Respiratory

G98 REDUCED LUNG FUNCTION AT ONE MONTH IS ASSOCIATED WITH ASTHMA AT ELEVEN YEARS

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Introduction: There are common risk factors for having reduced maximal flow at functional residual capacity (V'maxFRC) in infancy and also for wheeze that persists beyond three years.

Hypothesis: Reduced V'maxFRC at one month is associated with persisting wheeze throughout childhood.

Methods: A cohort of infants from an unselected population underwent an assessment that included V'maxFRC at one month. Wheeze was identified on an annual basis from three to six years and at eleven. At six and eleven years, an assessment of atopy, lung function and airway responsiveness (AR) was made.

Results: The number of infants initially assessed was 243. When compared with other children, those in the lowest tercile for percentage of predicted (%) V'maxFRC at one month (T1) experienced increased wheeze at four (OR 2.3 [95%CI 1.1-5.9] n=126, p<0.05), five (OR 2.5 [1.1, 5.9] n=106, p=0.03), six (OR 4.3 [95% CI 1.7, 10.8] n=117, p=0.001) and eleven years (OR 3.00 [95%CI 1.3, 6.8] n=183, p=0.006). In 14 cases with wheeze at both six and eleven years (asthmatics), % V'max FRC at one month was lower than in the 82 with no wheeze (72±45 % vs 106±52 %, p=0.03). Compared with non-asthmatics, asthmatics were more likely to be in T1 (p=0.02), to have increased airway responsiveness at six years (p=0.001) and have a parental history of asthma (p=0.04).

Conclusions: Reduced % V'maxFRC at one month is associated with increased childhood wheeze and asthma. Asthma at eleven years is also associated with increased airway responsiveness at six years, a parental history of asthma.

G99 MATERNAL NUTRIENT RESTRICTION IN LATE GESTATION REPROGRAMMES UNCOUPLING PROTEIN 2 AND VOLTAGE-DEPENDENT ANION CHANNEL ABUNDANCE IN THE LUNG DURING POSTNATAL DEVELOPMENT

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Aims: The mitochondrial proteins, uncoupling protein (UCP)2, located on the inner mitochondrial membrane, and voltage-dependent anion channel (VDAC), located on the outer mitochondrium have been proposed to regulate both energy metabolism and apoptosis. The extent to which abundance of these primary mitochondrial proteins may be reprogrammed by maternal nutrient restriction is unknown.

Methods: Fourteen twin bearing ewes were entered into the study. Six were fed and consumed 100% of total metabolisable energy requirements for that stage of gestation (C) whilst the remaining eight ewes were nutrient restricted (NR), consuming 60% of total ME requirements for the final month of gestation. Lambs were reared with their ewe until 28 days after birth when lungs were sampled following euthanasia. Mitochondria were analysed using immunoblotting with antibodies specific for UCP2 and VDAC producing single bands at 34 and 35 kD respectively. Results are expressed in arbitrary units (a.u.) as means with their standard errors.

Results: Although there was no difference in body or lung weights between groups, lambs born to NR ewes possessed lungs with a higher abundance of both VDAC (C 73±16; NR 117±6 a.u. (P<0.05)) and UCP2 (C 70±15; NR 106±17 a.u.).

Conclusion: Abundance of mitochondrial proteins proposed to regulate apoptosis are reprogrammed by maternal nutrient restriction in late gestation in the lung. This may contribute to altered tissue energy metabolism, as well as enhancing apoptosis, thereby placing these individuals at increased risk of respiratory disease in later life.

G100 CELLULAR DIFFERENTIAL, EOSINOPHIL CATIONIC PROTEIN AND METALLOPROTEINASE COMPOSITION OF BRONCHOALVEOLAR LAVAGE FLUID IN INFANT WHEEZE

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Wheezing in infancy is an increasingly common problem. Infant wheeze is generally associated with coryza but, in some children, symptoms may persist and develop into asthma. Little is known about the pathology of the persistence of wheeze and it has been assumed that allergic inflammatory processes drive the progression to asthma. Matrix Metalloproteinases (MMP) are involved in airway damage from inflammation. The aim of this study was to describe the cellular differential counts and inflammatory markers in bronchoalveolar lavage fluid (BALF) from infants diagnosed as having infant wheeze following bronchoscopy.

