[19] RRP lesions appear mostly at sites in which ciliated and squamous epithelia are juxtaposed.[20] This juxtaposition can also occur when ciliated epithelium is exposed to repeated trauma. Trauma can, for instance, be induced by a tracheostomy. The epithelium then undergoes squamous metaplasia, is replaced with nonciliated epithelium and acts as a new iatrogenic squamociliary junction.[18]

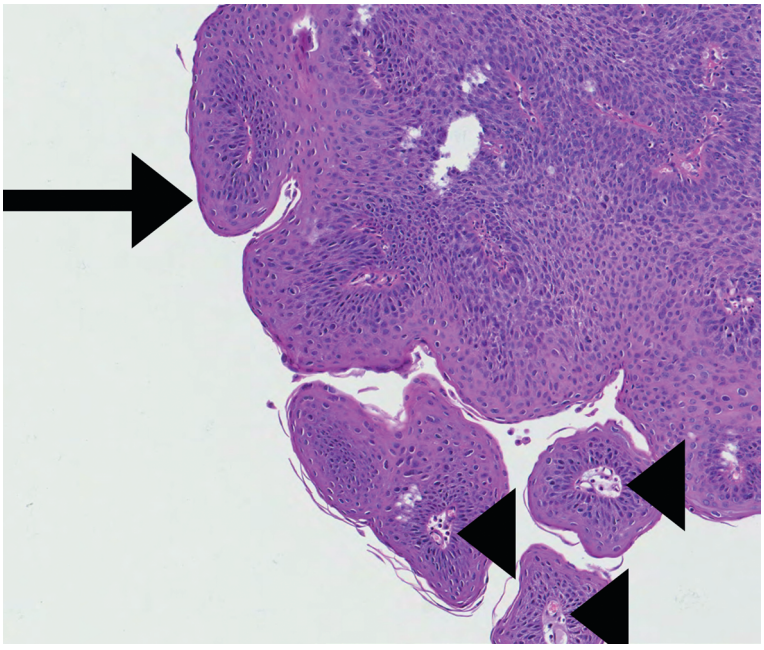


Figure 1. Histological view of RRP (magnification 100x). Fingerlike projections of non-keratinized squamous epithelium (arrow) and centrally fibrovascular tissue (triangles).[1]

2.3 Epidemiology

In many studies various estimations upon the incidence of both JoRRP and AoRRP were reported. Derkay and co-workers estimated an incidence of 4.3 per 100.000 in children and 1.8 per 100.000 in adults.[21] Whereas Omland and coworkers calculated a lower incidence of 0.17 per 100.000 for JoRRP and 0.54 per 100.000 for AoRRP.[10] Approximately 80% of RRP patients are men.[10, 22] The age of onset of RRP is thought to be bimodal with peaks of incidence at the age of 4 and 35, but this was never fully substantiated.[10, 23, 24]

2.4 Clinical presentation

RRP patients present with benign squamous lesions, called papillomas, throughout the respiratory tract, from the nasal vestibule to the peripheral lungs. However, the vocal folds are the most common place of expression (figure 2).[24, 25] The papillomas often spread during the course of the disease.[2]

The clinical presentation depends on the anatomical location of the papilloma. RRP patients mostly present with dysphonia.[26] In later stages of the disease course or if the papillomas are situated somewhere else in the airways the patients may present with stridor or respiratory distress.[26] Between 16 and 25% of all patients develop subglottic and more distally located papillomas.[24, 26, 27] Around 3% of patients develop RRP in the lungs.[28]

Besides these clinical symptoms, patients may present with multiple psychosocial complaints. They find their voice insufficient and suffer from voice problems in normal life.[29-31] Due to these complaints patients report a lower health related quality of life.[30-32] At present, it is not clear what factors can predict whether patients are prone to psychosocial distress and need additional psychosocial help.

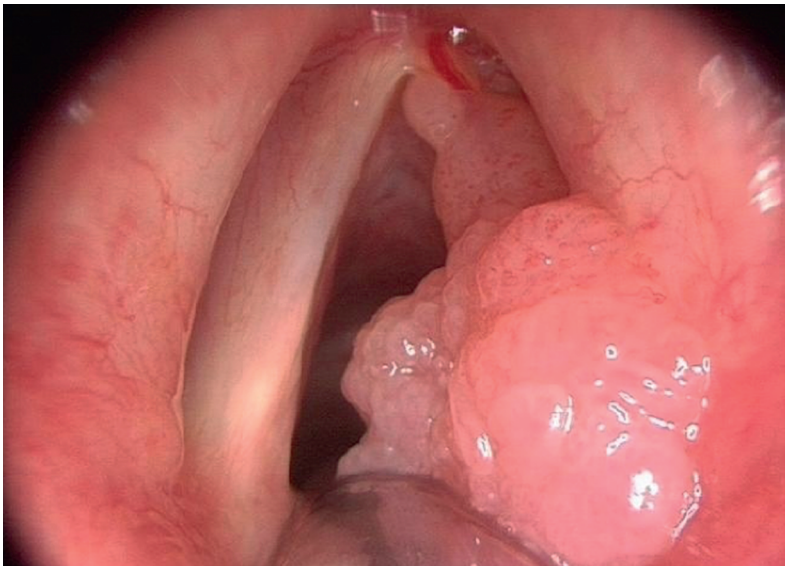


Figure 2. Papilloma at the right vocal fold to the right false vocal cord with anesthesiologic ventilation tube in situ.

2.5 Diagnostics

Diagnostics consist of anamnesis concerning voice and respiratory problems, followed by visual inspection with stroboscopic visualization of the glottic region.[33] The diagnosis of RRP should be confirmed by suspension microlaryngoscopy and consecutive histopathological examination. Recently a new visualization modality was introduced: Narrow Band Imaging (NBI).[1] NBI facilitates the recognition of RRP lesions by their vascular formation.[1] In suspect cases pulmonary involvement has to be excluded by a computed tomography scan of the lungs.[28]

Spread and extension of the disease are often described by three scoring systems, both in daily practice and clinical research. The Dikkers score describes anatomical spread and volume of the lesion.[34] The Derkay/Coltrera score describes the anatomical spread and volume in combination with a functional score.[35] The Voice Handicap Index (VHI-30) is often used to describe the psychosocial burden of the voice complaints of patients.[36]

2.6 Prevention and treatment

Acquisition of the disease is caused by a combination of infection with HPV on one hand, and genetic and immunologic susceptibility on the other. As the latter are not yet adaptable factors, prevention of HPV spread seems to be the most effective approach in eradicating RRP.[9] A quadrivalent vaccine, Gardasil®, was developed for prophylactic prevention of high-risk HPV16 and 18 and low-risk HPV6 and 11 associated disease.[37] Introduction of this vaccine in Australia lead to a highly significant decrease in genital disease associated with low-risk HPV.[38] It is thought that Gardasil® will also diminish the incidence of RRP.[39] The Dutch government provides the vaccine Cervarix®, which only protects against high-risk HPV16 and 18. Theoretically, incidence of RRP will therefore not diminish in the Netherlands.[40]

There is still no curative therapy for RRP. Multiple treatment strategies have been used over the years. The most common treatment is physical removal of the papillomas with 'cold' instruments (forceps and scissors), microdebrider or by laser surgery.[3] Due to the recurrent character of RRP patients may have to undergo more than 100 surgical interventions.[21] Furthermore, multiple adjuvant therapies such as interferon, photodynamic therapy, indole-3-carbinol, ribavirin and acyclovir are used and with still undefined success.[33]

2.7 Clinical course

The clinical course of RRP is highly variable. While some patients have to undergo only few surgical interventions, other patients have to undergo dozens of surgical interventions to reach remission.[2] Many factors are associated with a severe clinical course.[12] Firstly, HPV type seems to have influence on the disease course. Many studies have associated HPV11 with a worse clinical course.[22, 41-43] Few studies have addressed a worse clinical course to patients with HPV6.[44] Secondly, lower age of onset is thought to worsen the disease.[24, 27] It is postulated that the frequency of RRP diminishes naturally during the disease course.[24, 26, 27, 45] The influence of both asthma and gastroesophageal reflux disease on RRP is uncertain.[12] Nevertheless many otolaryngologists tend to use anti-reflux medication in the treatment of RRP.[46] The factors that influence the natural disease course should be analyzed in both AoRRP en JoRRP patients, to diminish unnecessary treatment and for prognostic reasons.

Complications of RRP are the need for a tracheotomy and malignant transformation. It is thought that 4-21% of patients eventually need to undergo tracheotomy to secure the airway.[2] In 2-33% of cases RRP has been reported to be associated with malignant progression.[42, 43, 47]

3. Scope of this thesis

The objective of this thesis is to analyze factors that predict and influence the clinical course of RRP. Furthermore, it gives insight in the effects of the clinical course on patients and provides methods to prevent psychosocial problems in patients.

Part I: Clinical course

It is unknown what age groups are prone for developing RRP. In **chapter 2** the age of onset of RRP is analyzed in a well-defined cohort of 639 European RRP patients.

In **chapter 3.1** the clinical course of RRP in HPV6 patients is compared to the clinical course in HPV11 patients. Other factors influencing disease course, like age of onset and duration of disease, are also studied.

Chapter 3.2 is a response letter to an article that did not take into account factors that naturally influence disease course. It summarizes the factors that should be included when treatment effect is analyzed.

One of the possible treatments to diminish the number of surgical interventions in the clinical course of RRP is therapeutic use of the quadrivalent HPV vaccine. The effect of vaccination on the immune response of RRP patients is shown in **chapter 4**.

Many studies report that gastroesophageal reflux disease negatively influences the clinical course of RRP. This assumption was evaluated by systematically reviewing the literature (**chapter 5**).

Part II: Psychosocial aspects of RRP

The uncertain and often severe clinical course of RRP could be a serious burden for RRP patients. In **chapter 6** RPP patients' perceptions of their quality of life are examined and factors associated with quality of life of RRP patients are analyzed.

Regular screening for distress could uncover the degree and nature of physical and psychosocial problems RRP patients may suffer. Also, patients in need of professional psychosocial care can be referred in time. Regular distress screening may prevent worsening of problems in RRP patients over time. An instrument to screen for distress in RRP patients is validated in **chapter 7**.

Information supply to patients and relatives is important for coping with RRP. A quality and readability analysis of English written online information is given in **chapter 8**.

References

1. Tjon Pian Gi RE, Halmos GB, van Hemel BM, et al. Narrow band imaging is a new technique in visualization of recurrent respiratory papillomatosis. Laryngoscope 2012;122:1826-1830.
2. Donne AJ, Clarke R. Recurrent respiratory papillomatosis: an uncommon but potentially devastating effect of human papillomavirus in children. Int J STD AIDS 2010;21:381-385.
3. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008;118:1236-1247.
4. Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401:70-79.
5. Mistry N, Wibom C, Evander M. Cutaneous and mucosal human papillomaviruses differ in net surface charge, potential impact on tropism. Virol J 2008;5:118.
6. Hebner CM, Laimins LA. Human papillomaviruses: basic mechanisms of pathogenesis and oncogenicity. Rev Med Virol 2006;16:83-97.
7. Doorbar J. Latent papillomavirus infections and their regulation. Curr Opin Virol 2013;3:416-421.
8. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30 Suppl 5:F55-70.
9. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev 2012;25:215-222.
10. Omland T, Akre H, Vardal M, Brondbo K. Epidemiological aspects of recurrent respiratory papillomatosis: A population-based study. Laryngoscope 2012;122:1595-1599.
11. Kashima HK, Shah F, Lyles A, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. Laryngoscope 1992;102:9-13.
12. Niyibizi J, Rodier C, Wassef M, Trottier H. Risk factors for the development and severity of juvenile-onset recurrent respiratory papillomatosis: A systematic review. Int J Pediatr Otorhinolaryngol 2014;78:186-197.
13. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003;101:645-652.
14. Shah KV, Stern WF, Shah FK, Bishai D, Kashima HK. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infect Dis J 1998;17:372-376.
15. Larson DA, Derkay CS. Epidemiology of recurrent respiratory papillomatosis. Apmis 2010;118:450-454.
16. Bonagura VR, Hatam LJ, Rosenthal DW, et al. Recurrent respiratory papillomatosis: a complex defect in immune responsiveness to human papillomavirus-6 and -11. Apmis 2010;118:455-470.
17. Rosenthal DW, DeVoti JA, Steinberg BM, Abramson AL, Bonagura VR. T(H)2-like chemokine patterns correlate with disease severity in patients with recurrent respiratory papillomatosis. Mol Med 2012;18:1338-1345.
18. Derkay CS. Recurrent respiratory papillomatosis. Laryngoscope 2001;111:57-69.
19. Sajan JA, Kerschner JE, Merati AL, Osipov V, Szabo S, Blumin JH. Prevalence of dysplasia in juvenile-onset recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2010;136:7-11.
20. Kashima H, Mounts P, Leventhal B, Hruban RH. Sites of predilection in recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 1993;102:580-583.
21. Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. Arch Otolaryngol Head Neck Surg 1995;121:1386-1391.
22. Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004;114:1-23.
23. Preuss SF, Klussmann JP, Jungehulsing M, Eckel HE, Guntinas-Lichius O, Damm M. Long-term results of surgical treatment for recurrent respiratory papillomatosis. Acta Otolaryngol 2007;127:1196-1201.
24. Campisi P, Hawkes M, Simpson K, Canadian Juvenile Onset Recurrent Respiratory Papillomatosis Working Group. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 2010;120:1233-1245.

25. Sanchez GI, Jaramillo R, Cuello G, et al. Human papillomavirus genotype detection in recurrent respiratory papillomatosis (RRP) in Colombia. Head Neck 2013;35:229-234.
26. Hawkes M, Campisi P, Zafar R, et al. Time course of juvenile onset recurrent respiratory papillomatosis caused by human papillomavirus. Pediatr Infect Dis J 2008;27:149-154.
27. Buchinsky FJ, Donfack J, Derkay CS, et al. Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. PLoS One 2008;3:e2263.
28. Gelinas JF, Manoukian J, Cote A. Lung involvement in juvenile onset recurrent respiratory papillomatosis: a systematic review of the literature. Int J Pediatr Otorhinolaryngol 2008;72:433-452.
29. Ilmarinen T, Nissila H, Rihkanen H, et al. Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis. Laryngoscope 2011;121:846-851.
30. Loizou C, Laurell G, Lindquist D, Olofsson K. Voice and quality of life in patients with recurrent respiratory papillomatosis in a northern Sweden cohort. Acta Otolaryngol 2014;134:401-406.
31. Chadha NK, James A. Adjuvant antiviral therapy for recurrent respiratory papillomatosis. Cochrane Database Syst Rev 2010;(1):CD005053.
32. Lindman JP, Lewis LS, Accortt N, Wiatrak BJ. Use of the Pediatric Quality of Life Inventory to assess the health-related quality of life in children with recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 2005;114:499-503.
33. Derkay CS, Darrow DH. Recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 2006;115:1-11.
34. Dikkers FG. Treatment of recurrent respiratory papillomatosis with microsurgery in combination with intralesional cidofovir--a prospective study. Eur Arch Otorhinolaryngol 2006;263:440-443.
35. Derkay CS, Malis DJ, Zalzal G, Wiatrak BJ, Kashima HK, Coltrera MD. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis. Laryngoscope 1998;108:935-937.
36. Hakkesteegt MM, Wieringa MH, Gerritsma EJ, Feenstra L. Reproducibility of the Dutch version of the Voice Handicap Index. Folia Phoniatr Logop 2006;58:132-138.
37. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.
38. Read TR, Hocking JS, Chen MY, Donovan B, Bradshaw CS, Fairley CK. The near disappearance of genital warts in young women 4 years after commencing a national human papillomavirus (HPV) vaccination programme. Sex Transm Infect 2011;87:544-547.
39. Haupt RM, Sings HL. The efficacy and safety of the quadrivalent human papillomavirus 6/11/16/18 vaccine gardasil. J Adolesc Health 2011;49:467-475.
40. Chow EP, Machalek DA, Tabrizi SN, et al. Quadrivalent vaccine-targeted human papillomavirus genotypes in heterosexual men after the Australian female human papillomavirus vaccination programme: a retrospective observational study. Lancet Infect Dis 2017;17:68-77.
41. Rimell FL, Shoemaker DL, Pou AM, Jordan JA, Post JC, Ehrlich GD. Pediatric respiratory papillomatosis: prognostic role of viral typing and cofactors. Laryngoscope 1997;107:915-918.
42. Gabbott M, Cossart YE, Kan A, Konopka M, Chan R, Rose BR. Human papillomavirus and host variables as predictors of clinical course in patients with juvenile-onset recurrent respiratory papillomatosis. J Clin Microbiol 1997;35:3098-3103.
43. Rabah R, Lancaster WD, Thomas R, Gregoire L. Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. Pediatr Dev Pathol 2001;4:68-72.
44. Padayachee A, Prescott CA. Relationship between the clinical course and HPV typing of recurrent laryngeal papillomatosis. The Red Cross War Memorial Children's Hospital experience 1982-1988. Int J Pediatr Otorhinolaryngol 1993;26:141-147.
45. Silverberg MJ, Thorsen P, Lindeberg H, Ahdieh-Grant L, Shah KV. Clinical course of recurrent respiratory papillomatosis in Danish children. Arch Otolaryngol Head Neck Surg 2004;130:711-716.
46. Goon P, Sonnex C, Jani P, Stanley M, Sudhoff H. Recurrent respiratory papillomatosis: an overview of current thinking and treatment. Eur Arch Otorhinolaryngol 2008;265:147-151.
47. Lee LA, Cheng AJ, Fang TJ, et al. High incidence of malignant transformation of laryngeal papilloma in Taiwan. Laryngoscope 2008;118:50-55.

Part I

Clinical course

Chapter 2

Age of onset of Recurrent Respiratory Papillomatosis: a distribution analysis

M.R.M. San Giorgi MD[1,2], E.R. van den Heuvel PhD[3], R.E.A. Tjon Pian Gi MD, PhD[1,2], J.W. Brunings MD, PhD[4], M. Chirila MD, PhD[5], G. Friedrich MD, PhD[6], M. Golusinski MD, PhD[7], M. Graupp MD, PhD[6], R.A. Horcasitas Pous MD, PhD[8], T. Ilmarinen MD, PhD[9], J. Jackowska MD, PhD[10], J.C. Koelmel MD, PhD[11], F. Ferran Vilà MD, PhD[12], V. Weichbold MD, PhD[13], M. Wierzbicka MD, PhD[10], F.G. Dikkers MD, PhD[1,2]

[1] Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Cancer Research Center Groningen, University of Groningen, The Netherlands
[3] Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, The Netherlands
[4] Department of Otorhinolaryngology/ Head & Neck Surgery, Maastricht University Medical Centre, Maastricht, The Netherlands
[5] Department of Otorhinolaryngology/ Head & Neck Surgery, Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania
[6] Ear, Nose and Throat University Hospital, Department of Phoniatrics, Speech and Swallowing, Medical University of Graz, Graz, Austria
[7] Department of Otorhinolaryngology, Greater Poland Cancer Centre, Poznań, Poland
[8] Pediatric Otolaryngology, Hospital Infantil del Estado de Chihuahua, Chihuahua, Mexico
[9] Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland
[10] Department of Otolaryngology - Head and Neck Surgery, Poznań University of Medical Sciences, Poznań, Poland
[11] Klinik für Hals-, Nasen-, Ohrenkrankheiten, Plastische Operationen, Klinikum-Stuttgart, Stuttgart, Germany
[12] Consulta d'ORL, foniatria i logopèdia, Hosp. Gral de Catalunya (Sant Cugat del Vallès), Barcelona, Spain
[13] Department for Hearing Speech and Voice Disorders, Medical University Innsbruck, Innsbruck, Austria

Clin Otolaryngol. 2016 Oct;41(5):448-53.

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.

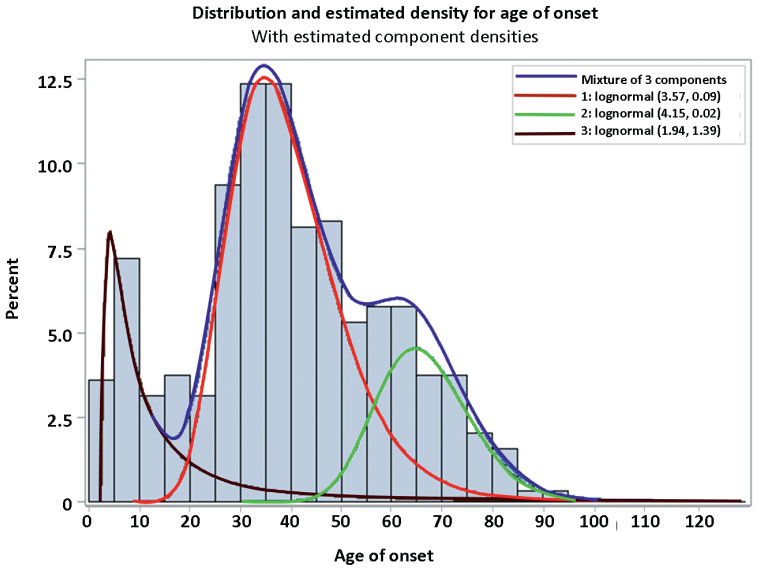


Figure 1. Distribution of age of onset of Recurrent Respiratory Papillomatosis. Included are the lines for the model of the total group and the three best fitting distributions (components) which determine this distribution. N = 639. Horizontal axis: age of onset. Vertical axis: percentage of included 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

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.

Acknowledgements

We would like to thank dr. H. de Gier (department of Otorhinolaryngology and Head & Neck surgery, Erasmus Medical Center, Rotterdam, The Netherlands) and dr. G. Lawson (Department of Otorhinolaryngology, University Hospital of Louvain de Mont-Godinne, Yvoir, Belgium) for their contribution in patient inclusion of this study. Furthermore we would like to thank prof. B.F.A.M. van der Laan (Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands) and prof. E.M. Schuuring (Department of Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands) for their constructive comments on the conception of this study.

References

1. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.
2. Chelimo C, Wouldes TA, Cameron LD, Elwood JM. Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer. J Infect 2013;66:207-217.
3. Kashima H, Mounts P, Leventhal B, Hruban RH. Sites of predilection in recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 1993;102:580-583.
4. Kimberlin DW. Pharmacotherapy of recurrent respiratory papillomatosis. Expert Opin Pharmacother 2002;3:1091-1099.
5. Omland T, Akre H, Vardal M, Brondbo K. Epidemiological aspects of recurrent respiratory papillomatosis: A population-based study. Laryngoscope 2012;122:1595-1599.
6. Armstrong LR, Preston EJ, Reichert M, et al. Incidence and prevalence of recurrent respiratory papillomatosis among children in Atlanta and Seattle. Clin Infect Dis 2000;31:107-109.
7. Campisi P, Hawkes M, Simpson K, Canadian Juvenile Onset Recurrent Respiratory Papillomatosis Working Group. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 2010;120:1233-1245.
8. Seedat RY. The incidence and prevalence of juvenile-onset recurrent respiratory papillomatosis in the Free State province of South Africa and Lesotho. Int J Pediatr Otorhinolaryngol 2014;78:2113-2115.
9. Marsico M, Mehta V, Chastek B, Liaw KL, Derkay C. Estimating the incidence and prevalence of juvenile-onset recurrent respiratory papillomatosis in publicly and privately insured claims databases in the United States. Sex Transm Dis 2014;41:300-305.
10. Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. Arch Otolaryngol Head Neck Surg 1995;121:1386-1391.
11. Lindeberg H, Elbrond O. Laryngeal papillomas: the epidemiology in a Danish subpopulation 1965-1984. Clin Otolaryngol Allied Sci 1990;15:125-131.
12. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. Obstet Gynecol 2003;101:645-652.
13. Shah KV, Stern WF, Shah FK, Bishai D, Kashima HK. Risk factors for juvenile onset recurrent respiratory papillomatosis. Pediatr Infect Dis J 1998;17:372-376.
14. Kashima HK, Shah F, Lyles A, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. Laryngoscope 1992;102:9-13.
15. Ruiz R, Achlatis S, Verma A, et al. Risk factors for adult-onset recurrent respiratory papillomatosis. Laryngoscope 2014;124:2338-2344.
16. Cohn AM, Kos JT,2nd, Taber LH, Adam E. Recurring laryngeal papilloma. Am J Otolaryngol 1981;2:129-132.
17. Tjon Pian Gi RE, Ilmarinen T, van den Heuvel ER, et al. Safety of intralesional cidofovir in patients with recurrent respiratory papillomatosis: an international retrospective study on 635 RRP patients. Eur Arch Otorhinolaryngol 2013;270:1679-1687.
18. Wit E, van den Heuvel E, Romeijn J. All models are wrong...: an introduction to model uncertainty. Statistica Neerlandica 2012;66:217-236.
19. Freedman L. Bayesian statistical methods. Bmj 1996;313:569-570.
20. Woertman WH, Groenewoud HM, van der Wilt GJ. Bayesian statistics: what, how and why? (in Dutch). Ned Tijdschr Geneeskd 2014;158:A7485.
21. Gale N, Poljak M, Kambic V, Ferluga D, Fischinger J. Laryngeal papillomatosis: molecular, histopathological, and clinical evaluation. Virchows Arch 1994;425:291-295.
22. Zacharisen MC, Conley SF. Recurrent respiratory papillomatosis in children: masquerader of common respiratory diseases. Pediatrics 2006;118:1925-1931.

23. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008;118:1236-1247.
24. Preuss SF, Klussmann JP, Jungehulsing M, Eckel HE, Guntinas-Lichius O, Damm M. Long-term results of surgical treatment for recurrent respiratory papillomatosis. Acta Otolaryngol 2007;127:1196-1201.
25. Gillison ML, Broutian T, Pickard RK, et al. Prevalence of oral HPV infection in the United States, 2009-2010. Jama 2012;307:693-703.
26. Castle PE, Schiffman M, Herrero R, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. J Infect Dis 2005;191:1808-1816.
27. Lazcano-Ponce E, Herrero R, Munoz N, et al. Epidemiology of HPV infection among Mexican women with normal cervical cytology. Int J Cancer 2001;91:412-420.
28. Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 2010;34:J258-65.
29. Garcia-Pineres AJ, Hildesheim A, Herrero R, et al. Persistent human papillomavirus infection is associated with a generalized decrease in immune responsiveness in older women. Cancer Res 2006;66:11070-11076.
30. Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004;114:1-23.
31. Buchinsky FJ, Donfack J, Derkay CS, et al. Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. PLoS One 2008;3:e2263.

Chapter 3.1

The clinical course of recurrent respiratory papillomatosis: a comparison between aggressiveness of HPV6 and HPV11.

M.R.M. San Giorgi MD*[1,4], R.E.A. Tjon Pian Gi MD, PhD*[1,4], L. Slagter-Menkema Bsc[1,2,4], B.M. van Hemel MD, PhD[2,4], B.F.A.M. van der Laan MD, PhD[1,4], E.R. van den Heuvel MD, PhD[3,4], F.G. Dikkers MD, PhD[#1,4], E.M.D. Schuuring PhD[#2,4]

** and # these authors contributed equally to this work*

[1] Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Department of Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[3] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[4] Graduate School of Medical Sciences (Groningen University Institute for Drug Exploration), University of Groningen, The Netherlands

Head Neck. 2015 Nov;37(11):1625-32.

Abstract

Background: Recurrent respiratory papillomatosis (RRP) is mainly associated with HPV6 or HPV11. The aim of this study is to compare clinical outcome, aggressiveness and treatment response between HPV6 and HPV11 associated RPP.

Methods: A retrospective cohort of 55 RRP patients (1974-2012) was used. Surgical interventions (n=814) were analyzed, and complications scored. HPV6/11 specific PCR was performed on RRP biopsies.

Results: Seventy-six percent (42/55) of patients were infected with HPV6 and 24% (13/55) with HPV11. The HPV11 group had anatomically more widespread disease. The expected number of surgical interventions was higher in the younger age (<22.4 years) HPV11 group, and the older age (>22.4 years) HPV6 group. Regardless of HPV type, earlier age of onset of RRP resulted in a higher number of surgical interventions.

Conclusions: Anatomically HPV11 associated RRP behaves more aggressively. Young age HPV11 and old age HPV6 patients experience a worse clinical course of RRP.

Introduction

The human papilloma virus (HPV) is a small double-stranded DNA virus [1]. Since it was firstly described, more than 90 HPV types have been found [2]. HPV has been reported to cause cervical cancer, anogenital warts, tonsillar cancer and recurrent respiratory papillomatosis (RRP) [3, 4]. Two low-risk HPV types, HPV6 and HPV11, occur in 83-100% of RRP cases, and these types are generally assumed to be a causative factor in RRP [5-11].

Traditionally, two clinical forms of RRP are recognized: the juvenile onset type (JoRRP) and the adult onset type (AoRRP). Two forms are differentiated by the age of onset, which for the former is usually below 18 years, and for the latter beyond 18 years. Omland et al. calculated an incidence of 0.17 per 100.000 for JoRRP and 0.54 per 100.000 for AoRRP [12].

Frequent surgical 'debulking' or removal of the RRP lesions is necessary to preserve the vocal folds for good phonation and to avoid dyspnea and tracheotomy . Multiple adjuvant therapies (e.g., cidofovir, bevacuzimab and interferon) have been used with variable success to limit the growth of papilloma [13].

Many studies showed that a worse clinical course is attributed to HPV11 (reviewed in [14]). However, others find that HPV6 is associated with a more aggressive behavior [10, 15, 16]. In addition to HPV type, age of onset has an important influence on the disease course of RRP [14]. Finally also comorbidity like asthma or gastroesophageal reflux disease (GERD) can worsen the clinical course of RRP [17, 18].

Knowledge of the clinical course could help to differentiate between treatment effects and the natural course and could thus help to describe the real effectiveness of treatment modalities. Understanding of disease influencing variables like age of onset, HPV type and comorbidities might help to better predict an individual disease course.

The aim of this study is to determine the difference in clinical course of RRP associated with the presence of either HPV6 or HPV11. For this purpose, we

collected 76 RPP patients. A multivariate statistical model, combining HPV type with age of onset, comorbidity and length of disease, was developed to describe severity of disease.

Material and methods

Patients' charts, surgical reports, video and photographic documentation of all 76 RRP patients of the Department of Otorhinolaryngology/ Head & Neck Surgery of the tertiary referral hospital University Medical Center Groningen (UMCG), University of Groningen, the Netherlands, and their surgical interventions were retrospectively analyzed. Inclusion criteria were: [1] histological confirmation of RRP by an experienced ENT-pathologist and [2] the presence of HPV6 or HPV11.

Biopsy and resection material of the included patients were available in our Pathology archives. Prevention of patient identification was provided by coding all patients with anonymous numbers. This study was performed according to the Code of Conduct for proper secondary use of human tissue in the Netherlands, as well as to the relevant institutional and national guidelines [19].

All patient charts were reviewed on date of birth, gender, date of diagnosis, comorbidities (GERD and asthma), follow-up, total number of surgeries and complications associated with RRP (carcinoma, tracheotomy).

All surgical interventions (n=814) were analyzed for surgical technique (cold steel, CO_2 laser and microdebrider) and adjuvant treatment (cidofovir). For 342 surgical interventions comprehensive surgical reports, video and photographic documentation were available. The surgical reports or photographic documentation of 472 surgical interventions were incomplete for scoring. The 342 surgical interventions for which documentation was complete, were scored for the number of anatomical sites and extensiveness per site of the papilloma by the Derkay/Coltrera Score [20] and the three stage Dikkers score [21]. An independent researcher checked accuracy of the scoring.

For each patient a stored paraffin block from the first biopsy with histopathologically confirmed papilloma was selected. An experienced pathologist revised all biopsies to confirm the presence of papilloma. When the quality or quantity of the first biopsy was not sufficient for analysis with polymerase chain reaction (PCR), the next sufficient biopsy was used. HPV negative biopsies were retested with the same technique.

HPV type specific Polymerase Chain Reaction

DNA was extracted from paraffin embedded tissue of RRP biopsies. A hundred nanogram of this DNA was analyzed by PCR on high-risk HPV, using HPV16 and HPV18 specific primers as described in literature [22]. The detection of the presence of the low-risk HPV6 and HPV11, genomic DNA was analyzed using specific HPV6-PCR-primers (HPV 6.1: 5'TAGTGGGCCTATGGCTCGTC and HPV 6.2: 5' TCCATTAGCCTCCACGGGTG) and specific HPV11-PCR- primers (HPV 11.1: 5' GGAATACATGCGCCATGTGG and HPV 11.2: 5' CGAGCAGACGTCCGTCCTCG) [23]. A general HPV PCR using the HPV consensus primer set GP5+/6+ with subsequent nucleotide sequence analysis was used on all HPV6/11-negative cases [22].

In all tests a serial dilution of DNA extracted from CaSki (ATCC; CRL1550; 500 integrated HPV16 copies), HeLa (ATCC; CCL2; 20–50 integrated HPV 18 copies), SiHa (ATCC; HTB35; 1– 2 integrated HPV16 copies), CC10B (HPV45-positive cell line) and CC11 (HPV67 positive cell line), and HPV-negative cell lines were included as control for the analytical specificity and sensitivity of each hrHPV-PCR. DNA extracted from HPV6- and HPV11-positive laryngeal papillomas that were previously identified, was used for the analytical specificity of the HPV6 and HPV11 PCR.

