.... but what do you do?

Dr Rob Black
Associate Professor, University of Queensland.
Senior Consultant in Paediatric Otolaryngology
Mater Children’s Hospital, Brisbane, Australia
UK Data

• 1930’s - Tonsillectomy – a prophylactic ritual carried out for no particular reason with no particular result. Medical Research Council

• 1957 – Are T’s & A’s really necessary? Fry J, BMJ 1,124-129 (1957)

• 1999 - Children suffer pointless tonsil operations. BBC
UK Data

• Scottish Intercollegiate Guidelines Network - Management of Sore Throat and Indications for Tonsillectomy. SIGN publication 34, 2001
  • Disabling tonsillitis – 5 per year

• National Prospective Tonsillectomy Audit. BAOHNS & RCS 2005
  • Accepts SIGN recommendations
  • Other indications for tonsillectomy may include obstructive sleep apnoea

• NESSTAC: a pragmatic randomised controlled trial with a parallel non-randomised preference study. Health Technology Assessment 14:13. 2010
  • Clinical & cost effectiveness

• Indications for Tonsillectomy Position Paper. ENT UK 2009
  • OSA – serious effects on health and well being

Rob Black
OSAS in children

- adeno-tonsillar hypertrophy
- mid-face development
- tone
Why do people sleep?

Why is sleep disordered breathing important?

• Coping with darkness;
• Low energy requiring;
• Essential for normal wake neuronal function.
Sleep duration evolution with age

Ontogeny of REM and NREM Sleep

Total Sleep Time

REM
nREM

28 Wk 35 Wk Term 1 Mo 5 Mo 12 Mo 2 Yr 5 Yr 10 Yr 16 Yr

Present understanding of the role of sleep

REM sleep

Infants and children

- Neuronal network formation REM dependant
- Myelination - maximal during REM sleep
- Memory - short term to long term REM enhanced
1 obstructive event per hour
1 obstructive event per hour

- Adult – time based
- Children
  - Obstruction of 2 respiratory cycles
  - Partial with alveolar hypoventilation
  - Includes hypopnoea (3% desaturation associated with a 50% drop in air flow)

Nixon GM, Brouilette RT: Sleep 8: paediatric obstructive sleep apnoea. Thorax 60(6), 511-516, 2005
Neurocognition

• Cardio-respiratory
• Growth
• Immunological
• Hypoxia / hypercapnia
• Arousals / sleep fragmentation
Cardio-respiratory

• Increased pulmonary vascular resistance
• cor pulmonale
• Left ventricular hypertrophy & raised diastolic


→ alteration in cerebral blood flow velocities (neuropsychological effects)

Growth

• Growth hormone ..... SWS

• IGF-1

• protective effect on neurocognition

• intelligence
Immunological

- C-reactive protein

  → neurotransmitter expression
  → obesity
Hypoxia / Hypercapnia

- Central abnormalities of regulation

- Intermittent hypoxia

  Beebe DW, Gozal D. Obstructive sleep apnoea and the pre-frontal cortex: towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioural deficits. J Sleep Res 11(1), 1-16. 2002
Hypoxia / Hypercapnia

• Central abnormalities of regulation

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  ➢ HIF-α
  ➢ Endothelial dysfunction
  ➢ Neuronal loss (pre-frontal cortex)
Arousals / sleep fragmentation

• Sleep fragmentation
  Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol 25(1), 117-129, 2005

• Arousal

• Disrupted sleep without OSAS

8% habitual snorers - 3% OSAS
10 point IQ difference


Recovery of function


Does adenotonsillectomy improve neurocognition in pre-school children with mild obstructive sleep apnoea

• The Children’s Hospital at Westmead (University of Sydney, NSW):
• The Mater Hospital, Brisbane (University of Queensland, QLD)
• John Hunter Children’s Hospital (Newcastle University, NSW)
• Women’s and Childrens Hospital (Adelaide University & University of South Australia, SA);
• Princess Margaret Hospital for Children (University of Western Australia, WA)

1. T&A improve IQ compared to no T&A over 24 months?
2. Health care costs for children with OSA change following T&A
Neurobehavioural & neurocognitive testing
  Woodcock-Johnson III Test of Cognitive Abilities

Behavioural parameters
  Parent Rating Scale of Behaviour Assessment System for Children II
  Behaviour Rating of Executive Functioning (Brief-P)