10 infants with wheeze were compared against 13 infants and children presenting with stridor. BALF was processed according to standard methods and cytocentrifuge slides prepared for cellular differential counts. Eosinophil Cationic Protein (ECP) was measured using RIA and MMP-9 and Tissue Inhibitor of MetalloProteinase-1 (TIMP-1) by ELISA. Mann-Whitney U tests were used to compare groups displayed as median (25%–75%).

Total cell counts were raised in the wheezers 12.5 (0.5–30.5) *v* 0.2 (0.1–0.2) × 10^6 /ml (p=0.023) although they were less viable 64%(61–81) *v* 81%(76-89) (p=0.065). BALF eosinophil counts and ECP were not significantly different. MMP-9 was higher in the wheezers 8.3 ng/ml (1.5–19.5) versus 0.9 ng/ml (0.8-0.9)(P = 0.036). This was also true of the ratio to its inhibitor (MMP-9/TIMP-1) 4.3%(3.2–5.9) *v* 1.2%(1.1–1.5)(p=0.039).

Allergic inflammation is not present in the lungs of infants with recurrent wheezing. This is in contrast to the lungs of asthmatic children and adults where it is clearly present. Infant wheezers show evidence of elevated and imbalanced matrix metalloproteinase activity, which may predispose to tissue damage. It seems that a non-allergic insult, that may cause remodelling, occurs prior to the onset of allergic lower airways disease.

G101 SENSITISATION AND EXPOSURE TO INHALED ALLERGENS AND THE DEVELOPMENT OF WHEEZE IN THE FIRST 3 YEARS OF LIFE

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In a prospective birth cohort study we assessed the effect of sensitisation and exposure to allergens on the development and the pattern of wheeze during the first 3 years of life. As part of the [NAC]Manchester Asthma and Allergy Study, 399 children with 1 atopic parent were followed from birth. Dust samples were collected from the living room floor and child's mattress early in year 1 and at 3 years of age. Der p 1, Fel d 1 and Can f 1 were measured by ELISA. Exposure data were treated as continuous variables or divided into quartiles. Children were reviewed at age 3 years for completion of respiratory questionnaire and skin prick testing (mite, cat, dog, pollen, egg, milk). 147 children (36.8%) wheezed at least once (wheeze ever), and 79 (19.8%) had reported wheeze within previous 6 months (recent wheeze). Proportion of children reporting wheeze ever or recent wheeze who were sensitised (SPT+; weal at least 3mm greater then negative control) is presented in table below.

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	SPT+ mite	SPT+ cat	SPT+ dog	SPT+ egg
Never wheezed	9.9%	5.6%	6.0%	2.8%
Wheeze ever	12.9%	7.5%	9.5%	4.2%
Recent wheeze	17.7%	11.5%	15.2%	6.6%

Data were further analysed using logistic regression. In the univariate analysis, sensitisation to any allergen was not a significant associate of wheeze ever. However, there was a strong trend for recent

wheeze to be associated with sensitisation (OR 1.74, 95%CI 0.99,3.04, p=0.054). Recent wheeze was significantly associated with sensitisation to indoor allergens (dust mite: OR 2.07, 95%CI 1.04,4.13, p=0.034; cat: OR 2.46, 95%CI 1.04,5.80, p=0.04; dog: OR 3.19, 95%CI 1.46,6.99, p=0.004; any inhalant allergen: OR 2.27, 95%CI 1.24,4.14, p=0.008). Exposure to mite, cat or dog allergen (either in early life or at 3 years of age) was not a significant predictor of wheeze ever or recent wheeze. In conclusion sensitisation to dust mite, cat or dog allergen was a significant associate of recent wheeze (i.e. wheeze after 2½ years of age) but not wheeze ever.

G102 DIMINISHED AIRWAY FUNCTION IN NEWLY DIAGNOSED INFANTS WITH CYSTIC FIBROSIS PERSISTS WHEN MEASURED LONGITUDINALLY

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Background: Infants with cystic fibrosis (CF) have diminished lung function soon after clinical diagnosis, but its natural history is unknown.