Contamination of amplification products was prevented by using separate laboratories for pre- and post-PCR handling, and applying all standard precautions,. Cross-contamination was prevented by using a new microtome blade any time a new case was sectioned. For quality control, genomic DNA was amplified in a multiplex PCR containing a control gene primer set resulting in products of 100, 200, 300, 400 and 600 bp according to the BIOMED-2/ Euroclonality protocol [24]. Only DNA samples with PCR products of 300 bp and larger were used for the detection of HPV. All samples were tested on DNA extracted from two independent slides (duplicates).

Statistical analysis

The HPV6 and HPV11 groups were compared on demographics, surgical interventions and characteristics indicating disease severity. The Fisher's exact test was used for categorical variables and the t-test was used for numerical data. The Mann-Whitney test was applied when the numerical data did not seem to follow a normal distribution. Analyses were performed using PASW statistics version 20.0 (SPSS Inc., Chicago, IL, USA) and SigmaPlot version 10.0 (Systat Software Inc., Chicago, IL, USA).

An independent researcher performed an accuracy check of the anatomical part of the Derkay score and the Dikkers score on 40 (12%) of the 342 scored surgical interventions (power analysis described by Walter et al.: n=2, α=0.05, β=0.20, ρ0=0.6 and ρ1=0.8 [25]). These surgical interventions were selected by 'random sample' modus in SPSS. Accuracy between observers of the Derkay anatomical score was assessed by a one-way random effects analysis of variance mode, from which the intraclass correlation coefficient was estimated.

To determine the expected surgical intervention course, a new model was generated. For this model the total number of surgical interventions was analyzed with a negative binomial distribution, an extension of the Poisson distribution to address overdispersion. The analysis involved three steps. The first step screened statistically relevant variables that influence the number of surgical interventions. The effect of this variable was used to correct for (the logarithmically transformed) follow-up time, since longer follow-up time is expected to be associated with larger numbers of surgical interventions. Variables were selected when the p value would be less than 0.25. The second step made a multivariate model that includes HPV6 and 11, the selected variables, and all possible interaction effects of the type of HPV and these variables, again corrected for follow-up time. The third step entailed backward elimination to eliminate non-significant terms from the model, always keeping the model hierarchical. The level for the p value for backward elimination was equal to 0.05. The final model indicated whether the type of HPV, possible through an interaction, would affect the number of surgical interventions. Variables that were investigated were age at first surgical intervention, sex, GERD, asthma and the percentage of surgical technique per patient (CO_2 laser, cold steel surgery and microdebrider). The average number of operations was

modeled through the log link function. The analysis was conducted with the GENMOD procedure of SAS® (SAS institute Inc, Cary, North Carolina), version 9.3.

Categorical variables are presented as number (percentage). Normally distributed variables are presented as mean ± standard deviation. Not normally distributed variables are given as medians [interquartile range]. P value of <0.05 was considered as statistically significant. Absolute reliability was assessed by the standard error of measurement and 95% limits of agreement.

Results

Seventy-six patients were registered with RRP at the Department of Pathology, UMCG, between 1974 and 2012 (figure 1). Seven patients were excluded due to absence of biopsies. Fourteen patients were excluded because no HPV6, HPV11 or other low/high risk HPV types were detected. Fifty-five patients were included for further analysis. Seventy-six percent of patients (42/55) were infected with HPV6 and 24% with HPV11 (13/55). No patients were infected with both HPV6 and HPV11. One patient infected with HPV6 was coinfected with HPV33. None of the other included patients were coinfected with HPV16 and HPV18, or other high-risk HPV types.

The 55 HPV6/11 positive patients underwent a total of 814 (100%) surgical interventions. Information on the surgical technique and adjuvant therapy was available for 602 (74%) surgeries. Video and/or photographic material of 342 (42%) surgical interventions were available for scoring of the Derkay/Coltrera and Dikkers score. The intraclass correlation coefficient for the Derkay score between the two observers was 0.845 ($p<0.001$). Accuracy between observers of the Dikkers score was assessed by Kappa statistics for ordinal variables on the same surgical interventions. Interrater agreement was found to have a Kappa of 0.817 ($p<0.001$).

No statistically significant differences were found between visually scored and textually scored surgical interventions for either the Derkay/Coltrera score or the Dikkers score ($p=0.691$ and $p=0.892$ respectively). Therefore the visually and textually scored Derkay and Dikkers scores were considered reliable.

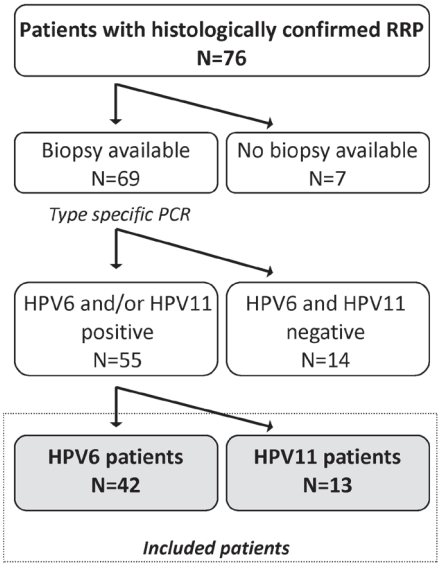


Figure 1. Flowchart of included and excluded Recurrent Respiratory Papillomatosis patients.

Table 1 shows the demographic characteristics and surgical technique per group. A statistically significant higher number of patients infected with HPV11 had asthma (p=0.009) although the number of patients with asthma represents only 5 cases (9.1%).

Table 1. Demographic characteristics and surgical technique compared between Recurrent Respiratory Papillomatosis patients infected with HPV6 (n=42) and HPV11 (n=13). Categorical data are presented as number (percentage). Not normally distributed variables are presented as median [interquartile range].

Patients	**All patients No. of patients 55**	**HPV6 No. of patients 42**	**HPV11 No. of patients 13**	**p *value***
Sex		32 (76.2)		0.709
Male	43 (78.2)	10 (23.8)	11 (84.6)	
Female	12 (21.8)		2 (15.4)	
Age at diagnosis in years	34 [21-44]	35 [23-45]	28 [6-39]	0.171
RRP type				
JoRRP	12 (21.8)	8 (19.0)	4 (30.8)	
AoRRP	43 (78.2)	34 (81.0)	9 (69.2)	0.448
Comorbidities				
Asthma	5 (9.1)	1 (2.4)	4 (30.8)	0.009
GERD	2 (3.6)	2 (4.8)	0 (0.0)	1.000
Treated with cidofovir	31 (56.4)	25 (59.5)	6 (46.2)	0.525
Duration of follow-up in years	9.4 [3.5-16.5]	8.5 [3.5-14.0]	13.5 [4.4-23.8]	0.148

Table 1. continued

Surgeries	Total No. of surgeries 602	HPV6 No. of surgeries 365	HPV11 No. of surgeries 237	
Surgical technique:				
Only cold steel	330 (54.8)	239 (65.5)	91 (38.4)	
CO_2 laser	235 (39.0)	99 (27.1)	136 (57.4)	
Microdebrider	37 (6.1)	27 (7.4)	10 (4.2)	<0.001*

Abbreviations: JoRRP, juvenile onset recurrent respiratory papillomatosis. AoRRP, adult onset recurrent respiratory papillomatosis. GERD, gastroesophageal reflux disease.
*By Chi square test.

More cold steel surgeries were performed in the HPV6 group (p<0.001). On the other hand more CO_2 laser surgeries were performed in the HPV11 group (p<0.001). Figure 2 shows the trend of surgical technique and the proportion of the diagnosis of HPV6 and HPV11 through time.

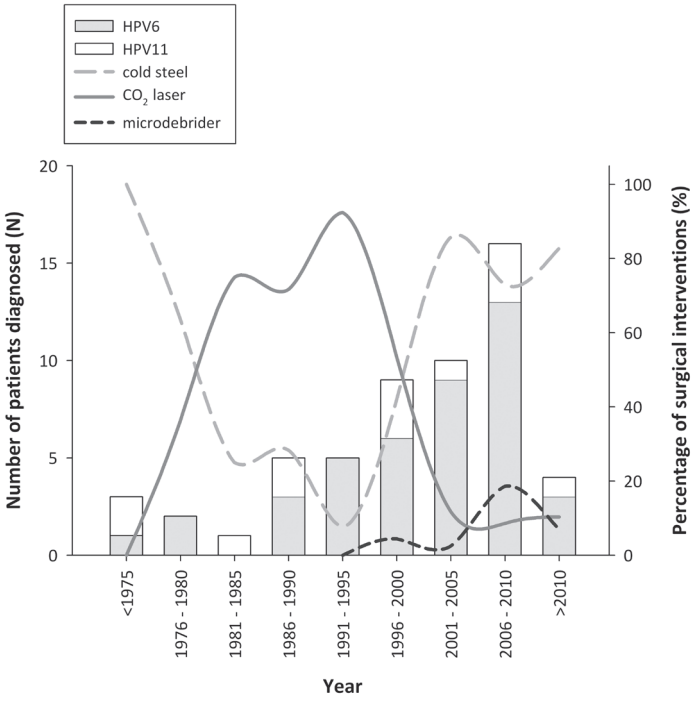


Figure 2. Percentage of used surgical techniques and the number of new diagnosed Recurrent Respiratory Papillomatosis patients with HPV6 and HPV11 through time.

The surgical course over time per patient is presented in figure 3. There is a wide variety in the number of surgical interventions, range 1-152 (respectively 2-78 for HPV6 patients and 1-152 for HPV11). Surgical intervals varied from 4 days to 34 years.

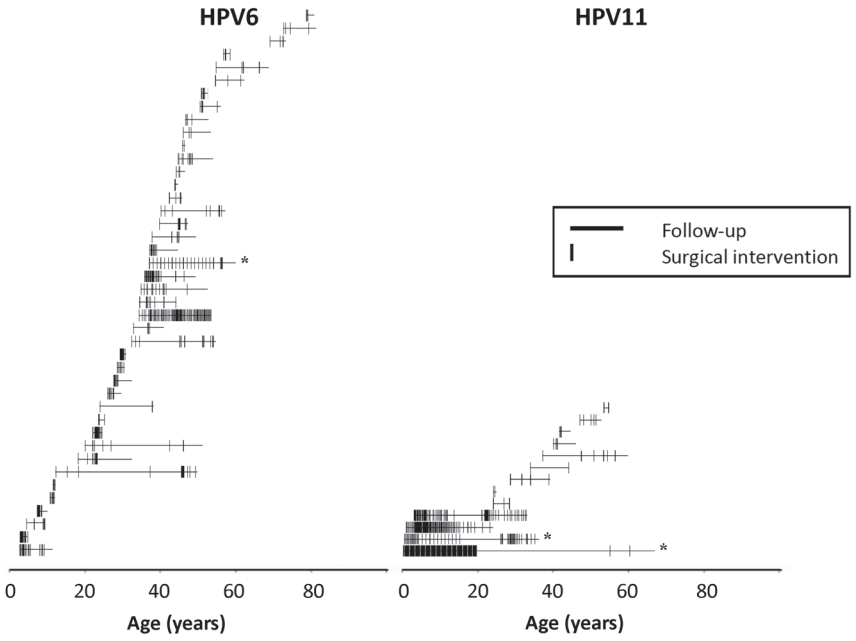


Figure 3. Follow-up with all surgical interventions per patient by age of the patient. Patients are grouped on HPV6 (n=42) or HPV11 (n=13).

*Exact number of surgical interventions known per period, exact day/month unknown.

At the start of the disease the surgical frequency is high in both HPV groups. The frequency of surgical interventions on average is reducing with follow-up time; this was demonstrated in the statistical analysis of the number of surgical interventions ($p<0.001$).

Table 2 summarizes the surgical outcome compared between patients with HPV6 positive and HPV11 positive RPP. The results have been split up in a section per patient and a section per surgical intervention.

Table 2. Outcome characteristics per patient and per surgical intervention compared between HPV6 (n=42) and HPV11 (n=13) infected Recurrent Respiratory Papillomatosis patients. Categorical data are presented as number (percentage). Normally distributed variables are presented as mean ± standard deviation. Not normally distributed variables are presented as median [interquartile range].

Results per patient	**HPV 6 No. of patients 42**	**HPV 11 No. of patients 13**	**p value**
Total number of surgeries per patient	6 [4-10]	5 [3-38]	0.889
Peak surgical frequency per year	3.8 ±2.2	4.2 ± 6.0	0.788
Surgical frequency in the first year	3.1 ± 2.2	3.2 ± 3.7	0.903
≥10 surgical procedures	12 (28.6)	4 (30.8)	1.000
Frequency ever ≥4 per year	20 (47.6)	4 (30.8)	0.349
Extralaryngeal involvement	5 (11.9)	5 (38.5)	0.045
Distal involvement	1 (2.4)	3 (23.1)	0.037
Tracheotomy	0 (0.0)	2 (15.4)	0.053
Malignancy	0 (0.0)	0 (0.0)	1.000
Results per surgery			
Total number of surgeries	254	88	
Anatomical Derkay/Coltrera score	6.1 ± 3.4	7.1 ± 4.7	<0.01
Number of anatomical locations*	2.6 ± 1.4	3.0 ± 1.4	<0.01
Dikkers score			
1	95 (37.4)	27 (30.7)	
2	28 (11.0)	7 (8.0)	
3	131 (51.6)	54 (61.4)	0.274†

* By the Derkay/Coltrera score. †By Chi square test.

Although the mean number of surgical interventions is much higher, the median number of surgical interventions per patient was 6 (range 2-78) for HPV6 patients and 5 (range 1-152) for HPV11 patients, yielding no statistically significant difference (p=0.889). No statistically significant differences were found in surgical frequency in the first year per patient or in peak surgical frequency per patient.

HPV11 patients had a statistically significant higher number of anatomical locations of the papillomata (by the Derkay/Coltrera score) in the respiratory tract than HPV6 patients (p<0.01). However, the Dikkers score per surgical intervention (p=0.274) did not differ statistically between groups. As a consequence the Derkay/Coltrera anatomical score per surgical intervention was higher in the HPV11 group (p<0.01).

Patients infected with HPV11 had statistically significant more often extralaryngeal spread of the papillomata (for instance in the nose, pharynx or

the trachea) than HPV6 infected patients (38.5% of HPV11 patients vs. 11.9% of HPV6 patients, p=0.045). HPV11 patients did have more distal involvement of papillomata (trachea)(23.1% vs. 2.4% respectively, p=0.037). Tracheotomies were only performed in the HPV11 group (in 1995 and 2008).

To describe the number of expected surgical interventions at any moment after diagnosis a model was designed on the patient population of 55 patients with their 814 surgical interventions. This model shows the influence of age of onset, HPV type (HPV6 or HPV11), co-morbidities and time after diagnosis. The percentages of surgical techniques used for a patient (CO_2 laser, cold steel surgery and microdebrider) were initially selected to build the multivariate model, but they did not contribute significantly to the final model. Figure 4 shows the visual representation of the clinical course of 5 exemplary patients (age of onset 1 year, 5 years, 20 years, 40 years and 60 years) with either HPV6 or HPV11, corrected for the influence of asthma and GERD.

Patients with a young age of onset are likely to run a more relapsing and longstanding course of the disease with a higher surgical frequency. Irrespective of age of onset, the surgical frequency is the highest in the first years, decreasing each year after diagnosis. At age of diagnosis of 1 year and 5 years the predicted number of surgeries is higher for HPV11 patients (resp. $p<0.001$ and $p<0.001$). At age of diagnosis of 40 years and 60 years the predicted number of surgical interventions is higher for HPV6 patients (resp. $p<0.001$ and $p<0.001$). At young age, HPV11 infected patients are expected to undergo more surgical interventions than HPV6 infected patients. At older age, however, patients are expected to undergo more surgical interventions when infected with HPV6 in comparison to patients infected with HPV11. Statistically the estimated switch point of this effect is at 22.4 years of age.

Discussion

Patients suffering from RRP will experience severity of disease on several parameters. Amongst them are number of surgeries, and comorbidity of disease as tracheostomy and development of malignancy. This study shows aggressiveness of the clinical course between HPV6 and HPV11 infected RRP patients.

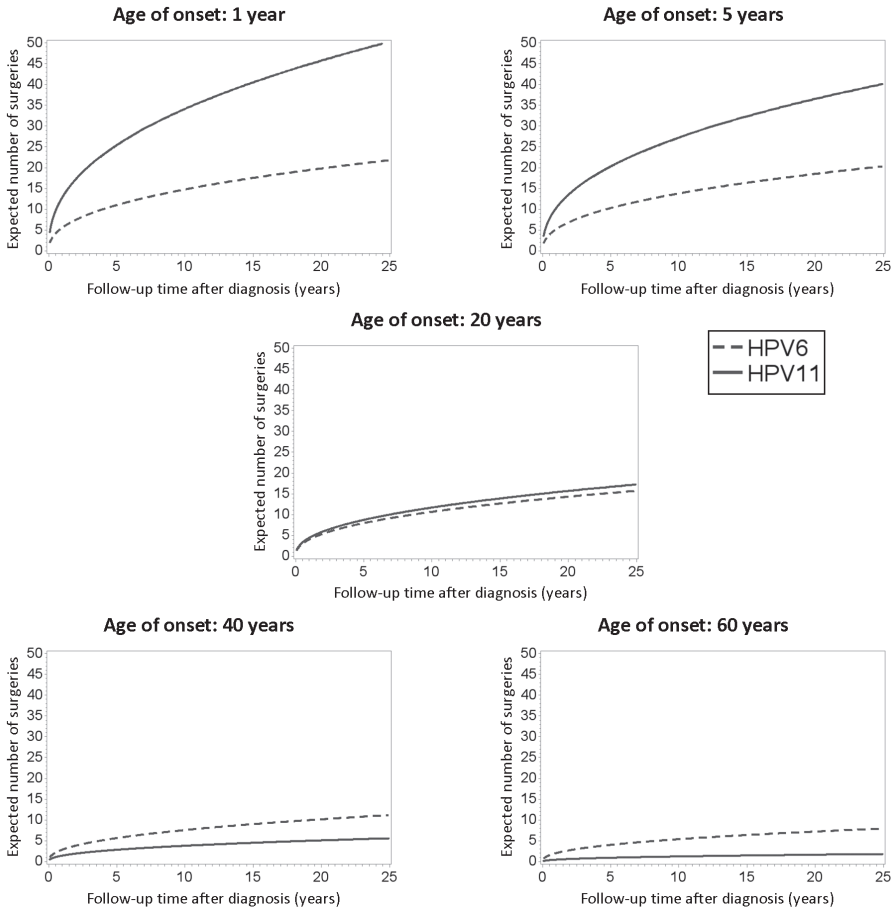


Figure 4. Outcome of the statistical model describing the difference between HPV6 and HPV11 patients concerning the expected number of surgical interventions in years after diagnosis for five exemplary groups (age 1 year, 5 years, 20 years, 40 years and 60 years)(resp. p<0.001, p<0.001, p=0.074, p<0.001 and p<0.001). A correction was made for the influence of gastroesophageal reflux disease and asthma.

The focus of this study was to investigate the clinical course of RRP associated with the two most reported causal HPV types, HPV6 and HPV11. More HPV6 patients than HPV11 patients were included. In literature there is a wide variety in incidence of HPV6 and HPV11 in RRP [26]. The causal factor might be the difference in geographic spread of both HPV types [27]. In fourteen (20%) of the 69 RRP patients with histologically proven RRP neither HPV6, nor HPV11 was detected. These patients were not included in this study. Twenty percent is high in comparison to percentages mentioned in literature (0-17%) [5, 6, 8, 10, 11]. We expect this value to normalize with a larger cohort. Using analytically sensitive

PCR, no patients with both HPV6 and HPV11 were found. Other researchers using the same HPV typing modalities found 2-14% of double infected patients [6, 10, 15]. Both JoRRP patients and AoRRP patients were included to describe the influence of HPV type on RRP for all ages of onset.

In this study, we compared HPV6 and HPV11 positive patients. Approximately 80% of the population was male, in agreement with earlier reports [8, 12, 14]. Lower age of onset has been described as an important predictor for a worse clinical course [14, 28, 29]. We found no difference in age of onset between groups and therefore groups were comparable. The higher number of AoRRP patients against JoRRP patients is in accordance with the population described by Omland et al [12]. Derkay et al. however described a higher incidence of JoRRP [30], which could be due to the worldwide difference in HPV rates [27].

There was no difference in the number of patients with gastroesophageal reflux disease (GERD). Prevalence of asthma in this study was comparable with the prevalence of asthma in the Netherlands [31]. A higher number of patients with asthma was found in the HPV11 group, which could potentially have worsened the clinical course. Due to the earlier described influence on disease course the statistical model was corrected for GERD and asthma.

Significantly different surgical techniques were used for either HPV6 of HPV11 patients, without the surgeon taking the causative virus as a decisive factor in choosing the established surgical technique. As shown in figure 2 the used surgical technique was time related, due to a changing vision on effectiveness of the different techniques. In line with common opinion, CO2 laser is almost not used anymore in the treatment of RRP. In the multivariate analysis on the total number of surgeries the surgical technique (either CO_2 laser, cold steel surgery or microdebrider) did not significantly correlate with the number of surgical interventions. Other researchers did not find a difference in disease eradication between surgical techniques either [28].

Interestingly HPV11 patients had statistically significantly more extralaryngeal spread of their papillomata. This has not been described in literature. In various studies 6-25% of JoRRP patients had distal spread [14, 32]. There are no reported numbers of distal spread in AoRRP. We observed that 7.3% of all patients had distal

spread (table 2). Interestingly this was more prominent within the HPV11 group. A few studies associated distal spread with incurable papillomas in the lung and eventually lung cancer [7, 33-35]. No such complications were found in this research.

None of the included patients developed a malignancy from RRP. In other studies, the presence of HPV6 and/or HPV11 was associated with malignant progression in 2-33% of the RPP cases [10, 36, 37]. Because HPV6 and HPV11 are considered low-risk HPV types, other factors might be responsible for progression. The coinfection with a high-risk HPV has been suggested to be associated with malignant progression [26]. This is in good agreement with our findings that none of the HPV6/11 positive RPP cases tested positive for HPV16/18 and none of our cases progressed to cancer with a median follow-up time of 9.4 years (table 1).

Limitations of this study include those inherent to a retrospective study. Therefore we were not able to perform the analysis of the Derkay/Coltrera and Dikkers score on all 814 surgical interventions. This could have influenced the outcome of the Derkay/Coltrera and the Dikkers score. But because of the long follow-up the scored number of interventions is still very high, this minimizes the effect of missing surgical data on outcome. Results show a higher Derkay/Coltrera score per surgery for the HPV11 group. This means that HPV11 patients had papillomata at more anatomical sites (by the Derkay/Coltrera score) and that these papillomata were more extensive per site. No statistically significant difference in the Dikkers score was found. This can be explained by the fact that the Dikkers score is designed for clinical use with therapeutic intent, and this scoring system differentiates between more extensive anatomical differences than the Derkay/Coltrera score does. Therefore we advocate to use the Derkay/Coltrera score in future studies, which describes the amount of papillomata.

A multivariate statistical model, combining HPV type with age of onset and time after diagnosis, was applied to study the aggressiveness of the disease course. Until now less complicated models for disease aggressiveness were described in literature, but our model clearly shows that both HPV type and age of onset are correlated with surgical intervention course. The analysis using this model revealed that a higher number of surgical interventions in RRP patients was correlated with a young age of onset. This multivariate statistical model shows

a positive logarithmic curve corresponding with more surgical interventions in the first years of the disease, as we call the 'modulating phase'. A higher number of surgical interventions at the beginning of the disease may have two causes. Firstly, RRP is characterized by a more aggressive course at the beginning of the disease. Secondly, at presentation patients have too widespread or extensive RRP to control at once. This is especially the case with bilateral glottic papillomas, where surgery in two steps is needed to avoid web formation.

Little is known about the etiological and immunological factors, which could explain differences in clinical course of RRP between HPV6 and HPV11. Further research is needed to analyze viral mechanisms of HPV6 and HPV11 and the cellular response to these viruses.

Our data show that even after 34 years the symptoms can relapse. Considering this, it is more accurate to use the term 'clinical remission' rather than 'the cure' of RRP.

Conclusion

HPV11 infected RRP patients have a higher number of papillomata, which are also more widespread in the respiratory tract in comparison with patients infected with HPV6. Therefore, HPV11 is associated with higher Derkay scores than HPV6.

The expected surgical frequency in patients with RRP is highest in the first years after diagnosis. Furthermore HPV11 induces a worse surgical prognosis. This difference is more pronounced in patients with a younger age of onset. Our statistical model indicates that there is a switch point for this effect of age in combination with HPV type. This would mean that at a higher age HPV6 infected patients need to undergo more surgical interventions, but further research with larger numbers is needed to confirm this finding. The symptom free period should more accurately be called 'clinical remission', as our data shows that RPP can recur even after 34 years.

This research shows the need for HPV typing in research on RRP treatment to determine the true effect of the treatment modality corrected for the influence of HPV type.

References

1. Mistry N, Wibom C, Evander M. Cutaneous and mucosal human papillomaviruses differ in net surface charge, potential impact on tropism. Virol J 2008;5:118.
2. Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401:70-79.
3. Chelimo C, Wouldes TA, Cameron LD, Elwood JM. Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer. J Infect 2013;66:207-217.
4. Gillison ML, Alemany L, Snijders PJ, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine 2012;30 Suppl 5:F34-54.
5. Sanchez GI, Jaramillo R, Cuello G, et al. Human papillomavirus genotype detection in recurrent respiratory papillomatosis (RRP) in Colombia. Head Neck 2013;35:229-234.
6. Draganov P, Todorov S, Todorov I, Karchev T, Kalvatchev Z. Identification of HPV DNA in patients with juvenile-onset recurrent respiratory papillomatosis using SYBR Green real-time PCR. Int J Pediatr Otorhinolaryngol 2006;70:469-473.
7. Gerein V, Rastorguev E, Gerein J, Draf W, Schirren J. Incidence, age at onset, and potential reasons of malignant transformation in recurrent respiratory papillomatosis patients: 20 years experience. Otolaryngol Head Neck Surg 2005;132:392-394.
8. Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004;114:1-23.
9. Moore CE, Wiatrak BJ, McClatchey KD, et al. High-risk human papillomavirus types and squamous cell carcinoma in patients with respiratory papillomas. Otolaryngol Head Neck Surg 1999;120:698-705.
10. Gabbott M, Cossart YE, Kan A, Konopka M, Chan R, Rose BR. Human papillomavirus and host variables as predictors of clinical course in patients with juvenile-onset recurrent respiratory papillomatosis. J Clin Microbiol 1997;35:3098-3103.
11. Pou AM, Rimell FL, Jordan JA, et al. Adult respiratory papillomatosis: human papillomavirus type and viral coinfections as predictors of prognosis. Ann Otol Rhinol Laryngol 1995;104:758-762.
12. Omland T, Akre H, Vardal M, Brondbo K. Epidemiological aspects of recurrent respiratory papillomatosis: A population-based study. Laryngoscope 2012;122:1595-1599.
13. Kimberlin DW. Pharmacotherapy of recurrent respiratory papillomatosis. Expert Opin Pharmacother 2002;3:1091-1099.
14. Buchinsky FJ, Donfack J, Derkay CS, et al. Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. PLoS One 2008;3:e2263.
15. Penaloza-Plascencia M, Montoya-Fuentes H, Flores-Martinez SE, Fierro-Velasco FJ, Penaloza-Gonzalez JM, Sanchez-Corona J. Molecular identification of 7 human papillomavirus types in recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2000;126:1119-1123.
16. Padayachee A, Prescott CA. Relationship between the clinical course and HPV typing of recurrent laryngeal papillomatosis. The Red Cross War Memorial Children's Hospital experience 1982-1988. Int J Pediatr Otorhinolaryngol 1993;26:141-147.
17. Robb PK,Jr, Weinberger PM, Perakis H, et al. Association of asthma with clinically aggressive recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2011;137:368-372.
18. McKenna M, Brodsky L. Extraesophageal acid reflux and recurrent respiratory papilloma in children. Int J Pediatr Otorhinolaryngol 2005;69:597-605.
19. Code for proper secondary use of human tissue in the Netherlands. 2002;2014.
20. Derkay CS, Malis DJ, Zalzal G, Wiatrak BJ, Kashima HK, Coltrera MD. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis. Laryngoscope 1998;108:935-937.
21. Dikkers FG. Treatment of recurrent respiratory papillomatosis with microsurgery in combination with intralesional cidofovir--a prospective study. Eur Arch Otorhinolaryngol 2006;263:440-443.

22. Wisman GB, Nijhuis ER, Hoque MO, et al. Assessment of gene promoter hypermethylation for detection of cervical neoplasia. Int J Cancer 2006;119:1908-1914.
23. Halmos GB, van der Laan TP, van Hemel BM, et al. Is human papillomavirus involved in laryngeal neuroendocrine carcinoma? Eur Arch Otorhinolaryngol 2013:719-725.
24. van Dongen JJ, Langerak AW, Bruggemann M, et al. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: report of the BIOMED-2 Concerted Action BMH4-CT98-3936. Leukemia 2003;17:2257-2317.
25. Walter SD, Eliasziw M, Donner A. Sample size and optimal designs for reliability studies. Stat Med 1998;17:101-110.
26. Donne AJ, Hampson L, Homer JJ, Hampson IN. The role of HPV type in Recurrent Respiratory Papillomatosis. Int J Pediatr Otorhinolaryngol 2010;74:7-14.
27. de Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis 2007;7:453-459.
28. Campisi P, Hawkes M, Simpson K, Canadian Juvenile Onset Recurrent Respiratory Papillomatosis Working Group. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 2010;120:1233-1245.
29. Derkay CS, Hester RP, Burke B, Carron J, Lawson L. Analysis of a staging assessment system for prediction of surgical interval in recurrent respiratory papillomatosis. Int J Pediatr Otorhinolaryngol 2004;68:1493-1498.
30. Derkay CS. Task force on recurrent respiratory papillomas. A preliminary report. Arch Otolaryngol Head Neck Surg 1995;121:1386-1391.
31. To T, Stanojevic S, Moores G, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health 2012;12:204-2458-12-204.
32. Hawkes M, Campisi P, Zafar R, et al. Time course of juvenile onset recurrent respiratory papillomatosis caused by human papillomavirus. Pediatr Infect Dis J 2008;27:149-154.
33. Silver RD, Rimell FL, Adams GL, Derkay CS, Hester R. Diagnosis and management of pulmonary metastasis from recurrent respiratory papillomatosis. Otolaryngol Head Neck Surg 2003;129:622-629.
34. Hasegawa Y, Sato N, Niikawa H, et al. Lung squamous cell carcinoma arising in a patient with adult-onset recurrent respiratory papillomatosis. Jpn J Clin Oncol 2013;43:78-82.
35. Ruan SY, Chen KY, Yang PC. Recurrent respiratory papillomatosis with pulmonary involvement: a case report and review of the literature. Respirology 2009;14:137-140.
36. Lee LA, Cheng AJ, Fang TJ, et al. High incidence of malignant transformation of laryngeal papilloma in Taiwan. Laryngoscope 2008;118:50-55.
37. Rabah R, Lancaster WD, Thomas R, Gregoire L. Human papillomavirus-11-associated recurrent respiratory papillomatosis is more aggressive than human papillomavirus-6-associated disease. Pediatr Dev Pathol 2001;4:68-72.

Chapter 3.2

The clinical course of recurrent respiratory papillomatosis after the use of cidofovir is influenced by multiple factors

M.R.M. San Giorgi MD[1,2,3], R.E.A. Tjon Pian Gi MD, PhD[1,2,3], F.G. Dikkers MD, PhD[1,2,3]

[1] Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Graduate School of Medical Sciences (Groningen University Institute for Drug Exploration), University of Groningen, Groningen, The Netherlands
[3] Groningen Papilloma Studies, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Eur Arch Otorhinolaryngol. 2015 Jul;272(7):1819-20.

Sir,

With great interest we read the article of Grasso et al. on the use of cidofovir in treatment of recurrent respiratory papillomatosis (RRP) [1]. The article discusses the positive influence regarding the number of interventions needed to eradicate papillomas after repeated administration of cidofovir. Although we have applied cidofovir for many years [2] and its long term safety has been shown [3], we would like to emphasize that treatment effect of cidofovir should be handled with great care.

In an article published online shortly after acceptation of the article of Grasso et al. we showed that the clinical course of RRP is influenced by multiple factors [4]. Changes in the clinical course of RRP should therefore only be considered as true treatment effect if these factors are taken into consideration or are corrected for.

The natural clinical course of RRP shows a decrease of aggressiveness trough the course of the disease [4]. Furthermore age of onset of the disease in combination with the HPV type (HPV6 or HPV11) are of great importance for the course of the disease [4]. The younger the age of onset, the worse the clinical course of the disease will be [4]. Especially younger HPV11 patients experience a more aggressive clinical course in comparison with their HPV6 peers [4]. Gastroesophageal reflux disease and asthma negatively influence the course of RRP [4]. In our opinion it is advisable to not use the term 'cure' or talk of 'remission' when the follow-up of patients is only one month, as is done in some of the presented patients. [1] In our series of 55 patients it was shown that the disease can recur after 1 week till 34 years after the last surgical intervention [4].

Unfortunately, Grasso et al. fail to give information on duration of the disease before administration of cidofovir, the age of onset, HPV type of all patients, and comorbidity [1].The true effect of cidofovir is therefore indeterminable.

Concluding, it is of utmost importance that future research on treatment effect of any therapy in RRP patients should take into account this multifactorial composition of disease course. All factors mentioned above should be reported and corrected for to protect patients against unnecessary interventions. A

multi-institutional randomized controlled trial should be considered to proof the effectiveness of cidofovir.