Polysomnography
  Mild OSA 1-5

Health economic data
  Health Related Quality of Life (HRQoL)
  Health Utilisation Index 2 (HUI2)

http://www.sleeptials.net/
Professor Karen Waters
Dr Margaret Harris
• Snoring - 8% all children
• OSA - 3% children

- 3% with OSA = 183,000 (England)  
  Office of National Statistics

- T & A’s performed = 28,000 = 0.46%  
  ENT UK publication
  = 7,000 = 0.12%

1 in 25 (1 in 7)
155,000 to 176,000
643,000
JoRRP

HPV 6 & 11
Incidence .24 per 100,000
Prevalence 1.11 per 100,000
Average number of procedures 7
Age as presentation 4 years
Majority are first born

Campisi P et al. The epidemiology of juvenile onset recurrent respiratory papillomatosis derived from a population level national database. Laryngoscope 120:1233-1245. June 2010
Young age at diagnosis = severe disease \( P < .0001 \) **

Buchinsky FJ, Donfack J, Derkay CS et al, Age of child, more than HPV type, is associated with clinical course in recurrent respiratory papillomatosis. Public Library Science 3:e2263. 2008

HPV 11

Natural History of JoRRP

Surgical procedures - non linear time course
64% had a decreasing rate of surgery
27% - constant rate
9% - increasing rate over time
Genital HPV is increasing


– 83,745 new diagnoses of genital warts

Transmission?
JoRRP

Diathermy & forceps
CO₂ Laser
**Microdebrider**
Interferon α 2a
**Cidofovir** (5mg/ml)
Vaccines
Life cycle of HPV

**Phases**
1. Primary infection
2. Cell proliferation
3. Viral genome ampl.
4. Assembly & release

Epidermal Cell Differentiation Pathway

- Stratum corneum (horny layer)
- Stratum granulosum (granular layer)
- Stratum spinosum (prickle cells)
- Mitosis
- Basal cell

Papilloma

Viral DNA (few copies per cell)

Virus Life Cycle

- Capsid proteins
- Virus particles
- Replicating viral DNA
- Expression of early genes
PROTOCOL
研究计划

A PHASE 1b, MULTICENTRE STUDY OF CICRVAX6
HPV 6L1 VLPs AS THERAPY FOR RECURRENT RESPIRATORY PAPILLOMATOSIS

1b阶段CICRVAX6

HPV 6L1 VLPs 多中心研究治疗复发性呼吸道乳头状瘤病

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UNIVERSITY OF QUEENSLAND
昆士兰大学免疫与癌症研究中心

*** Professor Ian Frazer
Gardasil

- Non-infectious quadrivalent vaccine
- Prepared from the purified virus like particles (VLP’s) of the major capsid protein (L1)
- Of HPV types 6, 11, 16, 18

→ CIRCVax6 HPV L1 VLP
+ Alum (aluminium potassium sulfate)

- B cell mediated Antibody response
  – i.e., prevention & not cure
CIRCVax6 HPV L1 VLP

• Non-infectious quadrivalent vaccine
• Prepared from the purified virus like particles (VLP’s) of the major capsid protein (L1)
• Of HPV types 6, 11, 16, 18
  ➔ CIRCVax6 HPV L1 VLP
  - Alum (aluminium potassium sulfate)

• T cell mediated immune response
  – i.e., “killer” cell response
Phase 1 trial of CIRCVax 6

- Study Design
- Inclusion criteria
- Exclusion criteria
- Immunogenic response
Recurrent Respiratory Papillomatosis (RRP)

• AIM
  • To evaluate the safety and tolerability profile of dose levels
  • To evaluate immunogenicity and efficacy as adjunct therapy for RRP
Recurrent Respiratory Papillomatosis (RRP)

- AIM – STATUS of this Phase 1 trial
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Recurrent Respiratory Papillomatosis (RRP)

- **AIM – STATUS** of this Phase 1 trial
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- lengthen the time between surgical procedures
- effect not uniform
Recurrent Respiratory Papillomatosis (RRP)

• AIM – STATUS of this Phase 1 trial
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RRP Quantiferon Assay
Brisbane RRP patients, Quantiferon results

Optical density 450/650 nm

Visit 1
Visit 3
Visit 4
Visit 5

CICR patient number

2116 2117 2127 2138 2148 2160 2161 2162 2163 2164 2165 2166

.... but what do you do?
best job