Aim: To determine if diminished airway function in infants, recently diagnosed clinically with CF, persists following initiation of treatment.

Methods: Infants were recruited from 5 London centres and tested when well and sedated. The raised volume technique was used to measure airway function on 2 occasions: soon after diagnosis and 6 months later in CF infants. Healthy controls were recruited locally. The forced expired volume at 0.4s ($FEV_{0.4}$) was calculated from at least 2 acceptable and repeatable flow-volume curves. Change in $FEV_{0.4}$ was compared between CF and control infants, after allowing for the effects of length, sex, exposure to maternal smoking and initial airway function.

Results: Thirty-seven infants with CF and 33 controls were recruited. Repeated measurements of $FEV_{0.4}$ were successful in 34 and 33 infants respectively. Although older, infants with CF were of comparable length to controls: median [range] length for the CF and healthy infants was 66 [54–87] cm and 58 [51–77] cm respectively on occasion 1 and 75 [68–91] cm and 72 [54–90] cm on occasion 2. 14 (41%) of the CF infants were male and 12 (32%) had been exposed to maternal smoking in pregnancy compared with 16 (38%) and 7 (21%) of the controls. $FEV_{0.4}$ was significantly diminished shortly after diagnosis in infants with CF (median age: 28 weeks). At time of follow up $FEV_{0.4}$ had increased by an average (95%CI) of 5.1% (4.7, 5.4) per cm increase in length. There was no significant difference in increase in $FEV_{0.4}$ with length for infants with CF compared with controls (p=0.87) and thus $FEV_{0.4}$ remained lower in CF infants at the second test (median age: 58 weeks) [p<0.001].

Conclusion: Airway function of infants with CF is diminished soon after diagnosis and does not appear to improve during infancy. Follow up is essential to establish the clinical significance of these findings.

G103 FIVE AND TEN YEAR FOLLOW UP OF THE EFFECT OF NEWBORN SCREENING FOR CYSTIC FIBROSIS: THE WALES AND WEST MIDLAND STUDY

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Background: An observational study in Australia, and a controlled study in Wisconsin (both of which had centralised management programmes) demonstrated benefits for newborn screening for cystic fibrosis (CF).

Aims: To determine the effect of newborn screening for CF in Wales and the West Midlands (neither of which had centralised management programmes).

Methods: Randomised controlled study of newborn screening for CF in all infants born in Wales between January 1 1985 and March 1 1990 and in the West Midlands between January 1 1985 and September 30 1989. Infants were randomly screened (S) or unscreened (U) for CF on an alternate week basis. Screened infants were identified through measurement of immunoreactive trypsin (IRT) in the heelprick blood sample, and if elevated a repeat IRT measurement was taken at 6 to 8 weeks. Infants with 2 elevated IRT levels proceeded to sweat test. Unscreened infants and those with false negative screening tests were enrolled at the time of clinical diagnosis. Clinical management was at the judgment of attending paediatrician. Data were collected on all subjects on a yearly basis, including weight SDS, height SDS and pulmonary function (FVC and FEV_1 as % predicted), and the 5 and 10 year data is presented. Infants with meconium ileus are excluded from analysis. Analysis is on "intention to treat" at randomisation to S or U group.

Results: There were 55 U and 66 S at 5 years, and 55 U and 64 S at 10 years. There were no significant differences between U and S for any parameter at 5 or 10 years.

Conclusions: In contrast to previous studies, we observed no benefit for newborn screening for CF. We speculate this may be due to the absence of centralised management programmes in the study areas at the time.

G104 NEONATAL SCREENING FOR CYSTIC FIBROSIS IN A MULTICULTURAL SOCIETY

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Objectives: Screening for Cystic Fibrosis (CF) will be universal in the UK by 2004. The hypothesis was tested that the mode of presentation and types of CF mutations were different between two different ethnic groups.

Methods: Data were analysed from the currently registered population of 5274 CF patients using the UK CF Database.