References

1. Grasso M, Remacle M, Bachy V, Van Der Vorst S, Lawson G. Use of cidofovir in HPV patients with recurrent respiratory papillomatosis. Eur Arch Otorhinolaryngol 2014;271:2983-2990.
2. Dikkers FG. Treatment of recurrent respiratory papillomatosis with microsurgery in combination with intralesional cidofovir--a prospective study. Eur Arch Otorhinolaryngol 2006;263:440-443.
3. Tjon Pian Gi RE, Ilmarinen T, van den Heuvel ER, et al. Safety of intralesional cidofovir in patients with recurrent respiratory papillomatosis: an international retrospective study on 635 RRP patients. Eur Arch Otorhinolaryngol 2013;270:1679-1687.
4. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.

Chapter 4

Immunological response to quadrivalent HPV vaccine in treatment of Recurrent Respiratory Papillomatosis

M.R.M. San Giorgi MD[#1,5], R.E.A. Tjon Pian Gi MD, PhD[#1,5], M. Pawlita MD, PhD[2], A. Michel PhD[2], B.M. van Hemel MD, PhD[3], E.M.D. Schuuring PhD[3,5], E.R. van den Heuvel PhD[4], B.F.A.M. van der Laan MD, PhD[1,5], F.G. Dikkers MD, PhD[1,5]

# These authors contributed equally to this work

[1] Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Division of Molecular Diagnostics of Oncogenic Infections, German Cancer Research Center, Heidelberg, Germany
[3] Department of Pathology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[4] Department of Mathematics and Computer Science, Eindhoven University of Technology, Eindhoven, The Netherlands
[5] Graduate School of Medical Sciences (Cancer Research Center Groningen), University of Groningen, Groningen, The Netherlands

Eur Arch Otorhinolaryngol. 2016 Oct;273(10):3231-6.

Abstract

Objectives: Aim of this study was to explore influence of the quadrivalent HPV vaccine (Gardasil®) on the immune status of recurrent respiratory papillomatosis (RRP) patients.

Design: Retrospective observational study

Setting and participants: Six RRP patients who received the quadrivalent HPV vaccine and whose HPV seroreactivity was measured were included.

Main outcome measures: Multiplex HPV Serology was used to determine HPV-specific antibodies pre- and post-vaccination. Surgical interventions and patient records were analyzed.

Results: Five HPV6 and 1 HPV11 infected patient were included. Mean antibody reactivity against the associated HPV-type rose from 1125 median fluorescence intensity (MFI) pre-vaccination to 4690 MFI post-vaccination ($p<0.001$). Median post-vaccination follow-up was 4 years. Poisson regression analysis showed that the quadrivalent HPV vaccine decreased the incidence rate of surgeries.

Conclusions: The immune system of RRP patients is able to increase antibody reactivity against the associated HPV-type. A double blind randomized controlled trial is needed to determine whether this immunological increase can cause decrease in number of surgeries.

Introduction

Infection with a subset of Human Papillomaviruses (HPV) can cause anogenital cancer, oropharyngeal cancer, condylomata acuminata and recurrent respiratory papillomatosis (RRP).[1, 2] Since 2006 many national vaccination programs have started with the bivalent HPV vaccine (Cervarix®, GlaxoSmithKline Biologicals s.a., Rixensart, Belgium) or the quadrivalent HPV vaccine (Gardasil®, Merck & co, Whitehouse Station, USA) targeting high-risk oncogenic HPV types 16 and 18. Papillomavirus vaccines are generally safe and highly effective.[3], The quadrivalent HPV vaccine is a subunit vaccine composed of the major capsid protein L1 primarily in the form of virus-like particles (VLPs) of low-risk HPV6 and 11 and high-risk HPV16 and 18. HPV6 and 11 cause 90% of genital warts.[4] It is expected that preventive global use of this HPV vaccine against cervical cancer will decrease the incidence of HPV6 and HPV11 related disease worldwide.[5]

Recurrent respiratory papillomatosis (RRP) is a wart-like disease characterized by its unpredictable clinical course. It is associated with HPV6 and 11 for 80-100% of cases.[6-10] Therapy focuses on repeated surgical removal of exophytic lesions. Some patients may need over a 100 surgical interventions to keep the airway open and the voice sufficient.[6]

Antibody response after vaccination with the quadrivalent HPV vaccine is higher than after natural infection in patients with high risk HPV.[3, 11] Little is known about the antibody response for low risk HPV. Increased seroreactivity after vaccination in RRP patients was only addressed in two case reports[12, 13] After vaccination with the quadrivalent HPV vaccine, HPV seropositive women were protected against cervical and anogenital diseases from the corresponding HPV type.[3]Therefore, vaccination of RRP patients could be a potential treatment against HPV re-infection or auto-inoculation. In this independent exploratory study we investigated whether vaccination with the quadrivalent HPV vaccine results in increase of antibodies against the associated viruses.

Materials and methods

Ethical considerations

Patients included in this retrospective cohort study were clinically treated off-label with the the quadrivalent HPV vaccine; there was no scientific intent. Due to great international interest in the use of this therapy, it was decided to publish these valuable data. Written approval of all patients was received.

Institutional Review Board approval for retrospective cohort research is not needed in the Netherlands. All patients approved use of information from their patient files, laboratory results and biopsy material, by signing a consent form.

Biopsy and resection material of the included patients were available in archives of our Department of Pathology. This study was performed according to the Code of Conduct for Proper Secondary Use of Human Tissue in the Netherlands, as well as to the applicable institutional and national guidelines.[14]

Patients

Patients' charts and surgical reports of all RRP patients treated at the Department of Otorhinolaryngology/ Head & Neck Surgery of the tertiary referral hospital University Medical Center Groningen , University of Groningen, The Netherlands were retrospectively analyzed. Inclusion criteria for this study were: [1] histological confirmation of RRP by an experienced head & neck pathologist, [2] the patient received the quadrivalent HPV vaccine with therapeutic intent, [3] HPV seroreactivity known pre- and post-vaccination.

Patient charts were reviewed on date of birth, gender, date of diagnosis, risk factors (gastroesophageal reflux disease (GERD) and asthma), follow-up, number of surgeries, complications of administration of the quadrivalent HPV vaccine and complications associated with RRP (carcinoma, tracheotomy). Patients with an age of onset younger than 18 years of age have juvenile onset RRP (JoRRP). Patients older than 18 years at onset of disease have adult onset RRP (AoRRP).

Vaccination

The quadrivalent HPV vaccine was clinically administered to RRP patients between March 2011 and January 2013. Vaccination was injected intramuscularly by normal dosage of VLP6 20 µg, VLP11 40 µg, VLP16 40 µg, and VLP18 20 µg per injection (0.5 ml). Injections were given following the same schedule as in preventive vaccination: at 0 months, 2 months and 6 months.[15] The time after the first administration was considered as 'post-vaccination'. The second and third vaccinations were administered for durability of the effect.[15]

Time frame

A blood sample was taken immediately before the first injection of the quadrivalent HPV vaccine (pre-vaccination seroreactivity). A second blood sample was taken immediately before the third vaccination (representing post-vaccination seroreactivity).

Patient material

HPV type specific polymerase chain reaction (PCR)

For each patient a stored paraffin block from the first formalin-fixed biopsy was selected, in which papilloma was confirmed histopathologically. To confirm presence of papilloma an experienced pathologist revised all biopsies. When quality or quantity of the first biopsy was not sufficient for PCR, the next sufficient biopsy was used. HPV typing was performed using the HPV consensus primer set GP5+/6+ with subsequent nucleotide sequence analysis. Details of this technique have been described before.[6]

Antibody seroreactivity

Seroreactivity to the HPV major capsid L1 protein for both HPV6 and HPV11 was measured to monitor antibody response against the quadrivalent HPV vaccine Blood samples were analyzed by the Multiplex Human Papillomavirus Serology, based on in situ-purified glutathione S-transferase proteins, as described by Waterboer et al.[16, 17] Briefly, full-length L1 proteins were bacterially expressed as fusion proteins with N-terminal glutathione-S-transferase (GST) and a C-terminal tagging peptide (tag) and were affinity-purified in situ from cleared bacterial lysates through binding to glutathione casein-coated fluorescence-labelled polystyrene beads. A fusion protein consisting of GST and tag (GST-

tag) without intervening viral antigen served for background determination. Each fusion protein was bound to a spectrally distinct bead set. Fusion protein-loaded bead sets were mixed. Sera were pre-incubated at 1:50 dilution in PBS containing 1 mg/mL casein, 2 mg/mL lysate from bacteria expressing GST-tag alone to block antibodies directed against residual bacterial proteins and GST-tag, 0.5% polyvinylalcohol (PVA, Sigma-Aldrich Chemie Gmbh Munich, Germany), 0.8% polyvinylpyrrolidone (PVP, Sigma- Aldrich Chemie Gmbh Munich, Germany) and 2.5% Superchemiblock (Millipore, Billerica, MA, USA) to suppress unspecific binding of antibodies to the beads themselves.[17] Serum dilutions were incubated with the same volume of mixed bead sets, resulting in a final serum dilution of 1:100. Bound antibodies were detected with biotinylated goat-antihuman IgG (H+L) secondary antibody and streptavidin-R-phycoerythrin. A Luminex analyser (xMAP, Luminex Corp., Austin, TX, USA) was used to identify the internal colour of the individual beads and to quantify their reporter fluorescence (expressed as median fluorescence intensity (MFI) of at least 100 beads per set per serum). Antibody reactivity, i.e. the amount of antigen-specific antibody bound per bead is expressed as net MFI values calculated as difference of MFI with HPV-protein minus MFI with GST-tag.

Statistical analysis

Analyses were performed using PASW statistics version 20.0 (SPSS Inc., Chicago, IL, USA) and SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Categorical variables are presented as number (percentage). Normally distributed variables are presented as mean ± standard deviation. Data presented as [x; x] represents 95% confidence interval. P value of <0.05 was considered statistically significant.

A paired t-test was used to analyze the difference between pre- and post MFI. Descriptive statistics were provided for the rate of surgical interventions (number of surgical interventions divided by time interval) before and after vaccinations. A Spearman correlation coefficient between the two rates was calculated. Poisson regression analysis (with a random intercept for subjects) was applied to investigate a possible effect of vaccine on the mean number of surgical interventions corrected for type of papilloma virus (HPV6 and HPV11) and age at onset. Subject's variable log time period was included in the

regression analysis as offset parameter to adjust for different time intervals for subjects.

Since the analysis is only preliminary and exploratory, a sample size for a parallel group randomized clinical trial was calculated on the basis of an effect size that vaccination reduces the mean number of surgical interventions with 50%. Formula four of Signorini et al. with a Bernoulli covariate was used.[18]

Results

Nine RRP patients of the University Medical Center Groningen received the quadrivalent HPV vaccine. For six of them seroreactivity pre- and post-vaccination were known; these six patients were included in this exploratory study. Patients were diagnosed with RRP between 1981 and 2011, followed until August 1, 2015. Characteristics per patient are presented in table 1. All included patients were male. The mean age of onset was 16 years (SD 16). Three patients (50%) had JoRRP, 3 patients (50%) had AoRRP. None of the patients had asthma or GERD. Five patients were infected with HPV6 and one patient was infected with HPV11.

Table 1. Characteristics per patient, pre- and post-vaccination.

Patient ID	Gender (M/F)	HPV type	Age of onset (years) – age at first vaccination(years)	JoRRP/ AoRRP	Asthma	GERD	Smoker	Tracheostomy	Cidofovir	Pre-vaccination follow-up (years)	Pre-vaccination surgeries (n)	Pre-vaccination antibody reactivity (MFI)	Post-vaccination follow-up (years)	Post-vaccination surgeries (n)	Post-vaccination antibody reactivity (MFI)
#1	M	11	2 – 33	JoRRP	-	-	-	+	+	30	79	171	3	7	4841
#2	M	6	39 – 46	AoRRP	-	-	-	-	+	7	9	1887	4	2	5516
#3	M	6	4 – 9	JoRRP	-	-	-	-	-	5	4	2422	3	5	3621
#4	M	6	29 – 31	AoRRP	-	-	+	-	+	2	11	925	4	1	5419
#5	M	6	21 – 23	AoRRP	-	-	-	-	+	2	11	1048	4	2	4549
#6	M	6	2 – 4	JoRRP	-	-	-	-	+	1	7	297	4	5	4199

Abbreviations: M=male, F=female, JoRRP=Juvenile onset Recurrent Respiratory Papillomatosis, AoRRP= Adult onset Recurrent Respiratory Papillomatosis, GERD=Gastroesophageal Reflux Disease, MFI=Mean Fluorescence Intensity, Cidofovir = Cidofovir in history.

The mean pre-vaccination antibody reactivity was 1125 MFI (standard deviation 884). The mean post-vaccination antibody reactivity was 4690 MFI (standard deviation 727). All individual antibody reactivities increased after vaccination, with a median rise of 3766 MFI (range 1199 – 4670). The mean MFI per patient rose significantly after vaccination ($p<0.001$). The change of pre- and post-vaccination antibody reactivity of the associated viruses are represented in figure 1.

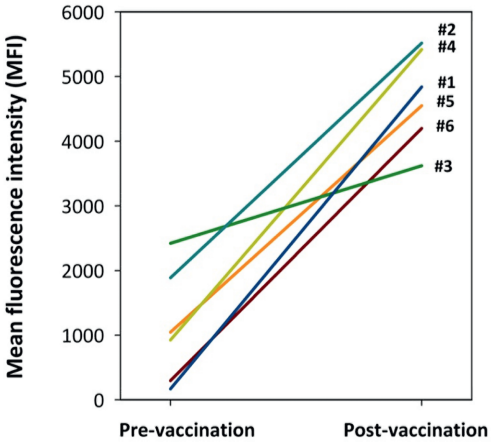


Figure 1. Antibody titer per patient against causative HPV type pre- and post-vaccination (#1: HPV11 patient. #2 to #6: HPV6 patients).

None of the patients experienced side effects or complications of the vaccination. The surgical course over time is presented in figure 2. The median pre-vaccination disease history was 3 years (range 1-30). The median post-vaccination follow-up was 4 years (range 3-4). The interval between surgeries ranged from 1 week to 7 years (Fig. 2). The average rates of surgical interventions for a period of a year were 4.34 [1.11; 7.57] and 0.99 [0.25; 1.73] before and after vaccination, respectively. Spearman correlation coefficient between the rates before and after was estimated at -0.20 ($p=0.704$).

Poisson regression analysis corrected for age at onset and type of papilloma virus demonstrated a clinical effect of vaccination. The effect size was estimated at -1.20 [-1.90; -0.50]. This meant that the mean number of surgical interventions in a specific time frame after vaccination decreased with approximately a factor of 3.3 ($=\exp^{1.20}$).

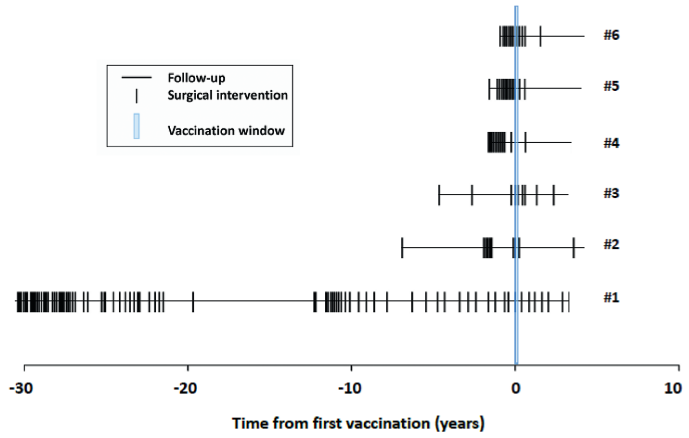


Figure 2. Follow-up with all surgical interventions by age of the patient (n=6), pre- and post- vaccination. Vaccinations were administered during the blue-marked period. #1: HPV11 patient, #2 to #6: HPV6 patients.

Based on the results of a simpler Poisson regression analysis (using only the vaccination variable and overdispersion), the sample size for detecting reduction in the mean number of surgical interventions after vaccination with a factor of 2 was calculated. If a theoretical trial period would be one year, the total number of patients in each group should be 57. If a trial would be extended to 1.5 years, the number of patients in each group should be 38, while for a trial of two years the number of patients should be 29 in each group.

Discussion

Many therapies have been tried to diminish disease burden of RRP. Nonetheless there is still no curative therapy for RRP patients. The primary goal of this exploratory study was to monitor effectiveness of the quadrivalent HPV vaccine during treatment of RRP as determined by increased seroreactivity. This is the first study that shows that vaccination of a group of RRP patients with the quadrivalent HPV vaccine results in increased seroreactivity against associated viruses.

Five of six patients were infected with low-risk HPV6, one was infected with low-risk HPV11. The ratio between HPV6 and HPV11 differs per cohort,[19]

probably because of geographical spread of both viruses.[20] This research consisted of both JoRRP and AoRRP patients. The immunological response is therefore representable for both groups. A difference in immune response is not expected. RRP patients with a pre-vaccination history of 1 year to 30 years were included.

The presented data show that RRP patients with HPV6 and HPV11 have low levels of seroreactivity against these viruses despite many years of disease. After administration of the quadrivalent HPV vaccine HPV seroreactivity against the causal HPV type rose in every patient. The vaccination induced higher seroreactivity than the natural infection in the same patients. Theoretically this induced increase in seroreactivity might influence the clinical course of RRP by intensifying immune response and preventing re-infection.

This study is the first study to measure seroreactivity in a group of RRP patients. Results could be biased due to the small sample size and short follow-up. An effect of other adjuvant therapy on immunological response was not expected as patients did not receive any adjuvant therapy one month before, neither during or after vaccination. More research is needed to analyze the duration of the immunological response.

Chirila et al. concluded that the quadrivalent HPV vaccine was effective to diminish the recurrence rate of RRP in 85% percent of patients, although that study was retrospective and lacked a control group.[21] Furthermore the natural decreasing surgical rate of RRP was not taken into account.[6, 22] It is unknown if there is a immune response after vaccination which explains a clinical response, therefore this study was conducted. The clinical response described in this article was only used for a power analysis for a future randomized controlled trial (RCT), as the sample size was too small to analyze the clinical course and to correct for the natural clinical course and other therapies (e.g. cidofovir). A RCT is needed to draw conclusions on the real clinical effect of the quadrivalent HPV vaccine. The proposed sample size for a trial with a follow-up of two years should be 29 patients per group.

Conclusion

RRP patients increase seroreactivity against the quadrivalent HPV vaccine, regardless of their age, age of onset, HPV-type and severity of disease. Antibody reactivities to the associated viruses of all patients rose significantly. A double-blinded randomized controlled trial is needed to evaluate the effect of this vaccination on the clinical course. The quadrivalent HPV vaccine could be of future help in the treatment of RRP, as this research showed that vaccination causes a robust immunological response.

References

1. Chelimo C, Wouldes TA, Cameron LD, Elwood JM. Risk factors for and prevention of human papillomaviruses (HPV), genital warts and cervical cancer. J Infect 2013;66:207-217.
2. Gillison ML, Alemany L, Snijders PJ, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine 2012;30 Suppl 5:F34-54.
3. Olsson SE, Kjaer SK, Sigurdsson K, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccin 2009;5:696-704.
4. Haupt RM, Sings HL. The efficacy and safety of the quadrivalent human papillomavirus 6/11/16/18 vaccine gardasil. J Adolesc Health 2011;49:467-475.
5. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. N Engl J Med 2007;356:1915-1927.
6. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.
7. Sanchez GI, Jaramillo R, Cuello G, et al. Human papillomavirus genotype detection in recurrent respiratory papillomatosis (RRP) in Colombia. Head Neck 2013;35:229-234.
8. Draganov P, Todorov S, Todorov I, Karchev T, Kalvatchev Z. Identification of HPV DNA in patients with juvenile-onset recurrent respiratory papillomatosis using SYBR Green real-time PCR. Int J Pediatr Otorhinolaryngol 2006;70:469-473.
9. Gerein V, Rastorguev E, Gerein J, Draf W, Schirren J. Incidence, age at onset, and potential reasons of malignant transformation in recurrent respiratory papillomatosis patients: 20 years experience. Otolaryngol Head Neck Surg 2005;132:392-394.
10. Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004;114:1-23.
11. Villa LL, Costa RL, Petta CA, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. Lancet Oncol 2005;6:271-278.
12. Forster G, Boltze C, Seidel J, Pawlita M, Muller A. Juvenile laryngeal papillomatosis--immunisation with the polyvalent vaccine gardasil. Laryngorhinootologie 2008;87:796-799.
13. Pawlita M, Gissmann L. Recurrent respiratory papillomatosis: indication for HPV vaccination? Dtsch Med Wochenschr 2009;134 Suppl 2:S100-2.
14. Code for proper secondary use of human tissue in the Netherlands. 2002;2014.
15. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;30 Suppl 5:F123-38.
16. Waterboer T, Sehr P, Michael KM, et al. Multiplex human papillomavirus serology based on in situ-purified glutathione s-transferase fusion proteins. Clin Chem 2005;51:1845-1853.
17. Waterboer T, Sehr P, Pawlita M. Suppression of non-specific binding in serological Luminex assays. J Immunol Methods 2006;309:200-204.
18. Signorini DF. Sample size for Poisson regression. Biometrika 1991;78:446-450.
19. Donne AJ, Hampson L, Homer JJ, Hampson IN. The role of HPV type in Recurrent Respiratory Papillomatosis. Int J Pediatr Otorhinolaryngol 2010;74:7-14.
20. de Sanjose S, Diaz M, Castellsague X, et al. Worldwide prevalence and genotype distribution of cervical human papillomavirus DNA in women with normal cytology: a meta-analysis. Lancet Infect Dis 2007;7:453-459.
21. Chirila M, Bolboaca SD. Clinical efficiency of quadrivalent HPV (types 6/11/16/18) vaccine in patients with recurrent respiratory papillomatosis. Eur Arch Otorhinolaryngol 2014;271:1135-1142.
22. San Giorgi MR, Tjon Pian Gi RE, Dikkers FG. The clinical course of recurrent respiratory papillomatosis after the use of cidofovir is influenced by multiple factors. Eur Arch Otorhinolaryngol 2015;272:1819-1820.

Chapter 5

The association between gastroesophageal reflux disease and Recurrent Respiratory Papillomatosis: a systematic review

M.R.M. San Giorgi MD[1,3], H.M. Helder MD[1], R.S. Lindeman MD[1], G.H. de Bock PhD[2,3], F.G. Dikkers MD, PhD[1,3]

[1] Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Department of Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[3] Graduate School of Medical Sciences (Cancer Research Center Groningen), University of Groningen, The Netherlands

Laryngoscope. 2016 Oct;126(10):2330-9.

Abstract

Objective: Anti-reflux therapy is incorporated in many treatment protocols for Recurrent Respiratory Papillomatosis (RRP), as gastroesophageal reflux (GERD) is thought to worsen the disease course of RRP. It is unclear if GERD really aggravates the disease course. The aims of this systematic review were to 1) evaluate incidence of GERD among RRP patients and 2) report if GERD changes the clinical course or tissue properties of RRP.

Study design: A search was conducted in Pubmed, Embase and Google Scholar, following the methods of Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines.

Methods: Articles with original data, published after 1 Jan 1990, on RRP with GERD as a determinant were eligible. There was no language restriction. Data on study design, study population, statistics, outcomes (incidence and influence of GERD) and risk of bias were collected and evaluated, following PRISMA protocols.

Results: Of 1277 articles, 19 articles were selected. GERD was objectified in 25-100% of RRP patients. Subjective GERD was present in 0-70% of patients. There is no proof that GERD aggravated the clinical course or tissue properties of RRP, as measured by the number of surgeries, severity scoring systems, or dysplasia. One study did find a higher chance of web formation in patients with anterior or posterior glottic papillomas who did not receive anti-reflux therapy, but these results should be interpreted with care due to the study's quality.

Conclusions: There is insufficient proof that GERD does or does not aggravate the clinical course or tissue properties of RRP.

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a disease characterized by recurrent growth of exophytic wart-like tumours throughout the airways, but most commonly in the larynx.[1] Eighty to one hundred percent of RRP is associated with HPV6 and HPV11.[1-8] Two entities are recognized: patients <18 years of age have Juvenile onset RRP (JoRRP), while patients ≥18 years of age at onset of disease have Adult onset RRP (AoRRP). To date no curative therapy exists. As a result of the recurrent character of the disease, frequent surgical debulking (sometimes up to 150 times per patient) is necessary to keep an effective voice and an open airway.[1] Many types of adjuvant therapies have been tried with variable influence on clinical course.[9]

Severity of the clinical course is often described by the spread of the papillomas throughout the airways, the complication rate (tracheostomy, cancer) and the number of surgeries needed.[1] The clinical course of RRP is mainly influenced by age of onset, time after diagnosis and HPV type.[1] It is commonly thought that gastroesophageal reflux disease (GERD) or laryngopharyngeal reflux also influences the growth rate of RRP.[10] GERD is characterized by the retrograde flow of gastric acids and bile salt.[11] As suggested by its name, GERD was originally restricted to the oesophagus.[12] Reflux to the pharynx or larynx is called laryngopharyngeal reflux (LPR). However, in literature GERD and LPR are often taken into account as the same disease.[13] The term GERD will thus be used in this research for both diseases. GERD is known to affect mucosa of the larynx and pharynx via several direct and indirect mechanisms.[14] Even without symptoms it causes inflammation and microtraumata.[11, 15] Microtraumata are thought to be the entry point of the HPV virus in the basal layer of epithelium, which then forms a viral reservoir from which the virus can act.[16] Furthermore, inflammation and irritation can provoke higher viral copy numbers, which can lead to reactivation of latent HPV virus and also increased growth of papillomas.[17] GERD can therefore theoretically lead to an impairment of the clinical course of RRP. Addition of anti-reflux therapy to RRP treatment is thus proposed by many authors and has become a common practice in many hospitals worldwide.[18-21]

It is unclear if GERD really aggravates the disease course of RRP. This systematic review was conducted to analyze the prevalence of GERD among RRP patients. Most importantly, however, it was conducted to determine if GERD has an effect on the clinical course of RRP or if GERD changes RRP tissue properties.

Materials and Methods

This systematic review was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (available at www.prisma-statement.org). All steps needed for a high quality systematic review were executed. The review protocol was reviewed and registered at the international register of systematic reviews PROSPERO (2015:CRD42015017616).

Eligibility criteria

The search strategy was developed according to the DDO method.[22] D (domain/ patients) was chosen as 'patients with recurrent respiratory papillomatosis'. D (determinant) was 'gastroesophageal reflux disease'. O (outcome) was 'any outcome'. For this, outcome was left undefined to enable a broad search, so that every possible indicator of the severity of the disease could be taken into consideration.

Articles considering Recurrent Respiratory Papillomatosis or Laryngeal Papillomatosis, and quantitatively describing Gastroesophageal Reflux Disease, laryngopharyngeal reflux or heartburn were included. To avoid missing important studies, articles in any language were considered eligible. Articles were excluded 1) when published before 1 Jan 1990. (as is often done in systematic reviews, this arbitrary date was chosen to avoid unmanageable numbers of retrieved articles), 2) when not concerning histopathologically confirmed RRP, 3) when gastroesophageal reflux disease was not used as a determinant, 4) when not containing original data (for instance reviews).

Information sources

Studies were identified by a systematic search in two databases: EMBASE and MEDLINE (through PubMed). An additional narrow search was conducted in

Google Scholar, to avoid the missing of articles that lacked one of the search terms in the title, abstract or index terms. The initial search was performed on 1 Jun 2014 in all three data sources. An updated search was performed till 15 Jul 2015 in EMBASE, Medline and Google Scholar. References lists of all included articles were scanned for additional eligible articles.

Search

The strategy for the EMBASE, Medline and Google Scholar electronic search was guided by a certified information expert, specialising in systematic reviews (KS). The systematic search strategy for these three databases is presented in Appendix 1. The search was performed without restrictions.

The Google Scholar search was deliberately narrowed to ensure a higher accuracy. The Google Scholar search was: 'GERD' 'reflux' 'recurrent respiratory papillomatosis'. Year of publication was restricted from 1 Jan 1990 through 15 Jul 2015.

Study selection

Articles selected by the systematic search strategy were imported into a reference programme, Refworks® (Proquest, Bethesda, Maryland USA). The search results of the Google Scholar search were imported into Refworks® using Harzing's Publish or Perish 4® (Tarma Software Research Pty Ltd, London, United Kingdom). Duplicate articles were removed. Three authors (MSG, HH and RJL) independently performed the selection procedure, which comprised a title and abstract selection as well as a full article selection. Differences in selection were evaluated and resolved by consensus.

Data collection process and data items

Data from the included studies were entered in a custom pilot form by author MSG. Data were independently verified by authors HH and RJL. Entered data per article were: title, authors, journal, publication year, city and country of origin, population, outcome measure, statistical methods, results, age of onset of GERD, duration of GERD, age of onset of RRP, duration of RRP, asthma (yes/no), HPV-status, which HPV-diagnostic test was used, tobacco use, and alcohol consumption.

Quality assessment and risk of bias analysis

Authors RJL and MSG independently scored the quality and risk of bias of the included articles, as measured by the 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' of the National Institute of Health (NIH).[23] Differences in scoring between authors were evaluated and resolved by consensus. The percentages of all 14 items scored with "yes" were calculated (inapplicable items were not taken into account). Higher percentages indicate a higher quality and smaller risk of bias. Studies were subjectively scored for their utility to answer the research question of this review by combining the NIH-score with the study's reporting of disease modifying factors other than GERD (age of onset of RRP, duration of disease course RRP and HPV-type). Subjective scoring was performed with consensus by authors MSG, HH and RJL. Utility was scored as low, fair, or good.

Data analysis

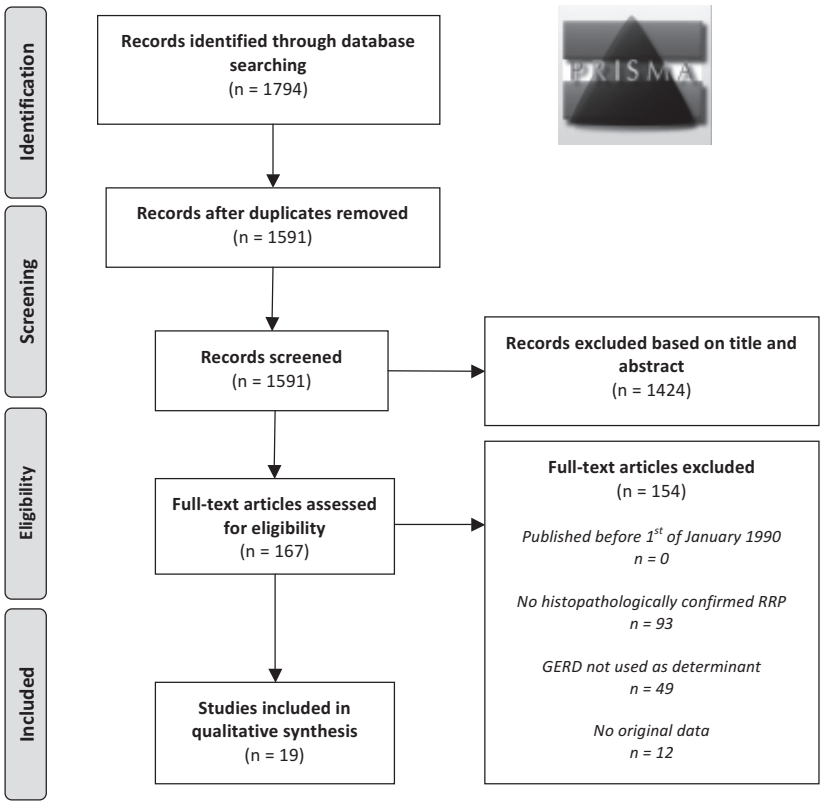
When information on the diagnosis GERD was collected from patients or patients' files it was classified as "subjectively determined" GERD in this review. When GERD was diagnosed with a quantitative or qualitative technique it was classified as "objectively determined" GERD.

Information on the percentage of RRP patients with GERD was summarized. Studies were stratified by the method used to determine GERD (subjective or objective) and by the patient population (AoRRP patients, JoRRP patients, or both groups combined). Data on the influence of GERD on several outcome measures of RRP were also summarized. Outcome measures were sorted into three categories: number of surgeries or recurrences, influence of GERD on severity of RRP, and effect of GERD on laryngeal tissue. Results were further categorized based on patient population. Due to the broad array of outcome variables and patient populations, no meta-analysis could be performed. $P<0.05$ was considered statistically significant.

Results

Study selection

The original database search through MEDLINE, EMBASE, and Google Scholar identified 1,794 studies (resp. 221, 511 and 1,062 studies; Figure 1). After removal of duplicates 1,591 studies were included in the screening. On the basis of titles and abstracts 1,424 articles were excluded. From the remaining 167 full text articles 19 articles were included in this systematic review. Screening of the reference lists of included articles did not result in the inclusion of additional articles.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews a *A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Figure 1. Flowchart of study selection in agreement with the PRISMA guidelines. RRP = recurrent respiratory papillomatosis, GERD = gastroesophageal reflux disease

Table 1. Main characteristics of all included studies, ordered alphabetically on first author.

First author, year, country	Population	diagnostic GERD	Study type	Data reported on				Quality of study to analyze effect of GERD on RRP#
				Age of onset RRP	Duration RRP	HPV-type	NIH%	
Bouchard, 1999, Canada	105 children with ENT disease, of which 8 had JoRRP	20-hour pH-metrics	Retrospective cohort	No	No	No	75	low
Caballero, 2013, Mexico	7 AoRRP patients who were able to undergo pH-metrics and an oesophagoscopy	24-hour pH-metrics	Prospective cohort	Yes	Yes	No	54	fair
Campisi, 2010, Canada	170 JoRRP patients	Information from patient files	Retrospective cohort	Yes	Yes	Yes	54	fair
Davids, 2014, USA	85 RRP patients older than 18 years	Information from patient files	Retrospective cohort	Yes	Yes	Yes	77	fair
Derkay, 2004, USA	17 JoRRP patients	Information from patient files	Retrospective cohort	No	No	No	62	fair
Holland, 2002, USA	31 JoRRP patients	24-hour pH-metrics	Retrospective cohort	Yes	Yes	No	54	fair
Ilmarinen, 2011, Finland	18 JoRRP patients	Information from patient files	Prospective cohort	Yes	Yes	No	54	fair
Koufman, 2000, USA	5 RRP patients (JoRRP or AoRRP unknown)	24-hour pH-metrics	Prospective cohort	No	No	No	67	low
Lazrak, 2004, Marocco	4 AoRRP patients	3 patients pH-metrics, 1 patient information from patient file	Retrospective case-series*	Yes	Yes	No	25	low
Maturo, 2010, USA	3 JoRRP patients	Patient history	Prospective case-series*	Yes	Yes	Yes	25	low
McKenna, 2005, USA	4 JoRRP patients with uncontrollable disease	24-hour pH-metrics (1 patient) and visual inspection of larynx (3 patients)	Prospective case-series*	Yes	Yes	No	42	low
Pignatari, 2007, Brazil	10 JoRRP patients	24-hour pH-metrics	Prospective cohort	No	No	No	50	low

Rodier, 2013, Canada	31 JoRRP patients	Information from patient files	Retrospective cohort	Yes	Yes	Yes	62	fair
Ruiz, 2014, USA	48 AoRRP patients	Patient history	Prospective cohort	Yes	Yes	No	77	fair
Sajan, 2010, USA	21 JoRRP patients	Information from patient files	Retrospective cohort	Yes	Yes	No	69	fair
Tjon Pian Gi, 2015, the Netherlands	55 RRP (JoRRP and AoRRP)	Information from patient files	Retrospective cohort	Yes	Yes	Yes	62	fair
Verguts, 2009, Belgium	51 AoRRP patients (34 entered in the analysis on remission)	Patient history and 46 patients pH-metrics or gastroscopy	Retrospective cohort	Yes	Yes	No	46	fair
Weinberger, 2009, USA	44 RRP patients (JoRRP or AoRRP unknown)	Information from patient files	Retrospective cohort	Yes	No	No	38	low
Wiatrak, 2004, USA	73 JoRRP patients	Patient history	Prospective cohort	Yes	Yes	No	69	fair

* study was scored case-series as cases were described as separate cases instead of group description
# low/fair/good
NIH% = National Institutes of Health quality assessment tool score

Characteristics of included studies

Table 1 shows the characteristics of the studies included in this review. Sixteen studies described the presence of GERD in the RRP population; 10 studies discussed the influence of GERD on different outcome measures of RRP, for instance on surgical interval, disease severity or tissue effect. Five studies objectively determined GERD in all patients by pH-metrics; 14 studies extracted information on GERD from the patient history (unknown if this was objectively determined by pH-metrics). Studies on JoRRP patient, AoRRP patients and both patient groups combined were included.

Quality assessment of studies

The mean quality score (%) was 55 ± 13, as measured by the NIH's 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies'. The lowest score was 25% (Lazrak et al. (2004) and Maturo et al. (2010)) and the highest score was 77% (Davids et al. (2014) and Ruiz et al. (2014)). The main issues with all included papers were the lack of sample size justification and the lack of repeated quantification of GERD. The study population and research question were clearly defined in most studies. Overall quality scores are shown in Table 1; quality scores for the separate NIH criteria are shown in Appendix 2.

Percentage of patients with GERD or symptoms of GERD

The 16 studies describing the presence of GERD in RRP were split in 7 studies that used pH-metrics to objectify GERD and 9 studies that searched for GERD in the patients' files (Table 2). GERD was objectively determined in 25-39% of JoRRP patients. McKenna (2005) et al. reported that 100% of JoRRP patients (n=4) with uncontrollable disease had GERD.[24] Two other small studies (N<10) found that 14-75% of AoRRP patients had GERD as measured with pH-metrics.[25, 26]

According to the patients' files, 0-15% of JoRRP patients reported subjective GERD.[5, 27-30] In comparison, 35-71% of AoRRP patients complained about GERD.[31, 32] Tjon Pian Gi et al. 2015) and Davids et al. (2014) found that 4-42% of a mixed group of both JoRRP and AoRRP patients listed complaints of GERD in their patients' files.[1, 33]

Table 2. Percentage of RRP patients with GERD, either objectively determined or subjectively acquired from the patients' files.

		Article (first author, year)	Number of patients (number)	GERD (% (n/n))	GERD diagnosed by (technique)	Percentage GERD per patient group* 0% 100%
Objectively determined	JoRRP	Bouchard 1999	8	25.0% (2/8)	20-hour pH-metrics	
		Pignatari 2007	10	50.0% (5/10)	24-hour pH-metrics (double probe)	
		Holland 2002	31	39.0% (12/31)	Interview followed by 24-hour pH-metrics (double probe)	
		McKenna 2005	4 (all with uncontrollable disease)	100.0% (4/4)	3 patients pH-metrics, 1 patient information from patient file	
	AoRRP	Caballero 2013	7	14.3% (1/7)	24-hour pH-metrics (double probe)	
		Lazrak 2004	4	75.0% (3/4)	pH-metrics (duration unknown)	
	Not specified	Koufman 2000	5	80.0% (4/5)	24-hour pH-metrics (double probe)	
Subjectively determined	JoRRP	Campisi 2010	170	2.9% (5/170)	Information from patients' files	
		Maturo 2010	3	0.0% (0/3)	Information from patients' files	
		Rodier 2013	31	9.7% (3/31)	Information from patients' files	
		Sajan 2010	21	15.0% (3/21)	Information from patients' files	
		Wiatrak 2004	54	14.8% (8/54)	Information from patients' files	
	AoRRP	Ruiz 2014	48	35.4% (17/48)	Information from patients' files	
		Verguts 2009	51	70.6% (36/51)	Information from patients' files or gastroscopy or pH-metrics	
	Both	Davids 2014	24 (all with dyplasia in their biopsies)	41.7% (10/24)	Information from patients' files	
		Tjon Pian Gi 2015	55	3.6% (2/55)	Information from patients' files	

* surface area of symbol represents relative group size:
■ (boxes=objectively determined)
● (circles=subjectively determined)

Influence of GERD on RRP

Studies on the influence of GERD on different outcomes of RRP are shown in Table 3. Three studies that analyzed surgeries in JoRRP patients found no effect of GERD on the number of surgeries needed.[5, 34, 35] In contrast, Derkay et al. (2004) stated that GERD is among their statistically significant findings as predictor of (shortened) surgical interval.[34] However, in their results p=0.10.[34] Two additional studies on AoRRP patients found no effect of GERD on either the number of surgeries or recurrences.[26, 32] Two studies, with 31 and 69 patients respectively, found no difference in severity score between JoRRP patients with or without GERD.[5, 29] Another study also did not find a difference in severity score in RRP patients of any age with or without GERD.[36] Two studies, one study

Table 3. Influence of GERD on RRP, divided in three different outcome categories (number of surgeries/recurrences, disease severity and tissue effects). Characteristics of the study methodology to analyze the effect on outcome are given per study.

		Article	Number of patients	Statistical method	Groups compared	Outcome variable	Outcome
Number of surgeries/recurrences	JoRRP	Derkay et al. 2004	17	Generalized estimating equations model	Patients with GERD* **(n=?)** vs. Patients without GERD **(n=?)**	Number of days between surgeries	Predicted decrease surgical interval with GERD = 95 days (CI 17-203, p=0.10)
		Ilmarinen et al. 2011	18	Pearson's correlation test	Patients with GERD* **(n=?)** vs. Patients without GERD **(n=?)**	Number of surgeries	No significant correlation between GERD and number of surgical procedures (no numbers given)
		Wiatrak et al. 2004	69	Multivariate linear regression	Patients with GERD* (n=10) vs. Patients without GERD (59)	Number of surgeries	No significant relation between GERD and the number of surgeries, p=0.2 (no numbers given)
	AoRRP	Caballero et al. 2013	7	McNemar's test	Patient with GERD* (n=1) vs. patients without GERD (n=6)	Number of recurrences per year	No relation (no numbers given)
		Verguts et al. 2009	34	X-square test	Patients with GERD* (n=24) vs. Patients without GERD (n=10)	Remission of RRP (disease free for 1 year)	No significant different chance of remmision with GERD, OR 0.257 (CI 0.053-1.254, p=0.134)
Severity	JoRRP	Rodier et al. 2013	31	Logistic regression	Patients with GERD* (n=3) vs. Patients without GERD (n=28)	Chance of having severe disease (Derkay-score>10 or >10 surgeries or tracheal papilloma)	Not a higher chance of severe disease with GERD, OR=1.11 (CI 0.08-15.53, p=0.94)
		Wiatrak et al. 2004	69	Multivariate linear regression	Patients with GERD* (n=10) vs. Patients without GERD (59)	Highest Derkay-score	No significant relation between GERD and highest Derkay-score, p=0.3 (no numbers given).
	Both	Weinberger et al. 2009	44	Unknown	Patients with GERD* **(n=?)** vs. Patients without GERD **(n=?)**	Aggresive disease (>4 surgeries in 1 year or distal spread of papillomas or progression to carcinoma)	No significant relation between GERD and aggresive disease, p>0.05. (no numbers given)
Tissue	JoRRP	Sajan et al. 2010	21	X-square test	Patients with GERD* **(n=?)** vs. Patients without GERD **(n=?)**	Dysplasia	Not a higher chance on dysplasie with GERD, p=0.025 (no numbers no given)
		Holland et al. 2002	24 patients with RRP in the anterior or posterior glottis	Fisher's exact test	Patients treated with anti-reflux therapy (n=10) vs. Patients not treated (n=14)	Development of laryngeal webbing	Patients treated with anti-reflux therapy have a lower chance on web formation, OR=0.068 (CI 0.009-0.508, p=0.011)
	Both	Davids et al. 2014	85 patients older than 18 years	Logistic regression	Patients with GERD* **(n=?)** vs. Patients without GERD **(n=?)**	Dysplasia	No relation (numbers not given)

? = information not given in article

* = information on possible treatment GERD not given

with JoRRP patients and one study with patients older than 18 years of age, analyzed the influence of GERD on the development of dysplasia in RRP.[30, 33] Both studies found no correlation between GERD and dysplasia in RRP.[30, 33] One study did find an effect of GERD on an outcome measure of RRP.[37] The authors determined that patients treated with anti-reflux therapy (prescribed to both patients with and without proven GERD) and with papillomas in the anterior or posterior commissure had a smaller chance of developing webs than patients not treated with anti-reflux therapy.[37] The analysis, however, was performed retrospectively, univariately and without specifying the terminology of web.[37]

Discussion

The aim of this systematic review was to analyze the prevalence of GERD among RRP patients and to evaluate the potential role of GERD in aggravating RRP. In general, included studies were of poor or fair quality to answer the research question. The prevalence of objectively determined GERD in RRP patients was found to be 25-100%, while the prevalence of subjective GERD in RRP patients was reported to be 0-71%. The influence of GERD on severity, measured by the number of recurrences or surgeries, was not demonstrated in any study. The influence of GERD on the severity of RRP, as measured by different scoring methods, was not proven in any study either. Similarly, none of the studies demonstrated the influence of GERD on the development of dysplasia. Only one study showed a significant effect of anti-reflux therapy on anterior or posterior glottic web formation in a group of patients with papillomas in the anterior or posterior commissure. However, results of that study should be interpreted with caution as will be discussed further on.

Percentage of patients with GERD or symptoms of GERD

As it is known that there is a difference between the number of patients with complaints of GERD and objectively determined GERD,[38] studies on both objectively determined as subjective GERD were selected in this review. GERD was objectified in 25-39% of unselected JoRRP patients and 100% of a small group of patients with severe disease.[24, 37, 39, 40] It was found that a lower proportion of JoRRP patients than AoRRP patients subjectively reported GERD, namely 3-15%.[5, 27-30]

In two studies with 4 and 7 AoRRP patients, GERD was objectified in 14-75% of patients.[25, 26] GERD was subjectively reported in 35-70% of AoRRP patients.[31, 32] In normal western populations, GERD is objectively determined in 17-28% of patients.[38] The number of JoRRP patients with GERD (children and adults) is thus comparable with the normal population. The number of patients with objectively determined GERD in AoRRP seems to be high, but this is only measured in two small case-series and it is not clear whether these numbers represent an unbiased and unselected series. The number of patients with objectively determined GERD in JoRRP is also comparable to the normal western population (11-24%),[38] while in AoRRP patients higher numbers are reported. A higher prevalence of GERD is found in AoRRP than in the normal population. However this does not imply a causal or consequential relationship.

Influence of GERD on RRP

The main goal of this research was to assess the influence of GERD on RRP. Outcomes were stratified into three categories: number of surgeries or recurrences, influence of GERD on severity of RRP and effect of GERD on laryngeal tissue. There is no conclusive evidence that GERD does or does not influence RRP.

First, five studies described the number of surgeries or recurrences. None of these studies found an effect of GERD.[5, 26, 32, 34, 35] Studies of the JoRRP patient group had fair quality, but lacked information on exact group sizes and were therefore difficult to interpret.[5, 34, 35] Although one study described a significant effect, it was based on a statistically non-significant p-value and was therefore considered as non-significant in this review.[34] Both studies describing an effect of GERD on the number of surgeries or recurrences in AoRRP used univariate statistics.[26, 32] This can lead to significant biases. Despite RRP can recur even after many years of disease free survival,[1] Verguts et al. (2009) described remission as a 1-year disease free period.[32] This implies that patients with recurrences after one year will be incorrectly scored as disease free.

Second, three studies determined the influence of GERD on severity of RRP, as described with three different scoring systems.[5, 29, 36] None of these three studies found an effect of GERD.[5, 29, 36] Two studies performed on the JoRRP patient group were of fair quality (as measured with Quality Assessment Tool

for Observational Cohort and Cross-Sectional Studies).[5, 29] The third study did not specify the age of onset of the disease, group sizes and/or exact p-values.[36] Three studies used scoring systems that were arbitrary, with different determinants that might easily lead to different results. An effect of GERD on severity of disease was thus not proven.

Last, the effect of GERD on laryngeal tissue was assessed. Two studies addressed this problem, one in JoRRP patients and one in both JoRRP and AoRRP patients. Both studies failed to prove that GERD was an inducer of dysplasia in papillomas.[30, 33] Both studies were of fair quality and described a sufficient group size.[30, 33] Unfortunately, one study only analyzed their data univariately,[30] and the other study did not mention exact numbers.[33] It is remarkable that GERD does not negatively influence the papilloma tissue by eliciting dysplasia, as longstanding exposure of oesophageal tissue to GERD is known to cause metaplasia and eventually dysplasia.[41] A similar effect might be expected in the epithelium of the larynx. The study describing the influence of GERD on web formation in a group of patients with papilloma in the anterior or posterior commissure should be interpreted with caution.[37] It found that anti-reflux therapy protected against web formation after surgery, irrespectively of the GERD status of the patient.[37] However, use of anti-reflux agents is not interchangeable with the condition of having or not having GERD. Also, the study was performed retrospectively using the patients' files, which could lead to underreporting of web formation.[37] Furthermore, the definition of web formation is not clarified and a highly select patient group is described.[37] The results of that study therefore are no reason to start anti-reflux therapy in all RRP patients. Care with anti-reflux therapy is necessary especially now that the complications and side effects of anti-reflux therapy are more recognized.[42, 43]

Strengths and limitations

Studies included in this review were generally not designed to assess the influence of GERD on RRP. Most studies treated GERD as secondary variable. Studies 1) were underpowered to prove an effect, 2) underreported their statistics and group sizes, 3) analyzed GERD with univariate statistics, 4) had insufficient methods of diagnosing GERD, and 5) did not report whether RRP patients with GERD received anti-reflux treatment. Results of these studies should therefore be considered with care in proving an effect of GERD on the

severity of RRP. Since GERD is seen as a secondary variable, studies can have fair quality and a good NIH-score, while the quality to answer the research question of this review is low. A subjective measure of utility was therefore introduced in Table 1. The severity scores used as outcome measure were mostly arbitrarily chosen. Other outcome measures were multifactor outcomes that were presented as if they were only determined by GERD, as for instance the number of surgeries. The search strategy in this review was designed to find articles on the influence of GERD on RRP. Articles on the prevalence of GERD in RRP could therefore theoretically be missed. Due to the wide variety of included patient groups a meta-analysis was not possible.

The strength of this review is that the chance of missing studies on GERD and RRP is very small due to the use of the extensive and precise PRISMA-methods and the inclusion of studies in all languages. As GERD is often described as a secondary variable and therefore not mentioned in the abstract or title, chances are high that studies will be missed when searching in EMBASE and Medline. A Google Scholar search was therefore included, as it scans the complete article.

Conclusion

GERD was objectively determined in 25-100% of RRP patients. Subjective GERD was present in 0-70% of patients. Although conceptually GERD could be of influence on RRP, there is insufficient evidence in literature to conclude that GERD does or does not influence the course or tissue properties of RRP. There is some evidence that anti-reflux therapy can be beneficial peri-operatively in patients with papillomas in the anterior or posterior commissure, but better designed research is needed to analyze the true effect of GERD on RRP. Till an evidential effect of GERD on RRP is proven, we should reconsider inclusion of anti-reflux therapy in evidence-based treatment of RRP patients.

Acknowledgements

We thank Karin Sijtsma, information expert, for her help with the search strategy and systematic search. Furthermore we thank Nathan Senner (PhD) for his help editing the article.

References

1. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.
2. Sanchez GI, Jaramillo R, Cuello G, et al. Human papillomavirus genotype detection in recurrent respiratory papillomatosis (RRP) in Colombia. Head Neck 2013;35:229-234.
3. Draganov P, Todorov S, Todorov I, Karchev T, Kalvatchev Z. Identification of HPV DNA in patients with juvenile-onset recurrent respiratory papillomatosis using SYBR Green real-time PCR. Int J Pediatr Otorhinolaryngol 2006;70:469-473.
4. Gerein V, Rastorguev E, Gerein J, Draf W, Schirren J. Incidence, age at onset, and potential reasons of malignant transformation in recurrent respiratory papillomatosis patients: 20 years experience. Otolaryngol Head Neck Surg 2005;132:392-394.
5. Wiatrak BJ, Wiatrak DW, Broker TR, Lewis L. Recurrent respiratory papillomatosis: a longitudinal study comparing severity associated with human papilloma viral types 6 and 11 and other risk factors in a large pediatric population. Laryngoscope 2004;114:1-23.
6. Moore CE, Wiatrak BJ, McClatchey KD, et al. High-risk human papillomavirus types and squamous cell carcinoma in patients with respiratory papillomas. Otolaryngol Head Neck Surg 1999;120:698-705.
7. Gabbott M, Cossart YE, Kan A, Konopka M, Chan R, Rose BR. Human papillomavirus and host variables as predictors of clinical course in patients with juvenile-onset recurrent respiratory papillomatosis. J Clin Microbiol 1997;35:3098-3103.
8. Pou AM, Rimell FL, Jordan JA, et al. Adult respiratory papillomatosis: human papillomavirus type and viral coinfections as predictors of prognosis. Ann Otol Rhinol Laryngol 1995;104:758-762.
9. Stern PL, van der Burg SH, Hampson IN, et al. Therapy of human papillomavirus-related disease. Vaccine 2012;30 Suppl 5:F71-82.
10. Gallagher TQ, Derkay CS. Pharmacotherapy of recurrent respiratory papillomatosis: an expert opinion. Expert Opin Pharmacother 2009;10:645-655.
11. Powell J, Cocks HC. Mucosal changes in laryngopharyngeal reflux--prevalence, sensitivity, specificity and assessment. Laryngoscope 2013;123:985-991.
12. Coca-Pelaz A, Rodrigo JP, Paccagnella D, et al. Reflux and aerodigestive tract diseases. Eur Arch Otorhinolaryngol 2013;270:417-423.
13. Coca-Pelaz A, Rodrigo JP, Takes RP, et al. Relationship between reflux and laryngeal cancer. Head Neck 2013;35:1814-1818.
14. Hawkshaw MJ, Pebdani P, Sataloff RT. Reflux laryngitis: an update, 2009-2012. J Voice 2013;27:486-494.
15. Erickson E, Sivasankar M. Simulated reflux decreases vocal fold epithelial barrier resistance. Laryngoscope 2010;120:1569-1575.
16. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30 Suppl 5:F55-70.
17. Doorbar J. Latent papillomavirus infections and their regulation. Curr Opin Virol 2013;3:416-421.
18. Goon P, Sonnex C, Jani P, Stanley M, Sudhoff H. Recurrent respiratory papillomatosis: an overview of current thinking and treatment. Eur Arch Otorhinolaryngol 2008;265:147-151.
19. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008;118:1236-1247.
20. Carifi M, Napolitano D, Morandi M, Dall'Olio D. Recurrent respiratory papillomatosis: current and future perspectives. Ther Clin Risk Manag 2015;11:731-738.
21. Venkatesan NN, Pine HS, Underbrink MP. Recurrent respiratory papillomatosis. Otolaryngol Clin North Am 2012;45:671-94, viii-ix.
22. Kramer B. Information Retrieval: Literature Searching in Today's Information Landscape. Hypothesis 2010;8:1-7.
23. NIH. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. ;2015.

24. McKenna M, Brodsky L. Extraesophageal acid reflux and recurrent respiratory papilloma in children. Int J Pediatr Otorhinolaryngol 2005;69:597-605.
25. Lazrak A, Nazih N, Filali AA, Kzdri M. Laryngeal papillomatosis in adults: report on 4 cases. Rev Laryngol Otol Rhinol (Bord) 2004;125:107-112.
26. Caballero M, Romero A, Gonzalez L, Gomez E. Reflujo gastroesofagico en papilomatosis respiratoria recurrente: incidencia e influencia en el curso clinico. Anales De Otorinolaryngologia Mexicana 2013;58:146-150.
27. Campisi P, Hawkes M, Simpson K, Canadian Juvenile Onset Recurrent Respiratory Papillomatosis Working Group. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 2010;120:1233-1245.
28. Maturo S, Hartnick CJ. Use of 532-nm pulsed potassium titanyl phosphate laser and adjuvant intralesional bevacizumab for aggressive respiratory papillomatosis in children: initial experience. Arch Otolaryngol Head Neck Surg 2010;136:561-565.
29. Rodier C, Lapointe A, Coutlee F, et al. Juvenile respiratory papillomatosis: risk factors for severity. J Med Virol 2013;85:1447-1458.
30. Sajan JA, Kerschner JE, Merati AL, Osipov V, Szabo S, Blumin JH. Prevalence of dysplasia in juvenile-onset recurrent respiratory papillomatosis. Arch Otolaryngol Head Neck Surg 2010;136:7-11.
31. Ruiz R, Achlatis S, Verma A, et al. Risk factors for adult-onset recurrent respiratory papillomatosis. Laryngoscope 2014;124:2338-2344.
32. Verguts MM, Genbrugge E, de Jong FI. Treatment results in adult-onset recurrent respiratory papillomatosis. B-Ent 2009;5:137-141.
33. Davids T, Muller S, Wise JC, Johns MM,3rd, Klein A. Laryngeal Papillomatosis Associated Dysplasia in the Adult Population: An Update on Prevalence and HPV Subtyping. Ann Otol Rhinol Laryngol 2014;123:402-408.
34. Derkay CS, Hester RP, Burke B, Carron J, Lawson L. Analysis of a staging assessment system for prediction of surgical interval in recurrent respiratory papillomatosis. Int J Pediatr Otorhinolaryngol 2004;68:1493-1498.
35. Ilmarinen T, Nissila H, Rihkanen H, et al. Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis. Laryngoscope 2011;121:846-851.
36. Weinberger P, Robb P, Carlson H, Perakis H, McChesney J, Postma G. Predictors of clinically aggressive recurrent respiratory papillomatosis. Laryngoscope 2009;119:104.
37. Holland BW, Koufman JA, Postma GN, McGuirt WF,Jr. Laryngopharyngeal reflux and laryngeal web formation in patients with pediatric recurrent respiratory papillomas. Laryngoscope 2002;112:1926-1929.
38. Ronkainen J, Agreus L. Epidemiology of reflux symptoms and GORD. Best Pract Res Clin Gastroenterol 2013;27:325-337.
39. Bouchard S, Lallier M, Yazbeck S, Bensoussan A. The otolaryngologic manifestations of gastroesophageal reflux: when is a pH study indicated? J Pediatr Surg 1999;34:1053-1056.
40. Pignatari SS, Liriano RY, Avelino MA, Testa JR, Fujita R, De Marco EK. Gastroesophageal reflux in patients with recurrent laryngeal papillomatosis. Braz J Otorhinolaryngol 2007;73:210-214.
41. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. Jama 2013;310:627-636.
42. FDA. Safety information on proton pump inhibitors. 24-6-2015;2016.
43. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. PLoS One 2015;10:e0124653.

Appendix

Appendix 1Search strategy for Embase, Medline (through PubMed) and Google Scholar

Search strategy Embase

(('papilloma'/exp OR 'papillomatosis'/exp OR 'larynx papillomatosis'/exp OR 'larynx tumor'/exp) OR ('Warts in the throat' OR 'recurrent respiratory papillomatosis' OR 'respiratory papilloma' OR 'laryngeal papilloma' OR 'larynx papilloma' OR 'rrp')) AND (('Gastroesophageal Reflux'/exp OR 'Heartburn'/exp) OR ('Gastric acid' OR 'Reflux' OR 'Gastroesophageal reflux' OR 'GERD' OR 'Esophageal reflux' OR 'Laryngopharyngeal reflux' OR 'Heart Burn' OR 'Pyrosis' OR 'Pyroses' OR 'Regurgitation' OR 'GER'))

Search strategy MEDLINE (through PubMed)

(("papillomavirus infections"[mesh terms] OR "Papilloma"[mesh terms] OR "Laryngeal Neoplasms"[mesh terms]) OR ("Warts in the throat" OR "recurrent respiratory papillomatosis" OR "respiratory papilloma*" OR "laryngeal papilloma*" OR "larynx papilloma*" OR "rrp")) AND (("Gastroesophageal Reflux"[mesh terms] OR "heartburn"[mesh terms]) OR ("Gastroesophageal Reflux" OR "Reflux" OR "Gastroesophageal reflux" OR "GERD" OR "Esophageal reflux" OR "Laryngopharyngeal reflux" OR "Heart Burn" OR "Pyrosis" OR "Pyroses" OR "Regurgitation" OR "GER"))

Search strategy Google Scholar

'Recurrent Respiratory Papillomatosis' AND 'GERD' OR 'reflux'

Appendix 2 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies' of the National Institute of Health (NIH). The percentages of all 14 items scored with "yes" were calculated (inapplicable items were not taken into account).Articles are ordered alphabetically. (NR=not reported; NA=not applicable).

Part 1	Bouchard (1999)	Caballero (2013)	Campisi (2010)	Davids (2014)	Derkay (2004)	Holland (2002)	Ilmarinen (2011)	Koufman (2000)	Lazrak (2004)
Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Was the participation rate of eligible persons at least 50%?	Yes	NR	No	Yes	Yes	Yes	Yes	Yes	NR
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	No	No	No	No
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	No	Yes	NR	No	Yes	No	No
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	No	No	No	Yes	No
Was the exposure(s) assessed more than once over time?	Yes	No	No	No	No	No	No	No	No
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	No
Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	NR	NR	NR
Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NA	No	Yes	Yes	Yes	No	No	NA	NA
Total (Yes/Total number of applicable questions)	75% (9/12)	54% (7/13)	54% (7/13)	77% (10/13)	62% (8/13)	54% (7/13)	54% (7/13)	67% (8/12)	25% (3/12)

Part 2	Maturo (2010)	McKenna (2005)	Pignitari (2007)	Rodier (2013)	Ruiz (2014)	Sajan (2010)	Tjon Pian Gi (2015)	Verguts (2009)	Weinberger (2009)	Wiatrak (2004)
Was the research question or objective in this paper clearly stated?	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study population clearly specified and defined?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes
Was the participation rate of eligible persons at least 50%?	NR	Yes	NR	Yes	Yes	Yes	Yes	Yes	NR	Yes
Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NR	Yes
Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	Yes	No	No	No	No	No
For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	NR	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes
Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No	No	Yes	No	Yes	Yes	No	No	No	Yes
Was the exposure(s) assessed more than once over time?	NR	No	No	No	No	No	No	No	No	No
Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	NA	NA	NA	Yes	No	No	NA	No	No	Yes
Total (Yes/Total number of applicable questions)	25% (4/12)	42% (5/12)	50% (6/12)	62% (8/13)	77% (10/13)	69% (9/13)	62% (8/13)	46% (6/13)	38% (5/13)	69% (9/13)

*CD, cannot determine; NA, not applicable; NR, not reported

Part II

Psychosocial aspects of RRP

Chapter 6

Quality of life of patients with Recurrent Respiratory Papillomatosis

M.R.M. San Giorgi MD[1,2,3], L. Aaltonen, MD PhD[4], H. Rihkanen MD, PhD[4], R.E.A. Tjon Pian Gi MD[1,2,3], B.F.A.M. van der Laan MD, PhD[1,2], J.E.H.M. Hoekstra-Weebers PhD[5], F.G. Dikkers MD, PhD[1,2,3].

[1] University of Groningen, University Medical Center Groningen, Department of Otorhinolaryngology/ Head & Neck Surgery, Groningen, the Netherlands
[2] University of Groningen, Cancer Research Center Groningen, the Netherlands
[3] Groningen Papilloma Studies, University of Groningen, the Netherlands
[4] Department of Otorhinolaryngology-Head and Neck Surgery, University of Helsinki, Helsinki University Hospital, Helsinki, Finland
[5] University of Groningen, University Medical Center Groningen, Wenckebach Institute, Groningen, the Netherlands

Laryngoscope. 2016 Nov 15. doi: 10.1002/lary.26413. [Epub ahead of print]

Abstract

Introduction: Recurrent Respiratory Papillomatosis (RRP) is a disease with a high disease burden. Few studies have assessed quality of life (QoL) of RRP patients. This study compares QoL of these patients with controls. Associations between QoL and sociodemographic and illness-related factors are examined, as is uptake of psychosocial care and speech therapy.

Study design: Prospective cross-sectional questionnaire research.

Methods: Ninety-one RRP patients (response=67%) from two university hospitals in the Netherlands and Finland completed the following patient reported outcome measures: HADS, 15D, VHI and RAND-36 assessing health-related QoL and voice handicap, and they provided sociodemographic, illness-related and allied health care use. Descriptive analyses, X2-tests, t-tests, ANOVAs and Pearson correlations were computed to describe the study population, and to examine differences between groups.

Results: RRP patients had significantly higher mean scores on depression, health-related QoL (15D) and on voice problems (VHI), and significantly lower mean scores on anxiety than controls. Dutch patients had more pain and a decreased general health perception (RAND-36) than controls. Dutch patients and older patients were more depressed; women were more anxious; older patients had lower health-related QoL; smoking was significantly associated with voice handicap. Patients who had received psychosocial care had significantly higher HADS-depression mean scores than patients who did not receive psychosocial care.

Discussion: Having RRP has significant effect on voice-related QoL and depression, but has no negative effect on anxiety and health-related QoL. Risk factors for decreased functioning are different than previously hypothesized by many authors. Prevention should be aimed at these risk factors.

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a chronic disease characterized by recurrent growth of exophytic wart-like tumors (papillomas) throughout the airways.[1] The disease is caused by human papilloma virus (HPV) types 6 and 11.[1] Most often these papillomas are located in the glottis.[2] Due to the location papillomas cause vocal problems and eventually dyspnea. As there is still no curative treatment for the disease, patients go through repetitive surgical removal of the papillomas.[3] RRP has three peaks in incidence around the age of 7, 35 and 64 years and can remain active for decades.[1, 4] The disease is traditionally separated in Juvenile onset RRP (JoRRP, onset before 18 years of age) and Adult onset RRP (AoRRP, onset at age 18 or older). Remission of disease cannot be predicted.[1]

The number of surgeries and the anatomical spread of the papillomas often indicate severity of disease.[1, 5] It is likely that the burden of the number of surgeries and the uncertain prognosis affect quality of life (QoL). Few studies have assessed QoL of RRP patients.

Two studies in children showed worse health related QoL, impaired social functioning and lower psychosocial health status.[6, 7] Although they still experienced significant voice problems, JoRRP patients reported only slightly lower QoL in their adult life.[8] Two studies in adults - including both JoRRP and AoRRP patients - confirmed that patients experience more voice problems than the general population.[9, 10] Both studies showed that in particular social functioning was impaired.[9, 10] Another study showed that only patients who had severe disease had a worse health related QoL.[11] Voice related problems have been reported to significantly affect QoL.[12]

None of these studies associated disease-specific (e.g. number of surgeries, duration of disease) or sociodemographic characteristics (e.g. gender, educational level, marital status) with QoL. It would be clinically relevant to determine which patients are prone to experiencing lower QoL, as preventive interventions can be targeted to those patients.