Results: 96.3 % of CF patients are Caucasian with a male preponderance that significantly increases with age (p<0.01 by regression analysis). ΔF508 is found in 85.7% of CF chromosomes and the 20 commonest CF mutations in the UK differ from mainland Europe. 1 in 27 patients has some non-Caucasian background; the majority are from the Indian Subcontinent (ISC), 1 in 84 are of Pakistani origin. No significant differences were found in mode of presentation between the above ethnic groups but the ISC group contains many mutations not recognised by commonly used genetic analysis. In the purely Caucasian CF population, 54 % are ΔF508 homozygotes whereas at 24%, the ISC CF population has significantly fewer ΔF508 homozygotes (95% CI, 0.2–0.4).

Conclusion: The UK CF population has distinct characteristics separate from other European CF Registries and changes to the screening protocol can increase true positives to 97.0% (for Caucasian) and 77.8% (for non-Caucasian) CF diagnoses. By including the commonest UK CF mutations plus seven mutations from the non-Caucasian population, the maximum yield of commoner CFTR mutations would occur, without disadvantaging ethnic minority groups. However, non-informative outcomes from combined immunological/DNA analysis should contain the category "not proven", particularly in non-Caucasian patients where the index of suspicion should remain high.

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G105 WHAT IS THE CLINICAL AND HEALTH ECONOMIC IMPACT OF RESPIRATORY SYNCYTIAL VIRUS (RSV) IN CHILDREN UNDER 2 YEARS OF AGE?

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Aims: To determine (i) rates of bronchiolitis-related and RSV-associated hospitalisations, (ii) contribution of RSV to hospitalisations from all causes, and (iii) clinical and health economic impact of RSV disease in a geographically defined population of children under 2 years of age.

Methods: We analysed the databases of the health authority, microbiology department, and paediatric and neonatal intensive care units to determine numbers and characteristics of hospitalisations due to bronchiolitis and RSV disease among 36,780 Shropshire resident children <2 years of age for 3 consecutive years (1996–99).

Results: There were 653 bronchiolitis related (30.8/1000 infants <1 yr) and 497 RSV associated hospitalisations (19.9/1000 infants <1 yr) in children <2 years old during 3 years. Bronchiolitis accounted for 7.7% of all admissions among children <2 yr old, and 76% of respiratory hospitalisations in infants <6 months of age. 6.3% of 841 preterm infants had RSV-proven hospitalisation during their first 2 years. Assisted ventilation during neonatal period and home oxygen therapy [OR (95% CI) - 2.2 (1.2–4.1) and 5.2 (1.8–14.9) respectively] were significantly associated with risk of RSV-related hospitalisation among preterm infants. Serious adverse outcomes were uncommon—1 child with complex heart disease died, 11 were admitted to intensive care and 6 infants (, 3 preterm) needed assisted ventilation for a total of 27 days. The 3-year direct health economic costs

of hospitalisations due to bronchiolitis and RSV disease were £460,399 and £340,134, respectively.

Conclusions: The rates of RSV related hospitalisations during infancy have nearly tripled in last 25 years[1], but serious adverse outcomes are very rare even among the high risk infants.

1. Martin AJ, et al. *Lancet* 1978;**ii**:1035–8.

G106 SLEEP RELATED DISORDER IN DUCHENNE'S MUSCULAR DYSTROPHY

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Aims: To assess the prevalence of sleep related disorder and benefits of non-invasive ventilation in Duchenne's muscular dystrophy.

Methods: Audit of patients attending a tertiary respiratory/sleep medicine unit over a 5 year period. The Neuromuscular clinic has included respiratory assessment as part of its multidisciplinary assessment and thus the sample selected is representative of DMD population in our region. Variables used in assessment were symptoms reported, lung function, and polysomnography.

Results: Total of 34 patients were identified. Age of referral varied from 1–15years (Median 10). Sixteen (47%) of them reported sleep related symptomatology. Forced vital capacity was between 15–103% predicted (Median 58%). Thirty-one progressed to have polysomnography of which 14 were normal studies. Eight had obstructive sleep apnoea and had adenotonsillectomy, which improved their symptomatology. Nine showed varying degrees of hypoventilation/respiratory failure and non-invasive ventilation was offered. The median FVC for this group was 27%. All 8 patients tolerated NIV well. There was significant improvement in symptoms (p=.003). There was no significant improvement in transcutaneous CO2 and respiratory events in sleep.