An international multicenter questionnaire study was performed in a sufficiently sized cohort of adult RRP patients (both JoRRP and AoRRP patients) with the following aims:

- to examine QoL and voice-related QoL in RRP patients by comparing them to controls;
- to examine the effect of disease-specific and sociodemographic variables on QoL;
- to find out how many RRP patients received additional care; how they appreciated it; and to quantify the relationships between care received and anxiety and depression.

Methods

Patients and procedure

All RRP patients from the departments of Otorhinolaryngology/ Head & Neck surgery of the University Medical Center Groningen, the Netherlands, and the Helsinki University Hospital, Finland, were screened for eligibility (by MSG and HR). Inclusion criteria were: histopathologically confirmed RRP by a certificated pathologist; current age ≥18 years; sufficiently mastering the Dutch respectively Finnish language and having had their last visit for RRP after January 1st, 2010.

Information about the goal of the study; a request to participate; a questionnaire; and a pre-paid return envelope were sent to all eligible patients by post. After a month, a reminder was sent by post to non-responders in Finland. In the Netherlands, non-responders were telephoned.

Sample size

Sample size was determined to prove medium strong correlation between two continuous variables (r=0.3).[13] For this, 84 patients had to be included (two-tailed test, r=0.3, α=0.05, power(1-β)=0.8) (calculated with G-power (version 3.1.9.2, Kiel, Germany).[13] Eight percent missing data were anticipated, yielding a necessary group of 91 respondents.

Institutional Review Board

Dispensation from Institutional Review Board approval was granted in Groningen (the Netherlands) and Helsinki (Finland).

Questionnaires

The HADS, validated in Dutch and Finnish,[14, 15] measures anxiety and depression. Maximum score per 7-item subscale is 21, yielding a maximum total score of 42. RPP patients were compared to Dutch controls.[14]

The 15D questionnaire, validated in Finland[16] and translated in Dutch, was used to evaluate health-related QoL of both Dutch and Finnish patients. 15D is a health-related QoL scale validated for many diseases.[16] Higher scores indicate higher QoL (range 0.00-1.00). The total 15D score from RPP patients was compared to Finnish controls.[17]

The Voice Handicap Index-30 (VHI), a reliable and valid 30-item scale, validated in Dutch and Finnish,[18, 19] was used to evaluate voice-related QoL. Higher scores indicate lower voice-related QoL (range 0-120). RPP patients were compared with Dutch controls.[20]

The RAND-36, a well-validated self-report questionnaire, used worldwide,[21] was used to measure health-related QoL. It contains nine subscales, measuring physical role limitations, emotional role limitations, physical functioning, social functioning, mental health, vitality, pain, general health perception, and health change. After transformation according to the manual, subscales scores range from very bad to very good QoL (scale 0- 100).[22] The RAND-36 was only presented to Dutch patients, due to IRB eligibility. Dutch RPP patients were compared to Dutch controls.[22]

Furthermore, patients filled in sociodemographic (gender, age, marital status, daily activities, living situation and smoking) and illness-related questions (comorbidity, age at diagnosis, care received from a healthcare provider other than the doctor for RPP related problems (psychologist, psychiatrist, social worker, pastoral counselor, dietician/ nutritional team and speech therapist)), and number of contacts and satisfaction with care received (from very low to high satisfaction, scale 0-10). Data on the number of surgical procedures (1-2; 3-5; 6-10; 11-25; >25) and date of onset of RRP were collected from the patients' files (by MSG and HR).

Questionnaires were translated using official medical translation standards.[23]

Statistical analysis

Independent sample t-tests were used to examine differences between the mean outcome of the study group on the HADS, 15D, VHI and RAND-36 and control data.[24-26] Effect sizes were calculated by dividing the difference between mean outcome of the control group and mean outcome of the study group by the standard deviation of the control group. Effect sizes between 0.20-0.49 reflect small clinically relevant difference, between 0.50-0.80 moderate clinically relevant difference, and >0.80 large clinically relevant difference.

Independent t-tests and X^2-tests were computed to compare Dutch with Finnish patients in sociodemographic and illness-related characteristics with the HADS, 15D and VHI.

Univariate effects of the sociodemographic and illness-related variables on the HADS, 15D and VHI were calculated by t-tests (for categorical variables with two categories), ANOVAs (for categorical variables with more than two categories), and Pearson correlation tests (for continuous variables). Multiple linear forward regression analysis was performed to examine independent effects of univariately-associated variables. A Pearson correlation coefficient <0.3 indicates weak relationship, between 0.3-0.5 moderately strong relationship, and >0.5 strong relationship. Associations between RAND-36 and sociodemographic and illness-related factors were not examined, as the Dutch patient group alone did not meet the needed sample size.

P-value <0.05 was considered as statistically significant. Analyses were performed using SPSS statistics 21.0 (SPSS, Chicago, USA).

Results

Sixty-seven percent (91/136) of the eligible patients responded. Of these, 45 patients were Dutch (response rate 78%) and 46 were Finnish (response rate 59%), a statistically significant difference (X^2=5.2, p=0.023). No significant differences were found between Dutch and Finnish patients in sociodemographic and illness-related variables, other than that significantly more Dutch than Finnish patients had smoked in the past (X^2=7.7, p=0.021)(table 1). Sample size was sufficient to meet the power.

Table 1. Sociodemographic and illness-related characteristics of included Dutch and Finnish Recurrent Respiratory Papillomatosis patients (n=91).

Age at time of diagnosis (Mean ± sd)		36±17
Duration of disease course RRP (years) (Mean ± sd)		14±16
Number of surgical procedure (number of patients per group) (N (%))	1-2	31 (34)
	3-5	25 (28)
	6-10	12 (13)
	11-25	14 (15)
	>25	9 (10)
Tracheostomy (N (%))	Yes	1 (1)
Co-morbidity, any (N (%))	Yes	39 (43)
(N(% of all patients))	Asthma	6 (7)
	Pulmonary disease	4 (4)
	Gastroesophageal reflux disease	9 (10)
	Gastro-intestinal disease	3 (3)
	Neurological disease	3 (3)
	Diabetes Mellitus	7 (8)
	Vascular disease	12 (13)
	Cancer	2 (2)
	Joint/bone disease	10 (11)
	Muscular disease	0 (0)
	Cardiac disease	8 (9)
	Psychiatric disease	3 (3)
	Other (e.g. glaucoma)	4 (4)

Comparison of anxiety, depression, health-related QoL, and voice problems, with controls

RRP patients had a significantly higher HADS-depression score, but lower anxiety score than controls (p=0.049 and p=0.005 respectively). Effect sizes were small (table 2).

Health-related QoL (total 15D score) was significantly higher in the total RRP group compared to controls (p=0.037). Effect size was large (table 2).

VHI scores of RRP patients were significantly worse than in the control group (p<0.001). Effect size was large (table 2).

Dutch RRP patients had significantly less pain and a lower general health perception than controls (RAND-36)(p=0.001 and p=0.003 respectively). Effect sizes were small (table 2).

Table 2. Comparison of outcomes of the HADS, 15D, VHI and RAND-36 between Recurrent Respiratory Papillomatosis patients and controls, with effect sizes.

Psychosocial test		Total	Controls	P-value*	Effect size
HADS (mean ± SD)	Total	8 ± 6	8 ± 6	0.417	
	Depression	4 ± 4	3 ± 3	**0.049**	0.33
	Anxiety	4 ± 3	5 ± 4	**0.005**	-0.25
15D~ (mean ± SD)	Total	0.93 ± 0.09	0.91 ± 0.01	**0.037**	2.00
VHI (mean ± SD)	Total	24.7 ± 22.0	3.6 ± 3.7	**<0.001**	5.70
RAND-36# (mean ± SD)	Physical role limitations	82 ± 31	79 ± 36	0.488	
	Emotional role limitations	87 ± 29	84 ± 32	0.430	
	Physical functioning	83 ± 27	82 ± 23	0.741	
	Social functioning	85 ± 23	87 ± 21	0.511	
	Mental health	82 ± 15	79 ± 18	0.102	
	Vitality	68 ± 19	67 ± 20	0.536	
	Pain	90 ± 18	80 ± 26	**0.001**	0.38
	General health perception	64 ± 19	73 ± 23	**0.003**	-0.39
	Health change	52 ± 19	52 ± 19	0.938	

* by independent sample t-test

only scored in Dutch patients

~ normative data on individual 15D items do not exist

Univariate associations between sociodemographic and disease-specific characteristics and the HADS, 15D and VHI (table 3)

No significant associations were found between sociodemographic and disease-specific characteristics and the HADS-total score. The HADS-depression score was significantly associated with country of origin (higher in Dutch patients, $p<0.001$); age ($r=0.300$, $p=0.004$); and age at time of diagnosis ($r=0.251$, $p=0.019$). Consequent comparisons showed that the Dutch HADS-depression score was significantly higher than that of Finnish and Dutch controls (both $p<0.001$), and that the Finnish HADS-depression mean score did not significantly differ from controls ($p=0.327$). Multiple linear regression including the three significantly associated disease-specific and sociodemographic characteristics with the HADS-depression score showed $R2=0.209$, $F=11.21$, $p<0.001$. Significant independent effects were found of country of origin ($\beta=.334$, $p=0.001$) and age ($\beta=.279$, $p=0.005$).

Table 3. Univariate effects of the sociodemographic and illness-related variables on the HADS, 15D and the VHI; statistically significant effects are marked.

	HADS	HADS depression	HADS anxiety	15D	VHI
	p value	*p value*	*p value*	*p value*	*p value*
Gender*	0.160	0.915	**0.023**	0.445	0.659
Country*	0.440	**<0.001**	0.080	0.766	0.506
Age#	0.152	**0.004**	0.947	**<0.001**	0.440
Marital status~	0.224	0.519	0.210	0.543	0.222
Living situation*	0.889	0.990	0.858	0.728	0.597
Educational level~	0.702	0.195	0.908	0.354	0.234
Smoking~	0.065	0.220	0.055	0.087	**0.002**
Co-morbidity*	0.495	0.253	0.866	**0.031**	0.300
Age at time of diagnosis#	0.769	**0.019**	0.146	**0.004**	0.279
Duration of disease course RRP#	0.331	0.791	0.188	0.683	0.715
Number of surgeries~	0.980	0.936	0.826	0.260	0.111

* Using student's t-test

Using Pearson correlation test

~ Using ANOVA

The HADS-anxiety score was significantly associated with gender (males have lower scores, p=0.023).

The 15D total score was negatively associated with age (r=-0.389, p<0.001); comorbidity (lower in patients with comorbidity, p=0.031); and age at time of diagnosis (r=-0.303, p=0.004). Multiple linear regression including the three significantly associated disease-specific and sociodemographic characteristics with the 15D score showed R2=0.150, F=15.30, p<0.001. A significant independent effect was found of age (β=-.387, p<0.001).

The VHI was significantly higher in former smokers (p=0.030) (Bonferroni post-hoc: former smokers versus current smokers p=0.011, former smokers versus non-smokers p=0.016).

Additionally, comparisons between patients who underwent 1-2 surgeries (N=31) and patients who received more than 2 surgeries (N=60) showed no significant differences on the mean scores of the HADS, HADS depression, HADS anxiety, 15D, and VHI (p=0.880, p=0.848, p=0.727, p=0.104, and p=0.342, respectively). No significant differences were found between JoRRP (n=9) and AoRRP (n=80) patients in mean scores on the HADS, HADS depression, HADS anxiety, 15D, and VHI (p=0.354, p=0.994, p=0.155, p=0.711, and p=0.166, respectively).

Care received by patients, their appreciation and associations between care received and depression and anxiety

Five RRP patients (6%) received psychosocial care from a psychologist, psychiatrist or social worker. The median number of psychosocial care sessions was 9 [range 2-21]. Median satisfaction score of these patients for psychosocial care was 7 [range 1-9]. The number of psychosocial care sessions was positively correlated with patients' satisfaction with these sessions (r=0.930, p=0.030).

Forty-one percent (37/90) of patients underwent speech therapy. Median number of speech therapy sessions for these patients was 10±12 [range 1-50] sessions. Mean satisfaction score of these patients for these sessions was 6.9±2.1 [range 1-10]. The number of speech therapy session was not significantly correlated with satisfaction with these sessions (r=0.279, p=0.128).

Patients who had received psychosocial care had a significantly higher HADS-depression mean score than patients who did not receive psychosocial care (respectively 6.2±4.3 versus 3.5±2.9, p=0.049, n=89). The HADS-anxiety score (p=0.820) or HADS total score (p=0.220) was not different between patients who did or did not receive psychosocial care. In comparison to patients who did not receive help from a speech therapist, patients who did receive such help had a significantly higher HADS total score (respectively 5.8±4.8 versus 9.8±5.7, p=0.001, n=89) and HADS-anxiety score (respectively 2.8±3.5 versus 5.4±3.1, p=0.001, n=90). The difference in HADS-depression mean score between these two groups just failed to reach significance (respectively 3.1±2.4 versus 4.4±3.7, p=0.050, n=89).

Discussion

This study examined QoL of RRP patients; factors associated with QoL, and allied health care they received. Compared to controls, RRP patients surprisingly reported a statistically significant and clinically relevant higher health-related QoL and less anxiety, but substantial voice problems. However, Dutch patients had higher depression scores, more pain, and a decreased general health perception than controls. Gender, country of origin, current age, age of onset of RPP, and presence of comorbidity significantly affected depression, anxiety

and/ or health-related QoL. Voice handicap is associated with smoking. Speech therapy was received by two-fifth of the patients and only a few patients received psychosocial care.

Anxiety, depression, QoL and voice problems and comparison with controls

To the best of our knowledge, no earlier study compared the QoL of RRP patients with controls. This study suggests that RRP patients experience less anxiety. However, more depression is found in the Dutch patient group than in controls; Finnish patients had comparable depression scores. It could well be that patients experience less anxiety as they have learned to handle the uncertain prognosis of RRP, but experience more depression as their voice problems cause psychosocial burden.

According to the RAND-36 Dutch RRP patients had significantly lower perception of their general health (not measured in Finnish patients). This was also shown in a British cohort.[26] Surprisingly, both Dutch and Finnish patients rate their overall health-related QoL as higher than the control group. The Dutch rate their functioning in the other RAND-36 QoL subscales comparable to controls. Habituation to a certain disease or health status can diminish the negative effect of disease on QoL. This is a well-known effect in QoL research, called response shift.[27] In case of RRP, this means that patients perceive their general health as lower, while at the same time they judge their overall QoL as comparable to controls. This study confirmed forgoing studies that voice is a significant problem for RRP patients.[9-11]

Differences in QoL between Dutch and Finnish RRP patients

There were no differences between Dutch and Finnish patients in sociodemographic data other than in smoking in the past: Dutch patients had smoked more often. Moreover, depression symptoms are more prevalent among Dutch RRP patients. It is known that the incidence of depression in the Netherlands is among the highest of the world, and higher than in Finland.[28] It seems reasonable to assume that the difference in depression score between RRP patients in the two countries might reflect the incidence of depression in the general population.

Factors associated with QoL

Some patients are prone to having a decreased QoL than others. This study found that female RPP patients; older patients; and Dutch patients were more vulnerable for depression, anxiety, and/ or lower health-related QoL. Our study showed that women were more likely than men to experience anxiety. This is in line with the finding that women in general are more prone to anxiety and fear, which also translates to female patients in many diseases.[29] Interestingly, older patients were more depressed and they had a lower health-related QoL. This effect of age in RRP was not shown before and could therefore lead to targeted psychosocial care for the older RRP patients. Number of surgeries; JoRRP or AoRRP, nor duration of disease were significantly correlated with health-related QoL, although these factors are often used as surrogate markers for severity of disease.[1] Regular use of a screening tool for distress could aid in early detection of distress in RRP patients, for this the RRP adapted Distress Thermometer and Problem List was validated.[30]

Smoking in the past was correlated with a higher voice handicap. Smoking is known to cause objective and subjective voice change.[31] It is unclear why current smokers have normal VHI scores. A higher number of surgical procedures did not correlate with more voice problems. This result is not in line with earlier findings reporting that numerous surgical interventions can cause vocal fold scarring, which reduces vocal capacity, lowers quality of the voice, and changes subjective voice.[32]

Psychosocial care and speech therapy

Only 6% of patients had received psychosocial care, while the mean HADS depression score is higher than in controls. Patients receiving psychosocial care had higher depression scores, even despite psychosocial therapy. Customized psychosocial care should therefore be aimed more at depression symptoms.

Although patients report more voice problems than controls, care by a speech therapist is received by only two-fifth of patients. Patients attending speech therapy had worse HADS scores (total, depression and anxiety) than those who did not receive such therapy. This emphasizes that voice and psychosocial problems are probably associated, as was shown in earlier research.[33] It has been reported that having a depression makes it more likely that one will receive speech therapy, due to subjective burden of voice problems.[33] A

median satisfactory score of these speech therapy sessions (7 out of 10) shows that improvement is still needed in the quality care of this therapy.

Strengths and limitations

This study had a satisfactory response rate (70%) and met the needed sample size. However, non-responders may have differed from responders and this may impact results. A higher percentage of Dutch patients responded, possibly because they were reminded by telephone, while Finnish patients were reminded by post. It was previously shown that a reminder by telephone results in a higher response rate.[34] However, this is the first study to examine QoL and associations between QoL and sociodemographic and illness-related characteristics in a sufficiently large number of patients.

Unfortunately RAND-36 could only be completed in the Netherlands due to IRB eligibility. Furthermore, Dutch control data was available for the HADS and the VHI while Finnish control data was available for the 15D. Therefore, RPP patients were compared to these respective groups. The fact that Dutch patients appeared to suffer from more depression than the Finnish suggests that cultural differences may exist. Comparing Dutch patient data with Finnish control data and vice versa could therefore distort results.

Conclusion

In comparison with controls, RRP patients have more voice problems; they have a lower general health perception but comparable QoL; and they are less anxious. In addition, Dutch RRP patients had higher depression scores. Anxiety, depression or health-related QoL was affected by gender, age and country of origin. Voice handicap was associated with smoking. Speech therapy is received by two-fifth of patients and psychosocial care by just a few patients with fair satisfaction.

Acknowledgments

We would like to thank prof. H. Sintonen (Professor of Health Economics, University of Helsinki, Helsinki, Finland) for his help with the 15D questionnaire.

References

1. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.
2. Kashima HK, Shah F, Lyles A, et al. A comparison of risk factors in juvenile-onset and adult-onset recurrent respiratory papillomatosis. Laryngoscope 1992;102:9-13.
3. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008;118:1236-1247.
4. San Giorgi M, van den Heuvel ER, Tjon Pian Gi RE, et al. Age of onset of Recurrent Respiratory Papillomatosis: a distribution analysis. Clin Otolaryngol 2015 [epub ahead of print].
5. Derkay CS, Malis DJ, Zalzal G, Wiatrak BJ, Kashima HK, Coltrera MD. A staging system for assessing severity of disease and response to therapy in recurrent respiratory papillomatosis. Laryngoscope 1998;108:935-937.
6. Chadha NK, James A. Adjuvant antiviral therapy for recurrent respiratory papillomatosis. Cochrane Database Syst Rev 2010;(1):CD005053.
7. Lindman JP, Lewis LS, Accortt N, Wiatrak BJ. Use of the Pediatric Quality of Life Inventory to assess the health-related quality of life in children with recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 2005;114:499-503.
8. Ilmarinen T, Nissila H, Rihkanen H, et al. Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis. Laryngoscope 2011;121:846-851.
9. Loizou C, Laurell G, Lindquist D, Olofsson K. Voice and quality of life in patients with recurrent respiratory papillomatosis in a northern Sweden cohort. Acta Otolaryngol 2014;134:401-406.
10. van Nieuwenhuizen AJ, Rinkel RN, de Bree R, Leemans CR, Verdonck-de Leeuw IM. Patient reported voice outcome in recurrent respiratory papillomatosis. Laryngoscope 2010;120:188-192.
11. Hill DS, Akhtar S, Corroll A, Croft CB. Quality of life issues in recurrent respiratory papillomatosis. Clin Otolaryngol Allied Sci 2000;25:153-160.
12. Merrill RM, Roy N, Lowe J. Voice-related symptoms and their effects on quality of life. Ann Otol Rhinol Laryngol 2013;122:404-411.
13. Cohen J. A power primer. Psychol Bull 1992;112:155-159.
14. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-370.
15. Aro P, Ronkainen J, Storskrubb T, et al. Validation of the translation and cross-cultural adaptation into Finnish of the Abdominal Symptom Questionnaire, the Hospital Anxiety and Depression Scale and the Complaint Score Questionnaire. Scand J Gastroenterol 2004;39:1201-1208.
16. Sintonen H. The 15D instrument of health-related quality of life: properties and applications. Ann Med 2001;33:328-36.
17. Mattila AK, Saarni SI, Salminen JK, Huhtala H, Sintonen H, Joukamaa M. Alexithymia and health-related quality of life in a general population. Psychosomatics 2009;50:59-68.
18. Hakkesteegt MM, Wieringa MH, Gerritsma EJ, Feenstra L. Reproducibility of the Dutch version of the Voice Handicap Index. Folia Phoniatr Logop 2006;58:132-138.
19. Alaluusua S, Johansson M. Äänihäiröiden aiheuttama psykososiaalinen haitta ja sen kuntoutuminen. Voice Handicap Index'n suomennoksen kokeilututkimus. MA-thesis, Logopedics. (Finnish). Helsinki: The University of Helsinki 2003.
20. Bouwers F, Dikkers FG. A retrospective study concerning the psychosocial impact of voice disorders: Voice Handicap Index change in patients with benign voice disorders after treatment (measured with the Dutch version of the VHI). J Voice 2009;23:218-224.
21. van der Zee KI. Psychometric qualities of the RAND 36-Item Health Survey 1.0: a multidimensional measure of general health status. Int J Behav Med 1996;3:104-22.
22. van der Zee K, Sanderman R. RAND-36, manual. Groningen: Northern Centre for Health Care Research, University of Groningen, the Netherlands 2012;2.

23. da Mota Falcao D, Ciconelli RM, Ferraz MB. Translation and cultural adaptation of quality of life questionnaires: an evaluation of methodology. J Rheumatol 2003;30:379-385.
24. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178-89.
25. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988. 25 p.
26. Jenkinson C, Stradling J, Petersen S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. J Sleep Res 1997;6:199-204.
27. Schwartz CE, Bode R, Repucci N, Becker J, Sprangers MA, Fayers PM. The clinical significance of adaptation to changing health: a meta-analysis of response shift. Qual Life Res 2006;15:1533-1550.
28. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med 2013;10:e1001547.
29. McLean CP, Anderson ER. Brave men and timid women? A review of the gender differences in fear and anxiety. Clin Psychol Rev 2009;29:496-505.
30. San Giorgi MR, Aaltonen LM, Rihkanen H, et al. Validation of the Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis. Otolaryngol Head Neck Surg 2016.
31. Pinar D, Cincik H, Erkul E, Gungor A. Investigating the Effects of Smoking on Young Adult Male Voice by Using Multidimensional Methods. J Voice 2015 [Epub ahead of print].
32. Friedrich G, Dikkers FG, Arens C, et al. Vocal fold scars: current concepts and future directions. Consensus report of the Phonosurgery Committee of the European Laryngological Society. Eur Arch Otorhinolaryngol 2013;270:2491-2507.
33. Marmor S, Horvath KJ, Lim KO, Misono S. Voice problems and depression among adults in the United States. Laryngoscope 2015;126:1859-1864.
34. MacLennan G, McDonald A, McPherson G, Treweek S, Avenell A, RECORD Trial Group. Advance telephone calls ahead of reminder questionnaires increase response rate in non-responders compared to questionnaire reminders only: The RECORD phone trial. Trials 2014;15:13-6215-15-13.

Chapter 7

Validation of the Distress Thermometer & Problem List in patients with Recurrent Respiratory Papillomatosis

M.R.M. San Giorgi MD[1,2,5], L. Aaltonen MD, PhD[3], H. Rihkanen MD, PhD[3], R.E.A. Tjon Pian Gi MD, PhD[1,2,5], B.F.A.M. van der Laan MD, PhD[1,2], J.E.H.M. Hoekstra-Weebers PhD[4], F.G. Dikkers MD, PhD[1,2,5]

[1] University of Groningen, University Medical Center Groningen, Department of Otorhinolaryngology/ Head & Neck Surgery, Groningen, The Netherlands
[2] Cancer Research Center Groningen, University of Groningen, The Netherlands
[3] Department of Otorhinolaryngology-Head and Neck Surgery, University of Helsinki, Helsinki University Hospital, Helsinki, Finland
[4] University of Groningen, University Medical Center Groningen, Wenckebach Institute, Groningen, The Netherlands
[5] Groningen Papilloma Studies, University Medical Center Groningen, Groningen, The Netherlands

Otolaryngol Head Neck Surg. 2016 Sep 6. pii: 0194599816668307.
[Epub ahead of print]

Abstract

Objective: There is no specific clinical tool for physicians to detect psychosocial and physical distress or health care need in patients with Recurrent Respiratory Papillomatosis (RRP). Main aim of this study is to validate the RRP-adapted Distress Thermometer & Problem List (DT&PL).

Study design: Prospective cross-sectional questionnaire research

Setting: Academic tertiary care medical centers in Groningen, the Netherlands and Helsinki, Finland.

Methods and subjects: Ninety-one Juvenile onset and Adult onset RRP patients from the departments of Otorhinolaryngology/ Head & Neck surgery of University Medical Center Groningen, the Netherlands and Helsinki University Hospital, Finland, participated. The Hospital Anxiety and Depression Scale was used as gold standard.

Results: A DT cutoff score of ≥4 gave best sensitivity and specificity. Thirty-one percent of patients had significant distress according to the DT cutoff. Significantly more patients with a score above than under the cutoff had a referral wish. The Problem List appeared to be reliable. Patients' opinions on the DT&PL were largely favorable.

Conclusion: The Dutch and Finnish versions of DT&PL are a valid, reliable screening tool for distress in RRP patients.

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a chronic disease leading to voice problems and eventually dyspnea.[1] There is no curative therapy.[2] Patients depend on repetitive surgical removal of the warts.[3]

Disease severity is often measured by the number of surgeries, luminal obstruction of the airway or anatomical spread of disease. Distress, voice complaints and quality of life (QoL) could also be an important clinical end-point. A number of studies evaluated perception of voice complaints and QoL among RRP patients. These studies showed that patients had significantly lower QoL than the average population.[4-6]

Distress has been defined as an unpleasant emotional experience of psychological, social or spiritual nature.[7] Individual RRP patients may experience distress to an extent that they should receive professional care.[6, 8] However, patients with a chronic disease often keep psychosocial problems for themselves.[9, 10] Distress can cause lower adherence to treatment; poorer QoL; worse satisfaction with care; and depression.[11] Systematic screening for distress can detect severity and nature of distress and helps in referring patients to appropriate care.[7] The Voice Handicap Index is a well-known questionnaire on distress due to voice problems.[12] However, this questionnaire does not provide insight into distress associated with problems in psychosocial and spiritual/ existential functioning or in other physical problems.

Screening for distress is performed worldwide in cancer patients, often using the Distress Thermometer & Problem List (DT&PL).[10] The DT is validated in many languages to detect severity of distress.[7] The Problem List that accompanies the DT provides information about the nature of distress. Reliability of the PL with varying items has been examined in oncology and chronic illness.[13-15] RRP shares chronic course, uncertainty and a broad set of possible complaints with malignant diseases. Until now there has been no specific clinical tool to detect severity and nature of psychosocial and physical distress and referral wish in RPP patients. Therefore, a multi-center questionnaire study was performed in a sufficiently sized cross-sectional RRP cohort. We expect that the RRP-adapted DT&PL will be a valid, patient friendly and useful screening tool for psychosocial and physical distress.

The main aim of this study is to examine the psychometric properties of a screening tool to detect severity and nature of psychosocial and physical distress and patients' wish for referral that can be used clinically: the RRP-adapted DT&PL. Secondary aims are to investigate patients' appraisal of this DT&PL and to examine socio-demographic and illness-related risk factors for distress severity.

Methods

Patients

Juvenile onset RRP (JoRRP) and adult onset RRP (AoRRP) patients from the departments of Otorhinolaryngology/Head & Neck surgery of the University Medical Center Groningen, Groningen, the Netherlands, as well as from the Helsinki University Hospital, Helsinki, Finland, were eligible for the study. Inclusion criteria were: histopathologically confirmed RRP by a certificated pathologist; current age ≥18 years; sufficiently mastering the Dutch or Finnish language; and last visit for RRP after 1/1/2010.

Ethical considerations

The research protocol was submitted for Institutional Review Board (IRB) approval in Groningen and Helsinki. Exemption of IRB approval was granted.

Sample size

Power analysis was performed on correlation between individual PL items and the DT score. Calculations were performed by G-power 3.1.9.2 (University of Kiel, Germany). Parameters were: two-tailed test, r=0.3 (medium), α=0.05, power (1-β)=0.8.[16] A sample size of 84 patients was calculated to accomplish the power. As precaution 8% missing data was calculated. Needed sample size was determined on 91 patients.

Procedure

Eligible patients were asked to complete a questionnaire. The questionnaire was sent to patients by post together with a letter explaining the goal of the study and a prepaid return envelope. Non-responders were reminded once by telephone or post. Data was collected from May 2014 through October 2014 to reach the desired sample size of 91 patients.

Questionnaire

The Hospital Anxiety and Depression Scale (HADS) (validated in Dutch and Finnish[17, 18]) is a 14-item instrument that measures anxiety and depression.[17] Calculation provides two subscales (anxiety and depression, maximum score per subscale: 21) and an overall score (maximum score: 42). An overall score >14 indicates elevated anxiety and depression. The HADS was used to examine the optimal cutoff score for the DT.

The DT&PL was originally developed and validated for patients suffering oncologic disease.[19] The Dutch version consists of the DT, a PL, and a referral wish question.[14] The DT is a single item scale that ranges from 0 to 10. Zero indicates no distress experienced during the past week, 10 indicates the experience of extreme distress during the past week. The PL was adapted for RRP patients by authors MSG and JWH, to adjust for RRP related physical problems and to include the domain of fear.

The RRP PL consists of 51 items covering 6 domains (table 1). Patients could indicate if they were bothered by a problem on a scale from 0 (not bothered) to 1 (slightly bothered) to 10 (yes, bothered extremely much)). Lastly, the DT&PL consisted of a question on the wish to be referred (answer options: yes, no or maybe) to a nurse, doctor, psychologist, social worker, pastoral counselor, dietician, physiotherapist, speech therapist, or someone else).

Table 1. The six RRP Problem List domains and the number of items per domain.

Domain	Number of items
Practical problems	8
Social problems	4
Emotional problems	10
Spiritual/existential problems	6
Physical problems	19
RRP related fear/anxiety	4

Patients further filled in questions on sociodemographic and illness-related characteristics (table 2). They could indicate their agreement with ten statements on the DT&PL (table 2) and they responded to the question whether they would recommend other RPP patients to complete DT&PL (answer options: yes, no). Surgical history was extracted from patients' files (table 2).

Table 2. Categories and subjects of sociodemographic, illness-related and satisfaction questions that patients filled in, and characteristics of the surgical history that were extracted from the patients' files.

Question category	Subject
Sociodemographic	Gender; age, marital status; living situation; educational level; daily activities; and smoking
Illness-related	Age at diagnosis; comorbidity*; and care received from healthcare worker other than doctor after RPP was diagnosed #
Satisfaction DT&PL	Pleasant; easy to complete; useful for myself; useful for caregiver; time consuming; stressful; providing insight into the nature of problems, giving insight into severity of problems; and if it helped in the conversation with the caregiver and in the conversation with others**
Surgical history (extracted from patients' files)	Date of onset of RRP; date of last surgical intervention; number of surgical interventions; and presence of a tracheostomy

** subcategories: asthma, chronic pulmonary problems, heartburn, gastrointestinal disease, neurological disease, diabetes mellitus, vascular disease, disease of bone and joints, muscle disease, coronary problems, psychiatric disease and other diseases*

 # subcategories: pastoral worker, psychologist, psychiatrist, social worker, dietician/nutritional team, and speech therapist

*** answer options: partly agree, agree, and partly disagree, disagree*

Translation

Official translations from Dutch into Finnish of all questions and the information letter were performed as described by Da Mota Falcao et al.[20]

Statistical analysis

Descriptive analyses were used to describe the study population and to examine anxiety, depression, distress, problems, referral wish, and care received. Independent t-tests and Pearson X^2-tests were used to compare Dutch and Finnish participants.

To examine discriminative power for clinical distress of the DT, a Receiver Operating Characteristics (ROC) curve was computed using HADS as gold standard. Per possible DT cutoff sensitivity, specificity, negative and positive predictive value and percentage of correctly classified patients were calculated. Internal consistency of the total PL and the six domains of the PL were calculated by Cronbach's α. Internal consistency of Cronbach's α <0.5 indicate unacceptable consistency, between 0.5-0.6 poor, 0.6-0.7 questionable, 0.7-0.8 acceptable, 0.8-0.9 good, and ≥0.9 indicate excellent consistency.[21] Pearson correlational analyses were computed to examine univariate relationships between the DT and PL scores. PL items strongly related to the DT were entered into a multiple linear forward regression to examine which of these

PL items were related to the DT. Descriptive statistics were used to explore patients' opinions on the DT&PL. Pearson correlation analyses, Pearson X^2-tests, independent student's t-tests and ANOVA were computed to examine univariate relationships between the DT&PL and HADS; between the DT and referral wish; between the referral wish and question on health care use; and between the DT and sociodemographic and illness related variables. Pearson's correlation coefficients <0.3 indicate weak relationship, between 0.3-0.5 moderate relationship, and >0.5 strong relationship.[15]

Normal distributed variables are presented as mean±standard deviation. Skewed variables are presented as median [range found]. Categorical variables are presented as number/total (percentage). Missing data per variable were dropped. the number of patients with a known value for the concerning variable were presented as (n=number). P value <0.05 was considered as statistically significant. Analyses were performed using PASW statistics version 21.0 (SPSS, Chicago, USA).

Results

In total 136 patients (58 Dutch and 78 Finnish) met the inclusion criteria and were asked to participate. Of these, 91 returned the questionnaire (response rate=67%, Dutch response rate 45/58=78%; Finnish response rate 46/78=59%). The response rate was significantly higher among the Dutch than among Finnish patients (X^2=5.2, p=0.023). The number of respondents (n=91) met the predetermined sample size.

Patient characteristics are shown in table 3. There were no statistically significant differences between Dutch and Finnish patients, with exception of smoking. More Dutch patients were former smokers compared to Finnish (X^2=7.7, p=0.021). Of the patients, 49% received extra care from a healthcare worker other than their doctor, specifically 41% received speech therapy, 7% psychosocial and/or 9% allied health care (table 3).

Table 3. Characteristics of patients diagnosed with recurrent respiratory papillomatosis, and comparison between Groningen (Dutch) and Helsinki (Finnish) respondents.

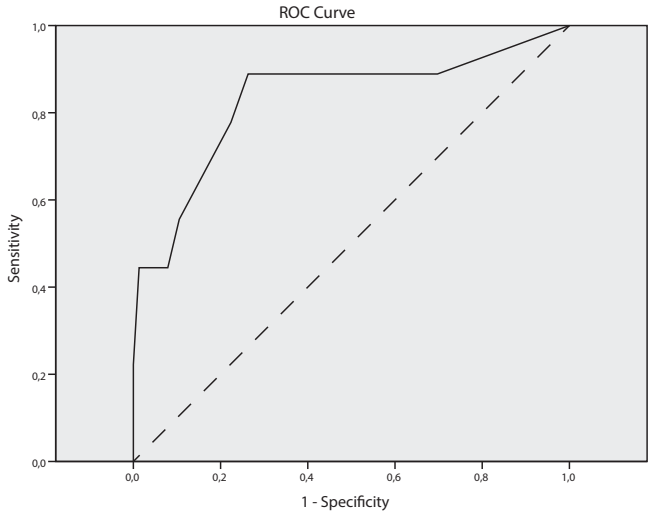
Variable		Total	Groningen	Helsinki	P between centers
Respondents (N)		91	45	46	
Response rate (%)		67	78	59	***0.023 ****
Gender (N (%))	Male	70 (69)	36 (80)	34 (73)	
	Female	21 (23)	9 (20)	12 (26)	0.491 *
Age (Mean ± sd)		51±15	52±16	50±15	0.558
Marital status (N (%))	Married/co-habiting	72 (79)	34 (76)	38 (83)	
	Divorced	5 (6)	1 (2)	4 (9)	
	Widowed	0 (0)	0 (0)	0 (0)	
	Single	14 (15)	10 (22)	4 (9)	0.114 †
Living situation (N (%))	Living with others	77 (84)	37 (82)	40 (87)	
	Living alone	14 (16)	8 (18)	6 (13)	0.531 *
Educational level (N (%))	Primary education	14 (15)	10 (22)	4 (9)	
	Middle level	40 (44)	20 (44)	20 (44)	
	High level	37 (41)	15 (33)	22 (48)	0.145 †
Daily activities (N (%))	Fulltime job	50 (56)	22 (49)	28 (62)	
	Parttime job	9 (10)	6 (13)	3 (7)	
	Household	4 (4)	1 (2)	3 (7)	
	Education	5 (6)	3 (7)	2 (4)	
	Unemployed	5 (6)	4 (9)	1 (2)	
	Incapacitated	3 (3)	3 (7)	0 (0)	
	Retired	14 (16)	6 (13)	8 (18)	0.238 *‡
Smoking (N (%))	Yes (currently)	10 (11)	6 (13)	4 (9)	
	No (never)	39 (43)	13 (29)	26 (58)	
	In the past	41 (46)	26 (58)	15 (33)	***0.021 ****
Age at time of diagnosis (Mean ± sd)		36±17	40±20	33±14	0.053
Duration of RRP (years) (Mean ± sd)		14±16	12±14	16±17	0.189
Comorbidity, any (N (%))	Yes	39 (43)	21 (47)	18 (40)	0.523 *‡
	Asthma	6 (7)	3 (7)	3 (7)	1.000 †‡
	GERD	9 (10)	6 (13)	3 (7)	0.485 †‡
	Psychiatric	3 (3)	1 (2)	2 (4)	1.000 †‡
Care after start RRP (N (%))	Yes	44 (49)	24 (53)	20 (44)	0.399 *
	Dietician/nutritional team	3 (3)	1 (2)	2 (4)	§
	Physiotherapist	5 (6)	3 (7)	2 (4)	§
	Psychologist	4 (4)	2 (4)	2 (4)	§
	Social worker	1 (1)	0 (0)	1 (2)	§
	Psychiatrist	2 (2)	0 (0)	2 (4)	§
	Pastoral worker	0 (0)	0 (0)	0 (0)	§
	Speech therapist	37 (41)	20 (44)	17 (38)	§

* Chi-square test
† Fisher's exact test
‡ N=90 (Groningen: 45, Helsinki: 45)
§ numbers too small for statistical analysis
GERD=gastroesophageal reflux disease, SD=standard deviation

DT and HADS

The mean DT score was 2.6±2.6 (n=86, range found 0-10). The mean DT score for Dutch patients (n=44) was 2.9±2.8 versus 2.4±2.5 for Finnish patients (n=42). Scores were not significantly different between countries (p=0.423). The mean HADS total score was 8±6 (n=90, range found 0-29). The HADS-anxiety and HADS-depression scores were 4±4 (n=91) and 4±3 (n=90) respectively. Nine (10%) patients had a score above the HADS cutoff (>14). The HADS total score and HADS anxiety score were not significantly different between countries. The HADS depression score was significantly higher in Dutch patients (5±2 versus 3±3, p<0.001). Correlation between DT and HADS was strong, namely r=0.531, p<0.001 (N=85), as was the correlation between DT and HADS-anxiety (r=0.505, p<0.001 (n=86)). Correlation between DT and HADS-depression was moderately strong (r=0.375, p<0.001 (n=85)).

Figure 1. Receiver operating curve of the distress thermometer scores versus the Hospital Anxiety and Depression (HADS) scale, yielding an area under the curve of 0.830.



The ROC curve for the DT (qualified by the HADS) is shown in figure 1. The area under the curve (AUC) was 0.830 (standard error 0.088, confidence interval 0.658-1.000, p=0.001). Table 4 shows sensitivity, specificity, predictive value and percentage of correctly classified patients. ROC analysis shows that a cutoff score of ≥4 seems optimal. At a DT cutoff score of ≥4, sensitivity was 0.89, specificity 0.74, positive predictive value 29%, and negative predictive value 98%. Not many patients will be indicated as false negative. However, more false positive patients will be detected. Of the patients, 28/91 (31%) scored above this cutoff.

Table 4. Receiver Operating Characteristics curve analysis per cutoff score of the RRP adjusted distress thermometer.

DT cutoff	Sensitivity	Specificity	Classified correctly (%)	PPV	NPV
≥0	1,00	0,00	10,59	0,11	
≥1	0,89	0,30	36,47	0,13	0,96
≥2	0,89	0,50	54,12	0,17	0,97
≥3	0,89	0,66	68,24	0,24	0,98
≥4	**0,89**	**0,74**	**75,29**	**0,29**	**0,98**
≥5	0,78	0,78	77,65	0,29	0,97
≥6	0,56	0,89	85,88	0,38	0,94
≥7	0,44	0,92	87,06	0,40	0,93
≥8	0,44	0,99	92,94	0,80	0,94
≥9	0,22	1,00	91,76	1,00	0,92
≥10	0,11	1,00	90,59	1,00	0,90

DT = Distress thermometer, PPV=positive predictive value
NPV=negative predictive value

Problem List

Median PL score was 23 [range 0-164, n=85] (potential range 0-510). Median scores and ranges found of the six RPP PL domains are demonstrated in table 5.

Table 5. Median scores, ranges found and potential ranges of the six domains of the RPP Problem List (n=91).

Domain	Median	Range found	Potential range
Practical problems	0	0-26	0-80
Social problems	0	0-18	0-40
Emotional problems	2	0-44	0-100
Spiritual/existential problems	0	0-29	0-60
Physical problems	13	0-97	0-190
RRP related fear/anxiety	1	0-32	0-190

Table 6. Listing of the correlation between Distress Thermometer and Problem List items. All correlation coefficients with r>0.213 are statistically significant. Showing three parts with respectively weak/no relationship, moderate relationship and strong relationship.

Relationship	PL item	Domain	Correlation coefficient (r)	PL item	Domain	Correlation coefficient (r)
Weak/no relationship	Stridor	Physical	0.032	Muscle strength	Physical	0.213
	Washing	Physical	0.058	Connection	Spiritual	0.218
	Transportation	Practical	0.085	Dyspnea	Physical	0.223
	Loss	Spiritual	0.088	Weight change	Physical	0.225
	Insurance	Practical	0.107	Physical fitness	Physical	0.234
	Mucus	Physical	0.115	Memory	Emotional	0.236
	Concentration	Emotional	0.116	Pain	Physical	0.255
	Meaning of life	Spiritual	0.131	Daily activities	Physical	0.264
	Sexuality	Physical	0.131	Dyspnea during speaking	Physical	0.265
	Trust	Spiritual	0.165	Finances	Practical	0.274
	Fear for narcosis	Fear	0.170	Loneliness	Emotional	0.278
	Making choices	Spiritual	0.185	Housekeeping	Practical	0.293
	Sleep	Physical	0.191	Coughing	Physical	0.296
	Trust in God/ faith	Spiritual	0.194			
Moderate relationship	Tiredness	Physical	0.306	Anxiety	Emotional	0.372
	Housing	Practical	0.319	Fear for surgeries	Fear	0.393
	Fear for dyspnea	Fear	0.321	Dealing with children	Social	0.394
	Emotional control	Emotional	0.323	Dealing with family/friends	Social	0.432
	Loss of control	Emotional	0.333	Self-esteem	Emotional	0.436
	Guilt	Emotional	0.335	Depression	Emotional	0.436
	Swallowing problems	Physical	0.337	Globus	Physical	0.443
	Sore throat	Physical	0.339	Sports	Practical	0.454
	Tension	Emotional	0.340	Feeling isolated	Social	0.494
	Child care	Practical	0.358			
Strong relationship	Dealing with partner	Social	0.518	Fear for worsening voice	Fear	0.620
	Work/school/ studies	Practical	0.587	Voice problems	Physical	0.649
	Intelligibility	Physical	0.601			

The RPP PL showed excellent consistency (Cronbach's α=0.928). The domains emotional problems (α=0.808) and physical problems (α=0.876) showed good consistency. The domains social problems (α=0.722), spiritual problems (α=0.756) and fear (α=0.756) had acceptable internal consistency. Consistency of the domain practical problems was questionable (α=0.622).

Relationships between DT and PL items

Table 6 shows the correlation coefficients between the DT and PL items. Five PL items were strongly related to the DT. Multiple linear regression including the five strongly related PL items on the DT showed R^2=0.607, F=41.62, p<0.001. Significant independent effects were found of voice problems (β=.460, p<0.001), dealing with partner (β=.234, p=0.003), and fear for worsening voice (β=.253, p=0.006)(table 7).

Table 7. Final model of the forward entered multiple linear regression including strongly related Problem List items.

Problem List item	Standardized beta	Unstandardized beta	S.E.	95% CI	p value
(Constant)		0.884	0.236	0.416-1.353	<0.001
Voice problems	0.460	0.405	0.081	0.244-0.567	<0.001
Dealing with partner	0.234	0.417	0.138	0.142-0.692	0.003
Fear for worsening voice	0.253	0.234	0.083	0.069-0.399	0.006

S.E.= standard error, CI= confidence interval

Relationships between DT and referral wish

Thirty-two of 86 patients (37%) replied that they wished additional care. Of those patients 22/32 (69%) wished referral to a doctor of another specialty, 5/32 (16%) to a speech therapist, 2/32 (6%) to a psychologist and 1/32 (3%) to a social worker. Two (6%) did not specify to whom they wanted to be referred, Of those having a score under the DT cutoff of ≥4, 4/58 (7%) 'wanted' and 10/58 (17%) 'maybe wanted' care from someone other than the doctor. Of those who had a score above the cutoff, 10/28 (36%) 'wanted' and 8/28 (29%) 'maybe wanted' additional care. Significantly more patients with a score above the DT cutoff had a referral wish than patients with a score <4 (X^2=15.6, p<0.001). Using the DT cutoff as indicator for referral would lead to a false negative rate of 24% and a false positive rate of 36%. Of patients who already had received additional care 10/44 (23%) 'wanted' and 13/44 (30%) 'maybe wanted' a new referral for

additional care. Of patients who had not received care, 5/44 (11%) 'wanted' and 5/44 (11%) 'maybe wanted' additional care. Significantly more patients who already received care from someone else than their doctor wished referral compared to patients who had not received care (X^2=7.705, p=0.021).

Appraisal of the DT&PL

Respondents were generally positive about the DT&PL (table 8). Dutch and Finnish patients differed significantly in one statement only: 91% of Dutch versus 64% of Finnish patients agreed that the DT&PL was useful for their caregiver (X^2=8.638, p=0.003).

Table 8. The eleven questions on patients' appraisal of the DT&PL.

Patient (completely or somewhat) agreed that ..	Percentage
..completing the DT&PL was pleasant	73
..filling in was stressful	30
..it was personally useful	69
..it was useful for caregiver	79
..it was easy	85
..it was time-consuming	38
..it gave insight into their own problems	66
..it gave insight into the severity of problems	71
..it helped in the conversation with family and friends	72
..it helped in the conversation with the caregiver	65
..he/she would recommend it to other patients	75

Predictors of distress

None of the fourteen sociodemographic or illness-related variables was significantly univariately associated with the DT score. Thus, no multivariate regression analysis was performed.

Discussion

RRP may cause significant distress.[4-6] Early detection of patients experiencing distress, appropriate referral and professional care is needed to address and to prevent the development of further problems. It was demonstrated that the RRP DT&PL is a reliable, easy and patient friendly tool to clinically detect distress

and referral wish. A cutoff score on the DT of ≥4 provided best sensitivity and specificity. Of the distressed patients, 89% was classified correctly as well as 74% of the non-distressed. The PL showed good consistency.

The HADS indicated that 10% had significant distress. A comparable incidence of 12% of RRP patients with a significantly increased HADS score has been found before.[22] Therefore, it seems that clinically elevated anxiety or depression is prevalent in a considerable number of patients.

Validation of DT&PL in RRP

Main aim of this study was to examine the psychometric properties of a screening tool to detect psychosocial and physical distress and referral wish that can be used clinically: the RRP-adapted DT&PL. This research showed that the RRP DT&PL is a valid and reliable screening tool for distress and for uncovering the specific problems a patient experiences.

Accuracy of the DT to screen for distress was qualified by the HADS with ROC analysis. The area under the curve (AUC) of the DT (0.83) was comparable to the AUC of a meta-analysis in cancer patients (0.84).[7] A cutoff for the DT score of ≥4 seems to be optimal for use in daily practice in RRP patients. With this cutoff the DT had a very high negative predictive value (98%) indicating the instrument's quality to rule out clinically elevated distress. However, the positive predictive value of 29% indicates that it is less suitable as a diagnostic tool. This may be due to the use of HADS as gold standard. HADS measures emotional distress, while distress as measured with the DT is multidimensional, including practical, social, spiritual and physical distress. The difference in constructs of distress is shown by the finding that more patients have clinically elevated distress according to the DT (31%) than according to the HADS (12%).

The cutoff was also a good predictor for referral wish of patients. Of the patients with a score above the cutoff, 65% wanted referral, while 24% of patients with a score under the cutoff wanted referral. Although the DT score is a good referral indicator, it should not be used as only indicator. Doctors are advised to discuss answers on the DT&PL to uncover for which problem(s) patients should be referred to which psychosocial or allied health care provider.

A practical distress screening tool should not only encompass distress, but also give insight into distress inducing factors.[15] Therefore, the PL including RRP-adapted physical and psychosocial problems is attached to the DT. Most problems were experienced in the domain physical problems, specifically voice problems. Voice problems were also one of three problems related to the DT in the multivariate analysis. Other PL domains had low scores, indicating that few patients experienced these problems. However, an individual patient may experience much distress caused by particular problems for which referral is needed. Deleting problems from the present PL because few patients suffer from that problem may prevent medical specialists or nurses to uncover the distress that particular problem causes and patients may not be referred.

Three PL items explained 60% of variance in the DT: voice problems, fear for worsening voice and dealing with partner. Of all problems, voice problems are most strongly related to the DT. Voice problems, even many years after disease onset, are found to be of major influence on QoL in RRP.[22, 23] The finding that dealing with partner is of influence is interesting, as relationship problems may not be addressed normally. This finding suggests that discussing the relationship between partners and how the partner copes with RRP might be an important step.

Appraisal of DT&PL

DT&PL is appreciated by patients: the majority of patients was positive. The percentage of patients who found it useful for the caregiver was statistically significantly higher in Dutch patients. This could be due to the fact that Dutch RRP patients are familiar with filling in questionnaires (e.g. VHI-30) in the waiting room. A third of patients found filling in time-consuming. Therefore, patients should be made aware that completing DT&PL before every outpatient clinic visit could aid in their conversation with their caregiver and that referral will take place if problems require additional support.

Relationships between DT and sociodemographic and illness-related variables

None of the sociodemographic or illness-related factors appeared to be associated with the DT. It has been observed before that no factors can predict distress in RRP.[22] This is interesting as a lower age of onset, higher number of surgeries or extended duration of disease are commonly considered as a sign of RRP severity.[24]

Proposed use of DT&PL in daily practice

Daily use of DT&PL at the outpatient clinic is easy. RRP patients are asked to fill in the DT&PL before attending their clinician at each visit. The clinician will obtain his/her normal clinical history, and he/she will then visually scan the DT&PL. Ticked PL items should be discussed with the patient if not yet discussed. Particular attention should be given to patients having a score above the cutoff of the DT. Furthermore, a shared decision on referral to which particular psychosocial or allied health care professional can be made.

Comparison of DT&PL with HADS and VHI

A fair question would be why the DT&PL should be used in daily practice, instead of HADS or VHI-30. DT&PL adds value due to the combination of physical, practical, psychosocial and spiritual/existential subdomains. HADS is limited to anxiety and depression,[17] while VHI-30 focuses on voice problems.[12, 22, 23] Additionally, fear for worsening of voice and dealing with partner are important determinants of distress in RRP. As DT&PL does address these factors, it is more complete.

Strengths and limitations

This is the first study to examine the psychometric properties of a screening tool for distress and referral wish in RRP. The multicenter study with cohorts from two countries resulted in inclusion of a sufficient number of patients. The study had a good response rate. A higher response rate was found among the Dutch compared to the Finnish. An explanation may be that Dutch non-responders were reminded by phone; Finnish by post. Sociodemographic and illness-related characteristics were comparable between countries. Future research will encompass validation of longitudinal DT&PL use, and evaluation of the clinical benefit. Further research on distress in RRP is needed to identify patients at risk for distress. Validation of the DT&PL in English is planned to make this screening tool available for larger groups of RRP patients and to facilitate validation into alternative languages.

Implications for practice

The Dutch and Finnish versions of DT&PL can be used to improve daily RRP care and to prevent or treat distress. DT&PL is a valid and reliable screening tool for distress and referral wish. DT&PL is appreciated by patients. No sociodemographic and illness-related factors were found for distress severity.

Acknowledgments

We would like to thank Ms. V. van Wijnen (MD) and Mrs. S. Mäkikärki (certificated Finnish-Dutch translator) for their help in translating the questionnaires and patient information. We would also like to thank Ms. B.A.C. van Dijk (epidemiologist) for her help with the power analysis.

References

1. Derkay CS, Wiatrak B. Recurrent respiratory papillomatosis: a review. Laryngoscope 2008;118:1236-1247.
2. Gillison ML, Alemany L, Snijders PJ, et al. Human papillomavirus and diseases of the upper airway: head and neck cancer and respiratory papillomatosis. Vaccine 2012;30 Suppl 5:F34-54.
3. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.
4. Lindman JP, Lewis LS, Accortt N, Wiatrak BJ. Use of the Pediatric Quality of Life Inventory to assess the health-related quality of life in children with recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 2005;114:499-503.
5. Chadha NK, Allegro J, Barton M, Hawkes M, Harlock H, Campisi P. The quality of life and health utility burden of recurrent respiratory papillomatosis in children. Otolaryngol Head Neck Surg 2010;143:685-690.
6. Loizou C, Laurell G, Lindquist D, Olofsson K. Voice and quality of life in patients with recurrent respiratory papillomatosis in a northern Sweden cohort. Acta Otolaryngol 2014;134:401-406.
7. Ma X, Zhang J, Zhong W, et al. The diagnostic role of a short screening tool--the distress thermometer: a meta-analysis. Support Care Cancer 2014;22:1741-1755.
8. Hill DS, Akhtar S, Corroll A, Croft CB. Quality of life issues in recurrent respiratory papillomatosis. Clin Otolaryngol Allied Sci 2000;25:153-160.
9. Petty L, Lester J. Distress screening in chronic disease: essential for cancer survivors. J Adv Pract Oncol 2014;5:107-114.
10. Donovan KA, Grassi L, McGinty HL, Jacobsen PB. Validation of the distress thermometer worldwide: state of the science. Psychooncology 2014;23:241-250.
11. Jacobsen PB, Donovan KA, Trask PC, et al. Screening for psychologic distress in ambulatory cancer patients. Cancer 2005;103:1494-1502.
12. Stuut M, Tjon Pian Gi RE, Dikkers FG. Change of Voice Handicap Index after treatment of benign laryngeal disorders. Eur Arch Otorhinolaryngol 2014;271:1157-1162.
13. Brennan J, Gingell P, Brant H, Hollingworth W. Refinement of the distress management problem list as the basis for a holistic therapeutic conversation among UK patients with cancer. Psychooncology 2012;21:1346-1356.
14. Tuinman MA, Gazendam-Donofrio SM, Hoekstra-Weebers JE. Screening and referral for psychosocial distress in oncologic practice: use of the Distress Thermometer. Cancer 2008;113:870-878.
15. Roskott AM, Huisman-de Waal G, Wanten GJ, et al. Screening for psychosocial distress in patients with long-term home parenteral nutrition. Clin Nutr 2013;32:396-403.
16. Cohen J. A power primer. Psychol Bull 1992;112:155-159.
17. Spinhoven P, Ormel J, Sloekers PP, Kempen GI, Speckens AE, Van Hemert AM. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363-370.
18. Aro P, Ronkainen J, Storskrubb T, et al. Validation of the translation and cross-cultural adaptation into Finnish of the Abdominal Symptom Questionnaire, the Hospital Anxiety and Depression Scale and the Complaint Score Questionnaire. Scand J Gastroenterol 2004;39:1201-1208.
19. Holland JC, Andersen B, Breitbart WS, et al. Distress management. J Natl Compr Canc Netw 2007;5:66-98.
20. da Mota Falcao D, Ciconelli RM, Ferraz MB. Translation and cultural adaptation of quality of life questionnaires: an evaluation of methodology. J Rheumatol 2003;30:379-385.
21. Kline P. The handbook of psychological testing. London: Routledge; 1993. 627 p.
22. van Nieuwenhuizen AJ, Rinkel RN, de Bree R, Leemans CR, Verdonck-de Leeuw IM. Patient reported voice outcome in recurrent respiratory papillomatosis. Laryngoscope 2010;120:188-192.

23. Ilmarinen T, Nissila H, Rihkanen H, et al. Clinical features, health-related quality of life, and adult voice in juvenile-onset recurrent respiratory papillomatosis. Laryngoscope 2011;121:846-851.
24. Tjon Pian Gi RE, Dietz A, Djukic V, et al. Treatment of recurrent respiratory papillomatosis and adverse reactions following off-label use of cidofovir (Vistide(R)). Eur Arch Otorhinolaryngol 2012;269:361-362.

Chapter 8

Quality and readability assessment of websites related to Recurrent Respiratory Papillomatosis

M.R.M. San Giorgi MD[#1,2,3], O.S.D. de Groot BSC[#1], F.G. Dikkers MD, PhD[1,2,3,4]

[#] These authors contributed equally to this work

[1] Department of Otorhinolaryngology/ Head & Neck Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
[2] Graduate School of Medical Sciences (Cancer Research Center Groningen), University of Groningen, Groningen, The Netherlands
[3] Groningen Papilloma Studies, University of Groningen, the Netherlands
[4] Current affiliation: Department of Otorhinolaryngology/ Head & Neck Surgery, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands

Laryngoscope. 2017 Feb 24. doi: 10.1002/lary.26521. [Epub ahead of print]

Abstract

Objective: Recurrent Respiratory Papillomatosis (RRP) is a rare disease of which a limited number of information sources for patients exist. The role of Internet in the patient-physician relationship is increasing. More and more patients search for online health information. Online health information should be of good quality and should be well readable. The study aim was to investigate the quality and readability of English online health information about RRP.

Study design: Quality and readability assessment of online information.

Materials and methods: Relevant information was collected using three different search engines and seven different search terms. Quality was assessed with the DISCERN instrument. The Flesch Reading Ease Score (FRES) and Average Grade Level (AGL) were determined to measure readability of the English websites.

Results: Fifty-one English websites were included. The mean DISCERN score of the websites is 28.1 ± 9.7 (poor quality). The mean FRES is 41.3 ± 14.9 (difficult to read) and the mean AGL is 12.6 ± 2.3.

Conclusion: The quality and readability of both English websites about RRP is alarmingly poor.

Introduction

Recurrent Respiratory Papillomatosis (RRP) is a rare illness caused by the Human Papilloma Virus (HPV).[1] The disease is characterized by multiple exophytic lesions of the mucosal squamous epithelium, called papillomata. The most common symptom is hoarseness, in particular if the lesions are located on the true vocal folds.[1] The disease has an unpredictable and sometimes recalcitrant course. Treatment of RRP is symptomatic: there is no known curative therapy. It is based on the surgical removal of the papillomata.[2]

The Internet is a very common source of information worldwide. Of the entire world population, 46.4% uses the Internet.[3] In Europe and North America, respectively 73.5% and 87.9% of the population uses the Internet.[3] The Internet is also an important source of health information for patients.[4-6] In 2014, 72% of the American Internet users searched for health information online.[7] It is estimated that, worldwide, 12.5 million health-related searches are performed on the Internet every day.[8] In 2002, only 13% of otorhinolaryngology patients used the Internet to obtain information before a consultation,[9] whereas in 2011 already 37% of the patients accessed Internet prior to their appointment.[10]

The impact of Internet on the patient-physician relationship has been discussed extensively.[11-13] The role of the patient has changed from a passive recipient of health information to an active consumer.[12] The Internet can be used to strengthen the patient-physician relationship and physicians should guide their patients to high quality websites.[14] As the Internet potentially influences patients' treatment choices, it is important that patients receive reliable health information online to reduce the risk of making incorrect clinical decisions based on Internet content.[15] This endorses the importance of both quality and readability assessment of online health information.

The aim of this study is to investigate the quality and readability of online patient information about RRP.

Materials and methods

Google.com (Google Inc., Mountain View, CA, USA), Yahoo.com (Yahoo! Inc., Sunnyville, CA, USA) and Bing.com (Microsoft Corp., Redmond, WA, USA) are the three search engines that were used. The three most used search engines worldwide are Google (71%), Baidu (13%) (Baidu Inc., Beijing, China) and Yahoo (7%).[16] Since Baidu is exclusively available in Asian languages, the search engine was not applicable for this study. Hence, the fourth most used search engine was selected, which is Bing.com (market share of 7%).[16]

The authors established the search terms used to obtain the relevant websites on RRP. Consensus was reached through consultation. To collect English websites containing relevant patient information, the search terms *"Recurrent Respiratory Papillomatosis"*, *"laryngeal papillomatosis"*, *"laryngeal papilloma"*, *larynx papillomatosis*, *larynx papilloma* were used. In addition, the search terms *wart throat* and *wart vocal cords* were used to simulate patients' search behavior. Searches were performed using Google Chrome v. 46.0 (Google Inc., Mountain view, CA, USA). The browser was set to 'incognito mode' to prevent the search engine from showing personalized results. Location and language settings were set to default.

Inclusion and exclusion

Each search term was entered into the three search engines. The first twenty hits were collected, since it is people's natural behavior to not look at search results past the first page.[17,18] Sponsored links and advertisements were ignored.

Websites were excluded when not containing information about RRP for patients; not written in English; they required an account/payment in order to view the content; being a discussion forum; being a scientific paper; being a PowerPoint presentation or video; and being dead links or security warnings.

Websites that were found using multiple search terms were marked as duplicate. The calculation of the average scores is based on unique hits, but the non-unique hits were used to compare search engines and terms. The term 'non-unique hits' is here defined as 'the amount of hits before the removal of duplicates'.

The websites were divided into four different categories by the authors: governmental, commercial, non-profit and university/hospital. Websites that stated that they were intended for layperson or patient readership were classified as 'for laypersons'.

The authors have no relationship or conflicts of interest with any of the evaluated websites.

Quality assessment

The DISCERN instrument was utilized to determine the quality of the selected websites. DISCERN is a reliable and valid tool for assessing the quality of written health care information.[19] It has been used to assess quality of health information about many different diseases and treatments,[20-25] including various otorhinolaryngological illnesses and interventions.[26-31]

The instrument consists of sixteen questions divided into three sections (possible range 15-80) (table 1). The first section, eight questions, addresses the reliability of the information and tests whether or not the information could be trusted as a source of information about treatment options. The second section, seven questions, deals with specific information about the treatment options themselves. The third section, one question, is an overall quality rating.[32] Scoring was performed by MSG and ODG.

Table 1. DISCERN score with corresponding quality level.

DISCERN score	Quality level
< 27	Very poor quality
27 - < 39	Poor quality
39 - < 51	Fair quality
51 - < 62	Good quality
> 62	Excellent quality

Readability assessment

Websites were assessed for readability using an online tool on www.readability-score.com. This tool determines the Flesch-Kincaid Reading Ease Score (FRES) and the Average Grade Level (AGL). The FRES is based on the number of words per sentence and the number of syllables per word, with FRES = 206.84 – (1.015 x average sentence length (ASL)) – (84.6 x average number of syllables per word

(ASW)).[33] Possible outcome is between 0-100, from very hard to understand to easy to understand. A FRES of 95 would indicate that a text is very easy to understand and a score of 65 suggests plain English, whereas a score of 15 indicates that a text is very difficult to comprehend.[33] Table 2 displays the FRES in terms of difficulty and American school level.

Table 2. Flesch-Kincaid Reading Ease Score (FRES) with corresponding readability and grade level.

FRES	Difficulty	School level (American)
90 – 100	Very easy	5th grade
80 – 90	Easy	6th grade
70 – 80	Fairly easy	7th grade
60 – 70	Plain English	8th/9th grade
50 – 60	Fairly difficult	10th – 12th grade (high school)
30 – 50	Difficult	College
0 – 30	Very difficult	College graduate

Apart from the FRES, the tool also generates the Average Grade Level (AGL). The AGL is the average of five different methods to determine the grade level. The methods are Flesch-Kincaid Grade Level, Gunning-Fog Score, Coleman-Liau Index, SMOG-index and Automated Readability Index. All of the above formulas produce an index that corresponds with the grade level in American education. It is recommended by the United States Department of Health and Human Services (USDHHS) that health information readability does not exceed 6th-7th grade level.[34-37]

Data collection

Inclusion and exclusion of English websites was performed between September 18 and 24, 2015. The quality assessment was done on October 1 and 2, 2015. Readability assessment took place on October 22 and 23, 2015.

Statistical analysis

Statistical analysis has been performed using IBM SPSS Statistics 22. The single measures Intraclass Correlation Coefficient (ICC) was used to measure inter-rater reliability (absolute agreement). The correlation between DISCERN and FRES, DISCERN score and AGL and DISCERN and Douma score was determined using Pearson's correlation coefficient. A multiple linear regression (method: enter) was performed to determine whether there are predictors for a high DISCERN score

or not. Dependent variables were language, FRES/Douma score and website category. One-way ANOVA is performed to compare the information found with the three search engines and the seven search terms. One-way ANOVA was also performed to compare information of the four different categories. P <0.05 was considered as statistically significant.

Results

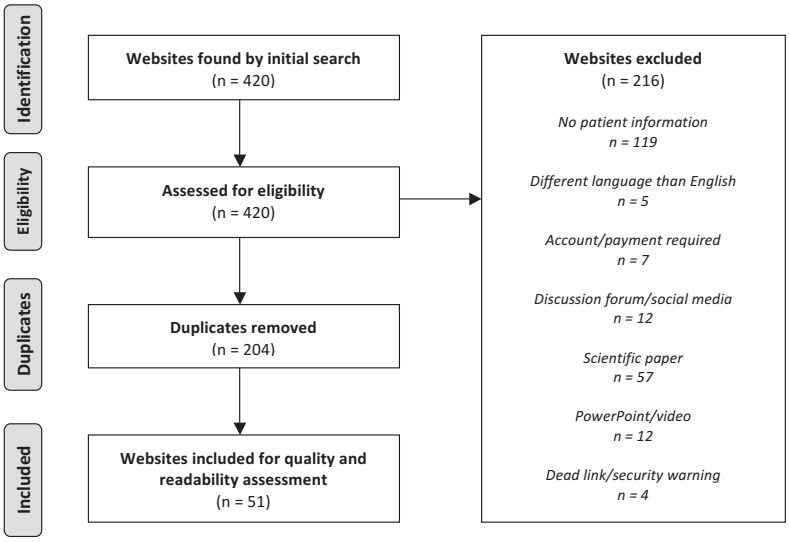


Figure 1. Included and excluded websites and the reason why websites were excluded.

The systematic search yielded 420 English hits. Two hundred and sixteen websites were excluded, leaving 204 websites, of which 188 were duplicates. Ultimately, 51 unique websites were assessed (figure 1). Websites were divided into the different categories as mentioned above (table 3). Sixty-nine percent (35/51) of websites were intended for lay readership.

Table 3. Number of English websites per category (governmental, commercial, non-profit, university/hospital) and their average DISCERN, Flesch-Kincaid Reading Ease Score (FRES) and Average Grade Level (AGL). Highest scores are bolded.

Category	Amount (n)	DISCERN	FRES	AGL
Governmental	3	27 ± 10.0	**50.1** ± 6.1	**10.6** ± 0.5
Commercial	17	27.2 ± 12.4	45.7 ± 15.1	12.5 ± 1.9
Non-profit	12	**31.7** ± 9.3	35.5 ± 15.2	12.9 ± 2.3
University/hospital	**19**	26.8 ± 7.1	39.6 ± 14.5	13.0 ± 2.6

Inter-rater reliability of DISCERN scoring

To determine exact inter-rater agreement, the Intraclass Correlation Coefficient was measured. Single measures Intraclass Correlation Coefficient (absolute agreement) was calculated at 0.843 ($P<0.010$), which indicates strong agreement.

Quality assessment

The mean DISCERN score was 28.1 ± 9.7 (poor). With a DISCERN score of 55.5 (good), the website http://emedicine.medscape.com/article/865758-overview scored highest.

The mean DISCERN score of non-profit websites was highest of all four categories: 31.7 ± 9.3 (poor), as shown in table 3. University or hospital websites scored lowest with a mean DISCERN score of 26.8 ± 7.1 (very poor). Twenty-six websites were of very poor quality, seventeen websites were of poor quality, seven websites were of fair quality and one website was of good quality. Not a single website scored high enough to be marked as excellent. All websites are shown in Appendix 1.

Readability assessment

Readability assessment of the websites by the Flesch Reading Ease Score and the Average Grade Level are shown in table 3.

The mean FRES of the websites was 41.3 ± 14.9 (difficult). The mean AGL was 12.6 ± 2.3. The website easiest to read was https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=134&contentid=239, with a FRES of 69 (plain English) and an AGL of 8.4.

As shown in table 3, of the English websites, the governmental websites were best readable, with a FRES of 50.1 ± 6.1 (fairly difficult) and an AGL of 10.6

± 0.5. Non-profit websites scored the worst on readability, with a FRES of 35.5 ± 15.2 (difficult) and an AGL of 12.9 ± 2.3. There was no significant difference between the four different categories in the mean DISCERN score (P=0.554), FRES (P=0.210) and AGL (P=0.261).

Predictors of DISCERN and readability statistics

There was no significant correlation between the DISCERN and FRES score (r=-0.094 (P=0.514)) and between the DISCERN score and AGL (r=0.084 (P=0.560)).

Predictors for DISCERN score

Multiple linear regression was performed to determine whether there are predictors for a high DISCERN score. FRES, AGL and website category did not predict for the DISCERN score (R^2=0.049, F=0.463 (P=0.801)).

Discussion

The quality and readability of online health information about RRP is substandard. Overall, the mean DISCERN score of the websites showed poor quality. The majority of English written websites, 26 out of 51, were qualified as very poor. Only one website was of good quality and none scored high enough to be qualified as excellent. None of the websites met the recommended values of readability. The mean FRES indicates difficult readability and the mean grade level is 12.6th grade.

The use of Internet by patients has increased dramatically over the past years.[37] One would expect that this development continues today. It was shown that the patients already seek online information due to the fact that they were inadequately informed about their disease, because there was lack of time for explanation, the physician was unwilling to explain, the patient is ashamed to ask questions or the physician did not succeed to provide comprehensible information.[38] Therefore, the importance of good quality online health information has been emphasized by Clarke et al. (2015) by stating that ensuring the availability of valid, usable, and accessible information is a priority.[15] To reduce the risk of patients making detrimental treatment choices based on online health information, it is important that patients receive reliable information online.

To the best of our knowledge, this is the first study that investigated the quality and readability of websites related to Recurrent Respiratory Papillomatosis. It aims to elucidate the current situation in terms of availability and quality of online information about RRP and to create awareness among physicians. Moreover, this study could lead to collaboration of the different information centers to improve the quality and availability of the information.

Interestingly, of the 51 included websites, 26 were of very poor quality, 17 were of poor quality, 7 were of fair quality and only one website was of good quality. University or hospital websites had the lowest scores, while these websites are often supposed to be more reliable than commercial websites. In the case of RRP information these websites were often disguised advertisements for certain treatments. Overall, websites were difficult to read (low FRES) and a fairly high school level was needed to comprehend the websites (high AGL). The high density of poor quality websites is potentially dangerous for patients' knowledge on RRP.

No significant correlation was found between the DISCERN score and both FRES score and AGL. This means that a good quality website is not necessarily well readable and vice versa. This is especially problematic for semiliterate patients. High quality websites that are hard to read are no problem for highly educated patients, but semiliterate patients might have trouble to understand the information. For example, the website with the highest DISCERN score has a FRES of 25.6 and an AGL of 14.4. In other words, the English website with the highest quality rating is very difficult to read and requires a school grade level of 14.4 to be able to read the information easily. In order to be useful to all patients, readability of the assessed websites must be improved.

It is impossible to build a model to predict a better DISCERN score based readability statistics and website categories. It follows that it is useless to guide patients exclusively to a certain 'type' of website and that all types of websites should improve, regardless of language, readability score or category.

Since RRP is a rare disease, it is comprehensible that there is no abundance of high quality online information. However, the outcome of this study is alarming. The lack of good quality information should be an incentive for physicians to guide their patients in their search for reliable, intelligible and correct information. Good quality websites should comply with the following

general requirements. First of all, the aims of the website should be clear. A good website begins with explicitly stating what the website is about and whom it is meant for. In that way, patients will know instantly if the website contains the information that they are looking for. Of the included websites together only two websites had clear aims. Clearly, this is an aspect of most websites that needs improvement. Secondly, websites should be evidence-based, which means that the sources (and their publication date) that were used to compile the website should be clear. Thirdly, the website should provide additional sources of information and should refer to areas of uncertainty. Information on treatment options should accurately describe each treatment, their benefits and risks and their impact on the patients' daily life.

Limitations

The DISCERN instrument, although being a reliable and valid tool to assess health information, has its limitations. The most important shortcoming of the DISCERN tool is that it does not take into account how the information is presented or how easy it is to navigate and find the information on a particular website. Furthermore, the DISCERN scoring has been performed by two researchers. It is not entirely clear if laypersons would assess the websites in the same way. However inter-rater agreement between these two researchers showed strong agreement, confirming the reproducibility of this score.

Readability statistics, such as the FRES and grade levels, have been criticized. Some argue that readability statistics based merely on word and sentence length do not adequately reflect the complexity and readability of a text, but that this depends on more factors than just word and sentence length.[39]

Recommendations

Of all 51 websites evaluated one, http://emedicine.medscape.com/article/865758-overview, had good quality. None of the websites met the study's criteria for readability.

Webmasters of websites containing health information are recommended to adjust their websites according to the above-mentioned criteria for good websites. Otorhinolaryngologists worldwide should consider the possibility of jointly making a website containing high quality, intelligible information in various languages for patients and their partner.

References

1. Derkay CS. Recurrent respiratory papillomatosis. *Laryngoscope*. 2001;111(1):57-69.
2. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. *Head Neck*. 2015;37(11):1625-1632.
3. Internet world stats 2015. november 30, 2015 http://www.internetworldstats.com/stats.htm. Accessed 01/21, 2016.
4. Tassone P, Georgalas C, Patel NN, Appleby E, Kotecha B. Do otolaryngology out-patients use the internet prior to attending their appointment? *J Laryngol Otol*. 2004;118(1):34-38.
5. Medlock S, Eslami S, Askari M, et al. Health information-seeking behavior of seniors who use the internet: A survey. *J Med Internet Res*. 2015;17(1):e10.
6. McMullan M. Patients using the internet to obtain health information: How this affects the patient-health professional relationship. *Patient Educ Couns*. 2006;63(1-2):24-28.
7. Pew Research Center. Health fact sheet. 2014 http://www.pewinternet.org/fact-sheets/health-fact-sheet/. Accessed 01/21, 2016.
8. Eysenbach G. The impact of the internet on cancer outcomes. *CA Cancer J Clin*. 2003;53(6):356-371.
9. Rokade A, Kapoor PK, Rao S, Rokade V, Reddy KT, Kumar BN. Has the internet overtaken other traditional sources of health information? questionnaire survey of patients attending ENT outpatient clinics. *Clin Otolaryngol Allied Sci*. 2002;27(6):526-528.
10. Shaw B. Internet and e-mail use in ENT: A survey of patient usage and satisfaction. *European Archives of Oto-Rhino-Laryngology*. 2012-3;269(3):1051-4.
11. Hart A. The role of the internet in patient-practitioner relationships: Findings from a qualitative research study. *Journal of Medical Internet Research*. 2004-9-30;6(3).
12. McMullan M. Patients using the internet to obtain health information: How this affects the patient-health professional relationship. *Patient Educ Couns*. 2006-10;63(1-2):24-8.
13. Iverson SA. Impact of internet use on health-related behaviors and the patient-physician relationship: A survey-based study and review. *JAOA: Journal of the American Osteopathic Association*. 2008-12;108(12):699-711.
14. Jeannot JG. [Patients, doctors and the internet]. *Revue médicale suisse*. 2015-5-13;11(474):1066-8.
15. Clarke MA. Health information needs, sources, and barriers of primary care patients to achieve patient-centered care: A literature review. *Health Informatics Journal*. 2015-9-15.
16. Desktop search engine market share. https://www.netmarketshare.com/search-engine-market-share.aspx?qprid=4&qpcustomd=0&qpsp=2015&qpnp=2&qptimeframe=Y. Updated 2016. Accessed 09/23, 2016.
17. Morahan-Martin JM. How internet users find, evaluate, and use online health information: A cross-cultural review. *CyberPsychology Behavior*. 2004-10;7(5):497-510.
18. Peterson G. How do consumers search for and appraise information on medicines on the internet? A qualitative study using focus groups. *Journal of Medical Internet Research*. 2003-12-19;5(4).
19. Charnock D. DISCERN: An instrument for judging the quality of written consumer health information on treatment choices. *J Epidemiol Community Health*. 1999-2;53(2):105-11.
20. Bruce JG. Quality of online information to support patient decision-making in breast cancer surgery. *J Surg Oncol*. 2015-11;112(6):575-80.
21. Yeung TM. Assessment of the quality of patient-orientated information on surgery for crohn's disease on the internet. *Diseases of the colon rectum*. 2015-9;58(9):857-61.
22. Sobota A. The quality and readability of online consumer information about gynecologic cancer. *International journal of gynecological cancer*. 2015-3;25(3):537-41.
23. Barnes JA. Reading grade level and completeness of freely available materials on thyroid nodules: There is work to be done. *Thyroid*. 2015-2;25(2):147-56.
24. Fioretti BT. Googling caesarean section: A survey on the quality of the information available on the internet. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2015-4;122(5):731-9.

25. Kaicker J, Debono VB, Dang W, Buckley N, Thabane L. Assessment of the quality and variability of health information on chronic pain websites using the DISCERN instrument. *BMC Medicine*. 2010;8(59):1-8.
26. Seymour N, Lakhani R, Hartley B, Cochrane L, Jephson C. Cochlear implantation: An assessment of quality and readability of web-based information aimed at patients. *Cochlear implants international*. 2015;16(6):321-325.
27. Alamoudi U. Readability and quality assessment of websites related to microtia and aural atresia. *Int J Pediatr Otorhinolaryngol*. 2015-2;79(2):151-6.
28. Veer V. The quality of snoring treatment information on the internet. *European Archives of Oto-Rhino-Laryngology*. 2014-12;271(12):3319-23.
29. Goslin RA. Evaluating internet health resources in ear, nose, and throat surgery. *Laryngoscope*. 2013-7;123(7):1626-31.
30. McKearney TC. The quality and accuracy of internet information on the subject of ear tubes. *Int J Pediatr Otorhinolaryngol*. 2013-6;77(6):894-7.
31. Langille M. Systematic evaluation of obstructive sleep apnea websites on the internet. *Journal of otolaryngology - head neck surgery = Le Journal d'oto-rhino-laryngologie et de chirurgie cervico-faciale*. 2012-8;41(4):265-72.
32. Charnock D. The DISCERN handbook; Quality criteria for consumer health information on treatment choices. http://www.discern.org.uk/discern.pdf. Updated 1998. Accessed 08/19, 2015.
33. Flesch RF. Readability formula. In: *How to write plain english: A book for lawyers and consumers*. University of Michigan: Harper & Row; 1979:20-32.
34. Walsh TM. Readability assessment of internet-based consumer health information. *Respir Care*. 2008-10;53(10):1310-5.
35. AlKhalili R. Readability assessment of internet-based patient education materials related to mammography for breast cancer screening. *Acad Radiol*. 2015-3;22(3):290-5.
36. Cherla DV. Readability assessment of internet-based patient education materials related to acoustic neuromas. *Otology neurotology*. 2013-9;34(7):1349-54.
37. Diviani N. Low health literacy and evaluation of online health information: A systematic review of the literature. *Journal of Medical Internet Research*. 2015;17(5).
38. Eysenbach G G. Labeling and filtering of medical information on the internet. *Methods Inf Med*. 1999-6;38(2):80-8.
39. Jansen C. Voorkomen is beter. op weg naar effectievere teksten in de gezondheidscommunicatie. http://www.careljansen.nl/Publications/oratie2012.pdf. Updated 2012. Accessed 01/22, 2016.

Appendix

Appendix 1. Included websites with information on Recurrent Respiratory Papillomatosis with their LINK, mean DISCERN score, the three Discern sections, Flesch Reading Ease Score and the Average Grade level.

	Link	DISCERN score	Sec. 1	Sec. 2	Sec. 3	FRES	AGL
1	http://www.nidcd.nih.gov/health/voice/pages/laryngeal.aspx/	38,5	18,5	16	4	54,2	10,8
2	http://emedicine.medscape.com/article/302648-overview	49	23,5	21	4,5	33,6	13,2
3	http://www.rrpf.org/whatisRRP.html	45,5	29,5	13,5	2,5	44,8	12,1
4	https://en.wikipedia.org/wiki/Laryngeal_papillomatosis	43	21	18,5	3,5	47,9	11,2
5	http://www.webmd.com/lung/recurrent-respiratory-papillomatosis	20,5	12	7,5	1	21,3	15,5
6	http://std.about.com/od/hpv/a/Recurrent-Respiratory-Papillomatosis.htm	31,5	17,5	12	2	50	11,7
7	https://rarediseases.info.nih.gov/gard/111/recurrent-respiratory-papillomatosis/resources/1	21	12,5	7	1,5	53	10
8	http://emedicine.medscape.com/article/865758-overview	55,5	24	27,5	4	25,6	14,4
9	http://misc.medscape.com/pi/android/medscapeapp/html/A302648-business.html	46,5	22,5	20,5	3,5	33,6	13,2
10	http://voicefoundation.org/health-science/voice-disorders/voice-disorders/recurrent-respiratory-papillomatosis/	41	15	23	3	40,3	12,7
11	http://www.cincinnatichildrens.org/health/r/rrp/	28,5	12,5	13,5	2,5	63,9	8,9
12	https://rarediseases.org/rare-diseases/recurrent-respiratory-papillomatosis/	43,5	17,5	22,5	3,5	34,1	13,7
13	http://www.hopkinsmedicine.org/otolaryngology/specialty_areas/voice_center/conditions/recurrent_respiratory_papillomatosis.html	24	10,5	12	1,5	37,8	14,2
14	https://rarediseases.info.nih.gov/gard/6864/laryngeal-papillomatosis/resources/1	21,5	13	7	1,5	43,1	10,9
15	http://www.gosh.nhs.uk/medical-information/search-medical-conditions/laryngeal-papillomatosis	32	13	16,5	2,5	56,4	10,5
16	http://www.ucdvoice.org/laryngeal-papilloma-2/	38,5	15	20,5	3	33,8	13,5
17	http://www.pathologyoutlines.com/topic/larynxpapilloma.html	24	13	9,5	1,5	-4,8	17,7

Appendix 1. continued

	Link	DISCERN score	Sec. 1	Sec. 2	Sec. 3	FRES	AGL
18	http://www.pathologyoutlines.com/topic/tracheapapilloma.html	22,5	13	8,5	1	18,6	14,2
19	http://pedimedicine.com/laryngeal-papilloma-children/	31,5	14,5	14,5	2,5	45,8	10,2
20	http://www.childrenshospital.org/conditions-and-treatments/conditions/laryngeal-papilloma	17	8	8	1	18,6	16,2
21	http://www.wisegeek.com/what-is-laryngeal-papilloma.htm	27,5	12	13	2,5	44,7	12,8
22	http://hospitals.jefferson.edu/diseases-and-conditions/laryngeal-papilloma/	17	9	7	1	22,2	15,9
23	http://voicehealth101.com/topics/papilloma	24,5	11,5	11	2	29,3	13,8
24	http://professionalvoice.org/HPV-Papilloma.aspx	43	15,5	24	3,5	45,8	12,1
25	http://www.rarecancers.org.au/directory/193/childhood-laryngeal-cancer-and-papillomatosis	20,5	11	8	1,5	45,3	10,8
26	http://www.massgeneral.org/voicecenter/services/treatmentprograms.aspx?id=1541	36,5	15	18,5	3	32	15,6
27	https://www.emoryhealthcare.org/voice-center/diseases-conditions/laryngeal-tumors.html	19,5	10,5	7,5	1,5	37	12,3
28	http://www.voicedoctorla.com/voice-disorders/vocal-papillomas/	28	12,5	13,5	2	46,6	11,2
29	http://www.ehow.com/way_5373766_treatment-throat-warts.html	21,5	9,5	10,5	1,5	63,1	10,3
30	http://www.thebody.com/h/symptoms-of-genital-warts-in-throat.html	15,5	7,5	7	1	68,5	8,4
31	http://www.wisegeekhealth.com/how-can-i-remove-throat-warts.htm	15,5	7,5	7	1	53,7	11,4
32	http://www.ehow.com/about_5633009_signs-hpv-throat.html	18,5	10	7,5	1	59,9	10,7
33	http://www.netdoctor.co.uk/ate/ent/203445.html	20	11	7,5	1,5	57,1	10,6
34	http://www.throatdisorder.com/blog/recurrent-respiratory-papillomatosis-rrp	22,5	10,5	10,5	1,5	46,2	11,5
35	https://www.ent.uci.edu/clinical-specialties/university-voice-and-swallowing-center/papilloma.asp	22	8,5	12	1,5	48	11,6
36	http://hpathy.com/cause-symptoms-treatment/vocal-cord-problems/	17	8	7,5	1,5	51,2	11,5
37	http://bryanking.net/human-papilloma-virus-hpv/	23,5	9,5	12,5	1,5	42,8	13,2

Appendix 1. continued

	Link	DISCERN score	Sec. 1	Sec. 2	Sec. 3	FRES	AGL
38	https://www.urmc.rochester.edu/encyclopedia/content.aspx?contenttypeid=134&contentid=239	25	13,5	9,5	2	69	8,4
39	http://www.chop.edu/conditions-diseases/recurrent-respiratory-papillomas#.Vfk5eNLtlHw	28,5	13,5	13	2	27,8	14,1
40	http://bastianmedicalmedia.com/recurrent-respiratory-papillomatosis-rrp/	26	12,5	11,5	2	35,1	16,3
41	http://www.timetohear.com/speech-services/laryngeal-papillomatosis/	27,5	14	11,5	2	48,6	11,9
42	http://www.medicinenet.com/script/main/art.asp?articlekey=8990	16,5	8,5	7	1	13,9	15,7
43	http://www.northshore.org/otolaryngology-head-neck-surgery/adult-programs/voice-center/conditions/laryngeal-papillomatosis/.	28	12	13,5	2,5	21,4	16,6
44	http://www.drjoannawalton.com/patient-info/conditions-procedures/throat-surgery/laryngeal-papilloma-surgery/	34	11,5	19,5	3	55,8	10,7
45	http://www.pediatricentillinois.com/laryngeal-papilloma-removal/	21,5	9,5	10,5	1,5	57,1	9,9
46	http://radiopaedia.org/articles/tracheobronchial-papillomatosis	33	21,5	9,5	2	31,8	13,3
47	http://www.drtbalu.com/pap_lx.html	27	9,5	15,5	2	40,9	11,4
48	http://www.simple-remedies.com/home-remedies/warts/warts-in-throat-symptoms-remedies.html	22,5	10,5	10,5	1,5	52,7	11,4
49	http://www.bbivar.com/vp_papilloma.php	28,5	12	14	2,5	26,8	15,9
50	http://www.hopkinsmedicine.org/healthlibrary/conditions/adult/otolaryngology/recurrent_respiratory_papillomatosis_22,recurrentrespiratorypapillomatosis/	27,5	11,5	14	2	36,2	15,3
51	http://www.capitalregionspecialsurgery.com/ent/disease-and-treatments/laryngeal-papillomas/	19,5	10	8	1,5	42,3	11,6

Sec. = section; FRES = Flesch Reading Ease Score; AGL = Average Grade Level

Chapter 9

Discussion

This thesis provides new insights in the factors that predict and influence the clinical course of RRP. The thesis can therefore be used as the basis of further research on prognosis and therapy. Furthermore, it gives insight in the effects of its clinical course on patients and provides methods to identify, timely treat and prevent psychosocial problems in patients. In the following paragraphs the findings of the thesis will be discussed and future aspects of patient care and research in RRP will be shown.

Part I: Clinical course

Chapter 2 describes the age of onset of RRP. The study describes a new peak of age of onset, namely a group of patients that develops RRP around the age of 65 years. As distribution of age of onset was previously described as bimodal, the older age group was not taken in account earlier. Possibly pathophysiological mechanisms, the disease course and immunological patterns of these older patients differ with the younger patients. Bonagura and co-workers already showed that there are indications that local immune response in RRP patients is inefficient. Due to HPV activity the T(h)1/T(h)2 leukocyte ratio is altered to an ineffective T(h)2 response,[1] while a T(h)1 response is needed. As the immune response alters due to aging,[2-4] it could well be that the mechanism of RRP infection and spread is different in this aging population. Research on the pathophysiology of RRP should first compare the elder group to the younger patient groups before all three groups of age of onset can be considered as one regarding therapy. Possible pathophysiological differences between the different age groups may affect therapeutic options. Strengthening the immune status of RRP patients might help the immune system in eradicating the virus.

Worldwide prevention of low- and high-risk HPV infection by prophylactic vaccination programs is currently aimed at adolescent girls and, in some cases, adolescent boys.[5] The vaccination program already showed to be effective in diminishing the incidence HPV16 and 18 associated disease, such as cervical cancer and head and neck cancer.[6] Furthermore, immediate decrease of HPV6 and 11 associated genital disease (condylomata acuminata) is seen in young adults as an effect of diminished horizontal transmission.[7-9] But even if the preventative effect holds, it will take decades till the elderly group consists of

merely vaccinated people. RRP will still develop in this age group. The elder group will therefore be an increasing proportion of the total RRP group.

The analysis of age of onset also showed that Juvenile onset RRP (JoRRP) and Adult onset RRP (AoRRP) are not simply divided by age of onset, as there is no specific age that would be a correct cut-off between both groups. Both age groups even show overlap and it is thus statistically impossible to say if a patient belongs to the first age group or the second. Furthermore, it was already shown that both entities are biologically the same disease.[10] We therefore propose to leave the terminology JoRRP and AoRRP, as there is no difference between both diseases.

Chapter 3 proposes a model to describe the needed number of surgical interventions in the disease course of RRP patients. In general RRP patients need to undergo many surgical interventions, due to the recurrent character of the papilloma growth. Preferably, the number of surgical interventions should be kept as limited as possible, as surgery can induce increased viral activity.[11] Furthermore micro-lesions can be caused, which are access areas for new HPV infection of the basal layer of the epithelium.[12] Lastly, surgery causes scars that are an iatrogenic form of transitional epithelium, the epithelium were papillomas generally occur.[13] The advantage is that surgery could induce immunological activity, which can be beneficial for the patient.[14] To limit the number of surgical interventions it is policy, in the University Medical Center Groningen, to only perform surgery when papillomas show exophytic growth or threaten the airway.

The proposed model in chapter 3 describes the clinical course of RRP, including the effects of age of onset, duration of disease, HPV-type and comorbidity (gastroesophageal reflux disease and asthma). Our studies show that clinical course is naturally softening. Correction for this natural effect is needed in research on RRP therapies. One of the therapies that should be analysed on short notice is cidofovir, as it is still used worldwide without a firm evidence based basis. Cidofovir is thought to inhibit HPV induced epithelial cell replication and would therefore diminish growth of papillomas.[15] There are many studies describing the clinical course of RRP after the use of cidofovir without taking into account the natural clinical course.[15-17] Data pooling should be performed,

followed by reanalysis of a larger patient group with the needed correction for natural course. The technique of reanalysing data would be applicable to all therapies that were tried in the past.

In chapter 4 the immune reaction to the therapeutic use of the quadrivalent HPV vaccine Gardasil® is analysed. The study showed reactivation of the humoral immune response after vaccination even though patients had active disease. Although this activated response is probably unable to eradicate HPV from already infected cells,[18] it might prevent further HPV spread throughout the airways. As already infected airway epithelium is not prevented from developing papilloma growth, surgical interventions will still be needed until all infected epithelium is resected. A similar effect was seen in condylomata acuminata (HPV6 and HPV11 associated). When these condylomata were surgically removed after post-infection vaccination, recurrence was seen significantly less frequently.[8] As the study described in chapter 4 was not designed to assess the clinical course after vaccination, a placebo controlled randomized controlled trial is proposed. The power analysis provided in the study showed that 29 patients and 29 controls are needed in a two-year double-blind placebo controlled randomized controlled trial.

Systematically reviewing the literature (chapter 5) showed that there is no clear evidence for the effect of GERD on RRP. Furthermore, anti-reflux therapy proves to be less harmless than always thought.[19,20] Anti-reflux therapy should be omitted in evidence-based RRP treatment protocols worldwide.

Apart from GERD there are other factors that were attributed to a worse clinical course. Examples are smoking, asthma, corticosteroid use and lifestyle.[21] Systematic reviewing or preferably a meta-analysis on these factors is needed to determine a relevant effect on the clinical course of RRP.

A fair question is why research on optimal treatment strategies in RRP is still needed, because preventative HPV vaccination programs will greatly diminish the incidence of HPV6 and HPV11 related disease like RRP. Firstly, eradication of the virus in the total population will take a while: as only adolescents are vaccinated, the virus will still spread under older adults. Secondly, it is still unclear how long the preventative effect of the vaccination will hold, while

revaccination is not performed. The virus might therefore recur. Thirdly, even in the Western world not all countries use the quadrivalent vaccine (containing virus-like particles of HPV6, 11, 16 and 18). For instance, in the Netherlands a bivalent vaccine is used (containing virus-like particles of HPV16 and 18). This will greatly delay group immunity for HPV6 and HPV11 in these communities, allowing the disease to still occur. In the fourth place, it is not realistic to assume that general vaccination can be introduced in the third world or even outside the Western world in the coming years. The disease is also a problem in those countries, as was demonstrated in two studies from developing countries.[22,23] In these countries preventative measures are expensive and logistics are difficult. Those four reasons make that effective therapeutic options are still options to be sought after.

Part II: Psychosocial aspects of RRP

The number of surgical interventions in almost any study most often measures the severity of disease.[24] Pathophysiologically this is reasonable, as it is associated with the growth of the papillomas. Nonetheless, disease burden is also an important factor in chronic diseases. Therefore the quality of life (QoL) as perceived by RRP patients was examined in chapter 6. It was shown that neither the number of surgical interventions, nor the duration of disease affected patients' perceptions of their QoL on any of the QoL parameters. However, keeping the number of surgeries lower to save the voice or to prevent scarring of the airways is still defendable, especially as voice problems did significantly affect QoL of patients.

Only a few patients indicated they received psychosocial support. Better screening for need of psychosocial care may be needed (chapter 7). Remarkably, although most of the patients experienced voice problems, less than half received speech therapy. It could well be that improvement of voice through speech therapy cannot be realized. Many patients will have limited benefit due to their scarred larynx.

In chapter 7 we also showed that the RRP adapted version of the Distress Thermometer & Problem List (DT&PL) is valid and useful. A significant percentage

(31%) of patients had a clinically elevated score on the DT, suggesting that they might benefit from additional professional health care. In fact, 37% indicated a wish for referral, mainly to a medical specialist or speech therapist. Only a few desired a referral to a psychosocial health care professional. Patients express that they appreciate the DT&PL as instrument. The tool is already used in clinical practice the Netherlands and Finland. It is currently unknown if use of the DT&PL in clinical practice will be associated with (sustained) decreased distress, anxiety and depression among RRP patients. A longitudinal analysis is being planned. Furthermore, an English version of the DT&PL is prepared for validation for English speaking RRP patients.

The validation of the RRP adapted DT&PL showed that distress was associated with patients who had difficulty sharing their problems with their partners. This finding affects patient care, as it implies that patient care not only encompasses informing and supporting patients efficiently, but their relatives as well. It is important that relatives understand the disease and are informed on the expected clinical course. Provision of information is very important for this. The quality of English written online information is poor and hard to understand (chapter 8). Our information website for RRP patients (www.RRP.nu) will be redesigned to make it comply with international rules for readability and quality.

Recommendations

Worldwide cooperation in research of relatively rare diseases as RRP should be intensified. Especially a worldwide database of treatment regimens and effects would be of great help to determine if treatments are effective. Furthermore we should focus on the older RRP patient group, as this group might need a different approach. Especially immune reactions in this group should be analyzed.

Research on T cell-based vaccines in high-risk HPV disease shows that selection and enrichment of autologous T cells of patients can be very efficient in the treatment of tumors.[25] Enhancement of the immune system of RRP patients by these T cell-based vaccines could well be the therapeutic option that can cure RRP. Further research on the subject is needed.

Distress in RRP patients should be addressed in every treatment center. Therapy regimens should include distress screening and timely referral. A multi-language information portal is favored for RRP patients with the shared knowledge of researchers around the world.

References

1. Bonagura VR, Hatam LJ, Rosenthal DW, et al. Recurrent respiratory papillomatosis: a complex defect in immune responsiveness to human papillomavirus-6 and -11. Apmis 2010;118:455-470.
2. Pinti M, Appay V, Campisi J, et al. Aging of the immune system: Focus on inflammation and vaccination. Eur J Immunol 2016;46:2286-2301.
3. Castelo-Branco C, Soveral I. The immune system and aging: a review. Gynecol Endocrinol 2014;30:16-22.
4. Pera A, Campos C, Lopez N, et al. Immunosenescence: Implications for response to infection and vaccination in older people. Maturitas 2015;82:50-55.
5. Schiller JT, Castellsague X, Garland SM. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;30 Suppl 5:F123-38.
6. Garland SM, Kjaer SK, Munoz N, et al. Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: A Systematic Review of 10 Years of Real-world Experience. Clin Infect Dis 2016;63:519-527.
7. Joura EA, Garland SM, Paavonen J, et al. Effect of the human papillomavirus (HPV) quadrivalent vaccine in a subgroup of women with cervical and vulvar disease: retrospective pooled analysis of trial data. Bmj 2012;344:e1401.
8. Olsson SE, Kjaer SK, Sigurdsson K, et al. Evaluation of quadrivalent HPV 6/11/16/18 vaccine efficacy against cervical and anogenital disease in subjects with serological evidence of prior vaccine type HPV infection. Hum Vaccin 2009;5:696-704.
9. Pomfret TC, Gagnon JM,Jr, Gilchrist AT. Quadrivalent human papillomavirus (HPV) vaccine: a review of safety, efficacy, and pharmacoeconomics. J Clin Pharm Ther 2011;36:1-9.
10. Gale N, Poljak M, Kambic V, Ferluga D, Fischinger J. Laryngeal papillomatosis: molecular, histopathological, and clinical evaluation. Virchows Arch 1994;425:291-295.
11. Doorbar J. Latent papillomavirus infections and their regulation. Curr Opin Virol 2013;3:416-421.
12. Doorbar J, Quint W, Banks L, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30 Suppl 5:F55-70.
13. Kashima H, Mounts P, Leventhal B, Hruban RH. Sites of predilection in recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol 1993;102:580-583.
14. Dabrowska AM, Slotwinski R. The immune response to surgery and infection. Cent Eur J Immunol 2014;39:532-537.
15. Durvasula VS, Richter GT. Intralesional cidofovir as adjuvant for the successful management of aggressive respiratory papillomatosis in an infant. Int J Pediatr Otorhinolaryngol 2013;77:1912-1915.
16. Grasso M, Remacle M, Bachy V, Van Der Vorst S, Lawson G. Use of cidofovir in HPV patients with recurrent respiratory papillomatosis. Eur Arch Otorhinolaryngol 2014;271:2983-2990.
17. Chadha NK, James A. Adjuvant antiviral therapy for recurrent respiratory papillomatosis. Cochrane Database Syst Rev 2012;12:CD005053.
18. Stanley MA. Epithelial cell responses to infection with human papillomavirus. Clin Microbiol Rev 2012;25:215-222.
19. FDA. Safety information on proton pump inhibitors. 24-6-2015;2016.
20. Shah NH, LePendu P, Bauer-Mehren A, et al. Proton Pump Inhibitor Usage and the Risk of Myocardial Infarction in the General Population. PLoS One 2015;10:e0124653.
21. Niyibizi J, Rodier C, Wassef M, Trottier H. Risk factors for the development and severity of juvenile-onset recurrent respiratory papillomatosis: A systematic review. Int J Pediatr Otorhinolaryngol 2014;78:186-197.
22. Orji FT, Okorafor IA, Akpeh JO. Experience with recurrent respiratory papillomatosis in a developing country: impact of tracheostomy. World J Surg 2013;37:339-343.
23. Seedat RY. The incidence and prevalence of juvenile-onset recurrent respiratory papillomatosis in the Free State province of South Africa and Lesotho. Int J Pediatr Otorhinolaryngol 2014;78:2113-2115.
24. Tjon Pian Gi RE, San Giorgi MR, Slagter-Menkema L, et al. Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11. Head Neck 2015;37:1625-1632.
25. Yang A, Farmer E, Lin J, Wu TC, Hung CF. The current state of therapeutic and T cell-based vaccines against human papillomaviruses. Virus Res 2016.

Chapter 10

Summary

Recurrent Respiratory Papillomatosis (RRP) is a rare disease, caused by human papillomavirus type 6 (HPV6) or 11 (HPV11). The disease presents as wart-like tumor growth (papillomas) throughout the airways, resulting in voice problems and eventually a compromised airway. As there is no curative therapy for the disease, patients depend on repeated surgical removal of the papillomas. The disease has an unpredictable course and severity is very different between patients. An overview of the disease characteristics is given in **chapter 1**. This thesis provides insights in confounders of the clinical course of RRP and the psychosocial wellbeing of patients.

Part I: Clinical course

Before, it was thought that RRP only occurred in newborns and young adults. **Chapter 2** describes the age of onset of RRP. Six hundred and thirty-nine patients from twelve European hospitals were included. A mixture model was selected using the Bayesian information criterion. The analysis revealed that instead of a bimodal distribution of age of onset, there is a trimodal distribution. RRP generally starts at the age of 7, 35 and 64 years. The elder patient group with a mean age of onset of 64 years is new entity, which is not accounted for in foregoing research.

In **chapter 3.1** we report on a cohort of 55 RRP patients, with either HPV6 (n=42) or HPV11 (n=13) associated disease. We observed that the disease course significantly worsens when the age of onset is lower. HPV11 patients have a significantly worse disease course compared to HPV6 patients at an age younger than 22. This effect reverses after the age of 22, although differences between HPV6 and HPV11 are smaller. Overall HPV11 associated RRP is characterized by a statistically significant wider spread of the papillomas, especially distally from the larynx. None of the included patients developed malignancy from RRP.

Not many studies on therapy in RRP take into account the natural decrease of the needed number of surgical interventions. Many therapies are therefore considered as effective, while this is accountable to the natural course. For this a response letter was edited as response to one of such articles to ask

for attention for the need to correct for the clinical course in these articles (**chapter 3.2**). As the method of correcting for the natural course is applicable on existing data, it is unnecessary to re-expose patients to different therapies. It would be better to reanalyse results of these articles with this correction.

Many therapies other than surgery to treat RRP have been tried with variable success. One of the proposed therapies is therapeutic use of the quadrivalent HPV vaccine (Gardasil®). Theoretically the vaccine could (re)activate the immune system in RRP patients and therefore prevent further spread of the papillomas by reinfection. In **chapter 4** a pilot study was performed to determine the immunological response on Gardasil® in 6 HPV6/11 positive RRP patients. First we show that seroreactivity on the associated HPV type (HPV6 or HPV11) rose significantly after vaccination, indicating reactivation of the humoral immune system even though patients had active disease. Although this pilot study was not designed to assess the clinical course of RRP or papilloma spread after vaccination, a decrease of the number of surgical interventions was seen in the majority of patients. However, this study lacked the power to draw firm conclusions. Given the course of disease in the 6 included patients, power analysis revealed that 29 vaccinated patients and 29 controls are needed in a two-year double-blind placebo controlled randomized controlled trial. To confirm the improvement by this therapy, this will be subject of future studies.

One of the factors that is generally assumed to worsen the clinical course of RRP is gastroesophageal reflux disease (GERD). It would theoretically provoke viral activity due to irritation, increasing the risk to induce papilloma growth. Many centres treating RRP patients had therefore included anti-reflux therapy in their general treatment protocols. To evaluate the influence of GERD on the clinical course of RRP a systematic review (PRISMA) of the literature was performed (**chapter 5**). This analysis revealed that till now no study proved that GERD influences the number of surgical interventions, severity of disease (as measured by different scoring systems) and histopathological parameters. One study showed that patients with papilloma in the anterior and posterior commissure benefitted from perioperative anti-reflux therapy. Anti-reflux decreased the chance of laryngeal web formation. However, the quality of that study (as defined by the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health) describing this effect

was moderate. It was also shown in chapter 5 that the incidence of objectified GERD in AoRRP patients is higher than in the general population.

Part II: Psychosocial aspects of RRP

Due to the unpredictable and frequently severe clinical course of RRP, it is thought that the disease causes a high psychosocial burden on patients. Few have studied this, most of those that did found voice-related quality of life (QoL) problems in many patients. In these studies it was unclear how RRP affected other domains of QoL. In **chapter 6** aspects of QoL in 91 Dutch and Finnish RRP patients are described. Analyses revealed that patients were on average slightly more depressed than the general population; they had more voice problems and a lower general health perception. Paradoxically, RRP patients had a better health-related QoL and less anxiety than the average population. The factors that were negatively associated with parameters of QoL were country of origin, gender, current age, age of onset of RRP, and presence of comorbidity. The number of surgical interventions the patient underwent and the duration of disease did not have a significant effect on any of the QoL parameters. Only a few patients received psychosocial support. Although most patients experienced voice problems, only two out of five received speech therapy, which number seems low.

In **chapter 7** an instrument to screen for severity and nature of distress is investigated (in Dutch and Finnish). On the Distress Thermometer and Problem List (DT&PL) patients can indicate the severity of distress they experience. Additionally, they can provide information about problems inducing this distress as well as their desire for professional care for the problems they experience. Other versions of the DT&PL have been used in the daily care of patients with chronic and malignant diseases. We showed that the RRP adapted version of the DT&PL is valid, useful and appreciated by patients. The tool is easy to use in the in- and outpatient clinic.

For mutual understanding it is important that patients and partners have extensive knowledge of the disease and its course. Provision of information is very important for this. In **chapter 8** we report on a quality and readability assessment of online English written patient information. The analysis was

designed as if a patient or layperson would search for information. Relevant information was collected using three different search engines and seven different search terms. Quality and readability were assessed. Fifty-one English websites were included. Mean quality of the included websites was considered poor and information presented on average difficult to read. Improvement of English online information is needed.

Finally, a discussion is presented including suggestions for future directions of research of this debilitating disease.

Samenvatting

Recurrent Respiratory Papillomatosis (RRP) is een zeldzame ziekte, veroorzaakt door het humaan papillomavirus type 6 (HPV6) of type 11 (HPV11). De patiënt presenteert zich met wratachtige afwijkingen (papillomen) door de gehele luchtweg. Deze afwijkingen veroorzaken stemproblemen en uiteindelijk een bedreigde luchtweg. Omdat er geen curatieve behandeling bestaat zijn patiënten afhankelijk van het herhaaldelijk chirurgisch verwijderen van de papillomen. Een overzicht van de ziektekarakteristieken wordt gegeven in **hoofdstuk 1**. Dit proefschrift geeft inzicht in beïnvloedende factoren op het klinische beloop van RRP en het psychosociaal welbevinden van patiënten.

Deel 1: Klinisch beloop

Van oudsher werd gedacht dat RRP alleen ontstond in pasgeborenen en jongvolwassenen. **Hoofdstuk 2** beschrijft de leeftijd van ontstaan van RRP. Zeshonderdnegenendertig patiënten uit twaalf Europese ziekenhuizen werden geïncludeerd. Een *mixture model* werd ingezet, gebruik makend van Bayesian informatie distributiecriteria. Over het algemeen ontstaat RRP met voorkeurspieken rondom het 7^{e}, 35ste en 64ste levensjaar. De oudste patiëntengroep, met een gemiddelde leeftijd van 64 jaar, is een nieuwe entiteit. Met deze groep werd geen rekening gehouden in voorgaand onderzoek.

In **hoofdstuk 3.1** bespreken we een cohort van 55 patiënten, met ofwel HPV6- (n=42) of HPV11- (n=13) geassocieerde ziekte. We observeerden dat het ziektebeloop verergert naarmate de leeftijd van ontstaan lager is. HPV11 patiënten hebben een significant zwaarder ziektebeloop (gemeten in het aantal chirurgische interventies) vergeleken met HPV6 patiënten als ze jong zijn tijdens het ontstaan van ziekte (jonger dan 22 jaar). Dit effect keert om na de leeftijd van ontstaan van 22 jaar, alhoewel de verschillen dan kleiner zijn. In het algemeen is HPV11-geassocieerde RRP gecorreleerd met een uitgebreidere verspreiding van de papillomen, met name distaal van de larynx. Geen van de geïncludeerde patiënten ontwikkelde een maligniteit uit RRP.

In de vakliteratuur, aangaande onderzoek naar de therapie bij RRP, wordt onvoldoende rekening gehouden met de natuurlijke afname in het aantal benodigde operaties tijdens het ziektebeloop van RRP. Veel therapieën werden daardoor gezien als effectief, terwijl de afname in aantal chirurgische ingrepen eigenlijk door het natuurlijk beloop veroorzaakt wordt. Daarom stuurden

wij een "response letter" naar aanleiding van een van dit soort artikelen, om aandacht te vragen voor de noodzaak om te corrigeren voor de natuurlijk afnemende ernst van het klinisch beloop (**hoofdstuk 3.2**). Omdat de methode van corrigeren ook toepasbaar is op bestaande data, is het onnodig om patiënten opnieuw bloot te stellen aan al eerder geprobeerde therapieën. Het zou beter zijn als resultaten uit het verleden opnieuw geanalyseerd werden met inachtneming van deze correctie.

Er zijn en worden veel verschillende therapieën geprobeerd om RRP onder controle te krijgen, helaas met wisselend effect. Een van deze therapieën is het quadrivalente HPV vaccin Gardasil®. Theoretisch zou dit vaccin activatie van het immuunsysteem van RRP-patiënten kunnen veroorzaken en daarmee verdere verspreiding van de papillomen door re-infectie kunnen voorkomen. In **hoofdstuk 4** wordt een pilot studie beschreven, welke de immuunreactie van 6 HPV6/HPV11-positieve RRP-patiënten op Gardasil® analyseert. Allereerst demonstreren we dat de seroreactiviteit op het geassocieerde HPV-type (HPV6 of HPV11) significant stijgt na vaccinatie. Dit wijst op een activatie van het humorale immuunsysteem, ondanks het feit dat patiënten al een actieve ziekte hadden. Alhoewel deze studie niet was ontworpen om het klinisch beloop van de RRP te analyseren na vaccinatie, werd een afname gezien van het benodigde aantal chirurgische interventies in bijna alle patiënten. De studie omvatte echter te weinig patiënten voor de benodigde bewijskracht van deze observatie. Op basis van het ziektebeloop van de 6 beschreven patiënten in deze studie werd een power analyse uitgevoerd. Deze liet zien dat 29 gevaccineerde patiënten en 29 controlepatiënten nodig zijn in een 2 jaar durende dubbelblinde, placebo gecontroleerde, gerandomiseerde studie naar het therapeutisch gebruik van dit medicijn. Het onderzoek naar het mogelijk gunstig effect van de therapie zal onderdeel zijn van toekomstige studies.

Een van de factoren van welke wordt aangenomen dat die het klinische beloop van RRP beïnvloedt is gastro-oesofageale reflux ziekte (GERD). GERD zou theoretisch virale activiteit kunnen uitlokken door irritatie, waardoor er papilloomgroei ontstaat. Veel centra die RRP-patiënten behandelen geven patiënten standaard anti-reflux medicatie. Om het werkelijke effect van GERD op het ziektebeloop van RRP te bepalen voerden we een systematische review van de literatuur uit volgens PRISMA-criteria (**hoofdstuk 5**). Deze analyse laat zien

dat tot nu toe geen enkele studie heeft aangetoond dat het aantal chirurgische interventies, de ernst van de ziekte of histopathologische kenmerken worden beïnvloed door GERD. Slechts een studie liet zien dat patiënten met papilloom in de voorste of achterste commissuur voordeel hadden bij perioperatieve anti-reflux therapie. Deze therapie verlaagde de kans op webvorming. Echter, de kwaliteit van de studie die dit effect beschreef (zoals gedefinieerd door de 'Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies of the National Institute of Health') was matig. In hoofdstuk 5 van dit proefschrift laten we ook zien dat de incidentie van geobjectiveerde GERD in AoRRP-patiënten hoger is dan in de algehele populatie.

Deel II: Psychosociale aspecten van RRP

Vanwege het onvoorspelbare en geregeld ernstige beloop van RRP wordt gedacht dat patiënten wellicht een zware psychosociale last dragen. Er zijn echter erg weinig studies over dit onderwerp. Stemgerelateerde kwaliteit van leven (QoL) problemen worden in deze studies geregeld beschreven. Het is in die studies onduidelijk hoe RRP andere domeinen van QoL beïnvloedt. In **hoofdstuk 6** worden die domeinen beschreven in 91 Nederlandse en Finse RRP-patiënten. Analyses toonden aan dat RRP-patiënten iets meer depressieve klachten vertoonden dan de algehele populatie; dat ze meer stemproblemen en een zwakker zelfbeeld van hun algehele gezondheid hadden. Paradoxaal genoeg hadden RRP-patiënten een betere gezondheidgerelateerde QoL en hadden zij minder angst dan de gemiddelde populatie. De factoren die negatief geassocieerd waren met de domeinen van QoL waren land van afkomst, geslacht, huidige leeftijd, leeftijd van ontstaan van RRP en het hebben van comorbiditeit. Het aantal chirurgische interventies dat patiënten ondergingen en de ziekteduur hadden geen significant effect op de QoL-domeinen. Slechts weinig RRP-patiënten kregen psychosociale hulp. Hoewel de meeste patiënten stemproblemen hadden, kregen slechts 2 van de 5 patiënten logopedische zorg.

In **hoofdstuk 7** wordt een meetinstrument (in het Nederlands en het Fins) onderzocht om te screenen op ernst en oorzaak van ongemak en onwelbevinden, zogenaamde distress. Met de Distress Thermometer en Probleem Lijst (DT&PL)

kunnen patiënten aangeven hoeveel distress zij ervaren. Daarnaast kunnen zij aangeven welke problemen deze distress veroorzaken en of zij doorverwezen willen worden om behandeld te worden voor hun klachten. Andere versies van de DT&PL worden al lange tijd gebruikt in de dagelijkse zorg van patiënten met chronische of kwaadaardige ziekten. We toonden aan dat de aan RRP aangepaste versie van de DT&PL een valide, praktisch en door patiënten gewaardeerd instrument is. Daarnaast is het meetinstrument gemakkelijk in gebruik in de dagelijkse praktijk.

Voor wederzijds vertrouwen tussen patiënt en arts is het belangrijk dat zowel patiënten als hun partners uitgebreide informatie verkrijgen over RRP. Beschikbaarheid van goede informatie is hierbij zeer belangrijk. In **hoofdstuk 8** beschrijven we een analyse van de kwaliteit en leesbaarheid van Engelse online patiëntinformatie. De analyse was dusdanig ontworpen dat gesimuleerd werd hoe een leek online op zoek gaat naar informatie. Relevante informatie werd verzameld door internet te doorzoeken met drie zoekmachines en zeven zoektermen. Kwaliteit en leesbaarheid werd met gevalideerde methodiek beoordeeld. Eenenvijftig Engelse websites werden geïncludeerd. De gemiddelde kwaliteit van het geschrevene op de websites was laag en de gepresenteerde informatie was moeilijk te lezen. Verbetering van Engelstalige online informatie is dus nodig.

Tenslotte wordt in **hoofdstuk 9** een beschouwing gedaan van het proefschrift, waarin ook suggesties worden gedaan voor toekomstig RRP-onderzoek.

Dankwoord

Dit proefschrift was er zonder samenwerking en steun nooit geweest. Ik wil iedereen danken die van mijn promotietraject een toptijd heeft gemaakt. Enkelen van jullie wil ik persoonlijk bedanken.

Allereerst wil ik alle papilloompatiënten bedanken vanwege hun bereidheid om mee te werken aan onze onderzoeken. Zonder hun enthousiasme en hulp was dit traject niet mogelijk geweest. Ik wens hen veel succes met de net opgezette patiëntenvereniging en ben altijd bereid te helpen indien nodig.

Geachte prof. dr. F.G. Dikkers, beste Freek, dankzij jouw onbegrensde enthousiasme en vertrouwen is het dit project zo voor de wind gegaan. Onze woensdagochtendsessies, waarin gelachen en fel gedebatteerd werd, zorgden altijd voor frisse ideeën en onbeperkte motivatie. Ik ben er trots op dat ik zo'n belangrijke tijd met je heb meegemaakt. Van dr. naar prof., als iemand het kan ben jij het! Ik durf niet op ons lijstje te kijken maar ik denk dat we nog voor ruim 15 jaar aan projecten hebben klaar staan. Laten we daar dan ook maar niet te lang mee wachten! Gelukkig leerde jij me dat je met minder woorden vaak meer zegt, anders kon ik hier nog pagina's lang doorschrijven om je te bedanken.

Geachte prof. dr. B.F.A.M. van der Laan, beste Bernard, ik wil je bedanken voor de geweldige sturing die je hebt gegeven tijdens dit traject. Jij zorgde ervoor dat ik niet te hard van stapel liep of te voorbarige conclusies trok. Daarnaast heb je me leren plannen. Door mij zelf de vraag te laten stellen of de oplossing te laten zoeken ben ik een stuk zelfstandiger geworden en durf ik knopen door te hakken. Ik zie uit naar de verdere opleiding onder je supervisie.

Geachte prof. dr. E.M.D. Schuuring, beste Ed, volgens mij stroomt er wetenschap door jou aderen en gun je anderen deze eigenschap ook. Je hebt me leren onderzoeken en leren schrijven. Van het commentaar werden stukken altijd beter, en ik een betere onderzoeker. Ik heb onze samenwerking altijd als inspirerend en prikkelend ervaren en hoop in de toekomst nog veel van je te leren. Wellicht komen er nog wel gezamenlijke trajecten op ons spoor.

Geachte dr. J.E.H.M Hoekstra-Weebers, beste Josette, dankzij jou had mijn traject in plaats van een klinisch gedeelte ook ineens een psychosociaal

gedeelte. Jouw kennis, enthousiasme en gedachten over goede hulpverlening zijn belangrijk voor de dagelijkse zorg van RRP patiënten. Ik ben dankzij jou ontzettend trots op dit gedeelte van het boekje.

Graag wil ik de leescommissie, prof. dr. H.A.M. Marres, prof. dr. C.A.H.H. Daemen en prof. dr. H. Hollema bedanken voor het positief beoordelen van mijn proefschrift.

Dr. R.E.A. Tjon Pian Gi, beste Robin, volgens mij had ik me geen betere sparring-partner en onderzoekmaatje kunnen bedenken dan jij. Enerzijds kunnen we het hartstochtelijk oneens zijn (altijd met een brede lach) en daardoor de mooiste compromissen vinden, anderzijds kunnen we vervallen in heerlijke meligheid waardoor projecten altijd een feestje waren. Dat we allebei een 5 voor Engels hadden maakte dat onze stukken altijd een 10 waard waren.

Dr. T.T.A. Peters, beste Tommie, dank voor de eindeloze uren discussiëren, lachen en tactieken uitdenken (vooral tijdens het inslaan op de training). Ik heb veel van je geleerd en je bent daarnaast zo ruimhartig geweest me onder je vleugels te nemen in je vriendengroep, de assistentengroep en je hockeyteam. Dat ik je op het veld inmiddels blind kan vinden zegt genoeg over onze vriendschap.

Prof. dr. E.R. van den Heuvel, beste Edwin, bedankt voor de statistische hoogstandjes die jij hebt bedacht om achter antwoorden op lastige vraagstukken te komen. Dat Robin en ik je soms omkochten met taart voor een plekje in je drukbezette agenda was niet alleen goed voor een gedegen statistische onderbouwing maar ook voor een brede glimlach door je hilarische grappen en eerlijkheid.

Dr. van Hemel, beste Bettien, jou wil ik zeer hartelijk danken voor het opvrolijken van de uurtjes dat ik even echt niet meer wist waar ik moest beginnen. Ik kwam altijd met frisse moed bij je vandaan.

Dear prof. dr. H. Rihkanen and dr. L.M. Aaltonen, thank you very much for the fruitful cooperation and enthusiastic help with two of our biggest projects. Your interesting vision have made them both a success.

Dear co-authors of the European Laryngological society thank you very much for your helpful cooperation and enthusiastic critics on our articles.

Beste mevr. Slagter-Menkema, beste Lorian, hoewel het al een tijdje geleden is dat we samenwerkten, ben ik niet vergeten hoe een belangrijke spil jij bent in alle histologie die uitgevoerd is. Bedankt!

Geachte prof. dr. G.H. de Bock, beste Truuske, dank voor je inzet om mij een belangrijke niche van het onderzoek eigen te laten maken. De systematische review zit vanaf nu in mijn onderzoeksbasispakket.

Beste Herman Helder en Robbert-Jan Lindeman dank voor jullie hulp aan dit proefschrift. Wat begon als een arbeidsintensieve samenwerking, eindigde in een internationale vriendschap. Een goed teken lijkt me.

Beste Olivier de Groot, ook jij bedankt voor je hulp bij het laatst hoofdstuk.

Dear Nathan Senner en beste Marije Verhoeven hartelijk dank voor jullie grammaticale hulp!

Beste Bertram de Kleijn, Bertje Bombastik (feeling fantastic), jou ben ik als kamergenoot en goede vriend veel dank verschuldigd! Je hebt zonder coauteur geweest te zijn stiekem heel veel bijgedragen aan mijn projecten. Je meningen, hulp en enthousiasme hebben de werkkamer tot een plek van positieve energie gemaakt. Gelukkig geeft onze liefde voor oude rommel genoeg reden om nog lang te blijven samen werken!

Beste Jelmer Humalda, hartelijk dank voor alle uren/kilometers uitblazen na intensieve werkdagen. We bespraken projecten en relativeerden alles tot we niet meer konden. Dat je in Sneek van me won, betekent dat ik je in Nijmegen pak!

Lieve (oud) assistenten van de KNO UMCG. Volgens mij kan ik met ieder van jullie een paar mooie verhalen opduikelen over de afgelopen tijd. Dat het zelfs na werktijd altijd enorm gezellig is en ik wekelijks moet huilen van het lachen geeft aan hoe veel geluk ik met jullie heb!

Beste opleidingsgroep van het UMCG, en sinds kort ook van het Martini Ziekenhuis, hartelijk dank voor jullie motiverende bijdrage aan mijn ontwikkeling tot KNO-arts. In ieder van jullie zie ik hoe je een goede KNO-arts moet zijn.

Beste collega's van A1VA, administratie en de polikliniek hartelijk dank voor de top samenwerking. Ik fiets elke dag met plezier naar het werk omdat ik weet hoe leuk samen werken daar is.

Alhoewel ieder van mijn vrienden op zijn of haar manier hebben bijgedragen, wil ik een aantal van hen in het bijzonder van harte danken. Geert van Rijt, dank voor je scherpe opmerkingen en eeuwige interesse! Bob Rollerman en Niels Pijnenburg, socialere beesten dan jullie ken ik niet! Frans Smits, volgens mij moeten wij het kanaal nog eens over. Jurre van Rooden, wij kennen elkaar al twee decennia, laten we er nog maar een paar aan vast plakken! Tante Nicole en Irene, dank voor jullie heerlijke humor en Amsterdamse kijk op het leven! Maarten Majoor, machientjes in Zeeland of parallel skiën in spijkerbroek, je bent geweldige inspirator! Hans en Pauline, biljarten, darten en rond een vuurtje zitten, samen zijn we echte stadsjutters. Bram en Emma, ondanks dat jullie je altijd ergeren als ik jullie helden noem, zijn jullie het wel. Elmi, Sjoukje en Douwe dank voor de topweekendjes en avondjes.

Soms komen vrienden ook in groepen. Ik wil hen in groepsverband bedanken zodat ik niemand vergeet en omdat ze het allemaal verdienen. Allereerst de skigroep, alle dinertjes, vakanties en voorpret maakten de afgelopen jaren een feest, dank jullie! Heren 5, dank dat ik, de man van kristal, elke woensdag en zondagmiddag weer briljante pasjes of snoeiharde missers van jullie mag ontvangen. JC B'nobo dank voor jullie geduld van de afgelopen jaren. Ik kijk er naar uit om binnenkort weer voor mindernacht op clubavond te zijn. Huize Villa Ductzicht, dank dat jullie mijn opvoeding succesvol hebben weten over te nemen van mijn ouders. Ik ben ook speciale dank verschuldigd aan ieder die mij van de straat heeft gehouden met mijn gemotoriseerde hobby. Wessel, Ireen, Kaye en Herman hartelijk dank voor alle avonturen! Familie Feltbrugge, lieve buurtjes, ik wist niet dat je zonder genetisch verwantschap toch een familiegevoel kon voelen. Buurman appel, buurvrouw peer en de Vespa-klussers, dank voor alle zorgeloze uren!

Lieve familie San Giorgi en opa en oma Segers, ik ben er trots op een van jullie te mogen zijn! Ik hoop dat ik met dit project ook ieder van onze families, die er helaas niet meer zijn, een beetje trots maak. Bedankt voor jullie steun!

Lieve familie Boudewijn; Nico, Jeannet, Lieke en Joske. Hoeveel geluk je kan hebben met je schoonfamilie heb ik al eindeloze keren mogen ervaren! Jullie staan altijd voor me klaar, zijn altijd geïnteresseerd en ik voel me al jaren een onderdeel van de familie. Ik kan me geen betere en lievere schoonfamilie wensen. Dank jullie wel!

Beste Eric, lieve Eek, hartelijk dank voor alle jaren aan woordgrappen en goede gesprekken. Ik ben enorm trots hoe jij je creativiteit overal op aarde weet te gebruiken om prachtige projecten neer te zetten. Ik weet zeker dat je het heel ver gaat schoppen. De kaft van het boekje is prachtig geworden. Beste Frédérique, lieve Vieze Freddie, ook jou ben ik enorm dankbaar voor al die topjaren dat jij mijn zusje bent. Gastvrijheid en intelligente humor tekenen jou. Je huis voelt als een pied-a-terre, ik voel me er altijd thuis. Je bent een topper.

Lieve pap en mams, ook jullie wil ik van harte bedanken voor de steun die jullie me al die jaren hebben gegeven. Als ik thuis kom helpen jullie me altijd mijn gedachtes te structureren en plannen te maken. Daarnaast voel ik me altijd vereerd als ik de oprechte trots voel als er projecten gelukt zijn. Voor dat gevoel zet ik graag een stapje meer. Dit boekje ligt er dankzij jullie. Pronto, pronto, pronto!

Lieve Ilse, allerliefste pilsje!! Ik heb al tientallen mensen bedankt maar als iemand het waard is dan ben jij het! Eigenlijk promoveer jij vandaag ook een beetje. Je bent een enorme lieverd, met een bewonderenswaardig geduld! Ik heb immers veel van onze gezellige avonden opgeofferd voor dit project. Ik beloof dat je al die avonden terugkrijgt, dubbel en dwars. Je pittigheid en scherpe humor houden me wakker en ik geniet van elke discussie of knuffel. Altijd heb je met me meegeleefd en gedacht. Laten we de komende jaren met een tentje rond gaan trekken, ik zou dit met niemand anders liever doen!

Publications

San Giorgi MRM, van den Heuvel ER, Tjon Pian Gi REA, Brunings JW, Chirila M, Friedrich G, Golusinski W, Graupp M, Horcasitas Pous RA, Ilmarinen T, Jackowska J, Koelmel JC, Ferran Vilà F, Weichbold V, Wierzbicka M, Dikkers FG.
Age of onset of Recurrent Respiratory Papillomatosis: a distribution analysis.
Clin Otolaryngol 2016 Oct 13;41(5):448-453.

San Giorgi MRM, Tjon Pian Gi REA, Slagter-Menkema L, van Hemel BM, van der Laan BFAM, van den Heuvel ER, Dikkers FG, Schuuring EMD.
Clinical course of recurrent respiratory papillomatosis: Comparison between aggressiveness of human papillomavirus-6 and human papillomavirus-11.
Head Neck 2015 Jun 23;37(11):1625-1632.

San Giorgi MRM, Tjon Pian Gi REA, Dikkers FG.
The clinical course of recurrent respiratory papillomatosis after the use of cidofovir is influenced by multiple factors.
Eur Arch Otorhinolaryngol 2015 Jul;272(7):1819-1820.

San Giorgi MRM, Tjon Pian Gi REA, Pawlita M, Michel A, van Hemel BM, Schuuring EMD, van der Heuvel ER, van der Laan BFAM, Dikkers FG.
Immunological response to quadrivalent HPV vaccine in treatment of recurrent respiratory papillomatosis.
Eur Arch Otorhinolaryngol 2016 Oct;273(10):3231-3236.

San Giorgi MRM, Helder HM, Lindeman RJ, de Bock GH, Dikkers FG.
The association between gastroesophageal reflux disease and recurrent respiratory papillomatosis: A systematic review.
Laryngoscope 2016 Oct;126(10):2330-2339.

San Giorgi MRM, Aaltonen LM, Rihkanen H, Tjon Pian Gi REA, van der Laan BFAM, Hoekstra-Weebers JEHM, Dikkers FG.
Quality of life of patients with recurrent respiratory papillomatosis.
Laryngoscope, accepted 15 Nov 2016.

San Giorgi MRM, Aaltonen LM, Rihkanen H, Tjon Pian Gi REA, van der Laan BFAM, Hoekstra-Weebers JEHM, Dikkers FG.
Validation of the Distress Thermometer and Problem List in Patients with Recurrent Respiratory Papillomatosis.
Otolaryngol Head Neck Surg. 2017 Jan;156(1):180-188.

San Giorgi MRM, de Groot OS, Dikkers FG.
Quality and readability assessment of websites related to recurrent respiratory papillomatosis.
Laryngoscope, accepted 24 Feb 2017.

Tent H, Lely AT, Toering TJ, San Giorgi MRM, Rook M, Lems SP, Hepkema BG, Hofker HS, Ploeg RJ, Homan van der Heide JJ, Navis GJ.
Donor kidney adapts to body dimensions of recipient: no influence of donor gender on renal function after transplantation.
Am J Transplant 2011 Oct;11(10):2173-2180.

Curriculum vitae

Michel René Mario San Giorgi was born on the 29th of July 1987 in Nijmegen, the Netherlands, where he grew up with his parents and younger brother and sister. He graduated cum laude from the Stedelijk Gymnasium Nijmegen in 2005. Subsequently, he studied Medicine at the Rijksuniversiteit Groningen He fulfilled internships in Groningen, Deventer, Willemstad (Curaçao) and Cuzco (Peru). Apart from several smaller committees during his studies, he was member of the Examination Committee of the study Medicine; member of the organ transplantation assistance and research team Prometheus; and fulltime daily board member of the 15th International Student Congress of Medical Sciences (ISCOMS). Nevertheless he found some spare time to spend as field hockey player at competitive level, and as sailing instructor, in addition with tinkering with vintage cars.

Michel wrote his master thesis, named 'HPV6 and HPV11 induce a different clinical course in Recurrent Respiratory Papillomatosis', at the department of Otorhinolaryngology and Head & Neck Surgery, University Medical Center Groningen (UMCG), supervised by prof. dr. F.G. Dikkers and dr. R.E.A. Tjon Pian Gi. This thesis evoked his interest in Recurrent Respiratory Papillomatosis. After his final internship at the same department he obtained his Master's degree in 2013. In July 2013 he started his PhD research, described in this thesis, at the same department, in collaboration with the department of Pathology (UMCG) under the supervision of prof. dr. F.G. Dikkers, prof. dr. B.F.A.M. van der Laan, prof. dr. E.M.D. Schuuring and dr. J.E.H.M. Hoekstra-Weebers. From June 2014 to date he is daily board member and secretary of the AIOS-vereniging of the UMCG. Since November 2015 Michel is resident at the department of Otorhinolaryngology and Head & Neck Surgery (UMCG) under prof. dr. B.F.A.M. van der Laan.