Conclusions: The prevalence of sleep related disorders in DMD is underdiagnosed. Early assessment with polysomnography helps in identifying and alleviating obstructive symptomatology and initiating non-invasive ventilation. Non-invasive ventilation is well tolerated and results in improvement of symptoms. In a progressive neuromuscular condition like Duchenne's the non-progression of respiratory indices, by itself would suggest benefit from non-invasive ventilation.

G107 PULMONARY FUNCTION ABNORMALITIES IN CHILDREN WITH SICKLE CELL DISEASE

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Background: Chronic lung disease is a cause of premature death in sickle cell disease (SCD) patients. Affected young adults have restrictive lung abnormalities. Studies of pulmonary function in SCD children have yielded conflicting results, demonstrating restrictive, obstructive or no abnormality. Comprehensive pulmonary function testing is therefore required to accurately assess SCD children.

Aim: To determine whether the lung function of SCD children differed from that of children of similar age and ethnic origin (controls).

Methods: Children were recruited from two specialist clinics in South Thames. FEV1, FVC, FEV1/FVC and PEFR were determined by spirometry, functional residual capacity was assessed both by whole body plethysmography (FRC_{pleth}) and a helium gas dilution technique (FRC_{HE}) and specific airway conductance (SGaw) was also determined by whole body plethsmography. Diffusing capacity was measured using the single breath carbon monoxide gas transfer technique, correction was made for the lower haemoglobin levels of the SCD children and the results related to alveolar volume (KCOc). All pulmonary function test results were expressed as a percentage of that predicted for height.

Patients: Twenty four SCD children mean age 10.3 (range 6.5–12.0) years and twenty controls mean age 9.9 (range 7.0–11.8) years were studied.

Results: Compared to the controls, the SCD children had a lower mean FEV1 (p=0.002), FVC (p<0.0001) and PEFR (p=0.01), but similar FEV1/FVC and SGaw. The mean KCOc, however, was higher in the SCD compared to the control children (p=0.003).

Conclusions: These results suggest that SCD children have restrictive lung function abnormalities, their higher mean KCOc may reflect an elevated lung blood volume.

G108 NATIONAL SURVEY (UK) OF ADRENAL CRISIS DUE TO INHALED CORTICOSTEROIDS

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Aims: Adrenal crisis due to inhaled corticosteroids (ICS) has been very rarely reported. We investigated the prevalence of adrenal crisis due to ICS prescribed in the UK—beclomethasone (BDP), budesonide (BUD) and fluticasone (FP).

Methods: A postal survey of 2912 paediatricians and endocrinologists. Affirmative replies were followed up with a detailed questionnaire. Cases with probable contribution from oral or topical steroids were excluded.

Results: There were 31 cases (, 26 children, 5 adults). Clinical presentations were hypoglycaemic convulsions (8), hypoglycaemic coma (12), hypotension, fatigue, nausea (10), fatal sepsis with hypoglycaemia (1).

ICS; FP (28 cases) dosage range 500–2000µg/day, BDP (2 cases) ,_FP + BUD (1 case). Most frequent inhaling device was metered dose inhaler plus spacer (17 cases). All cases had moderately severe asthma, except 6 in retrospect had other diseases.

Conclusions: 1. Adrenal crisis due to ICS is more common than expected. 2. FP (>500µg/day) was responsible in more than 90% of cases. However FP accounts for only 15% of prescriptions for ICS in the UK. We believe the higher lipophilicity of FP may be responsible for these very serious clinical effects at higher doses.

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G109 HOW WELL CAN AIRWAY RESISTANCE MEASURED BY THE INTERRUPTER TECHNIQUE (R_{INT}) IDENTIFY CHANGE?

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To describe the accuracy of a measurement and how well true change can be identified, its repeatability must be known. Immediate repeatability of a lung function test reflects stability of the measuring system. Between occasion repeatability reflects, in addition, the biological variation of the subject.

Aim: To measure the within- and between-occasions repeatability of R_{int}

Method: Subjects were aged 2–10 years who had (1) no respiratory symptoms, (2) persistent isolated cough or (3) doctor-observed wheeze 4–6 weeks previously with no current symptoms. R_{int} was measured before and 15 min after placebo, and repeated within 2–20 weeks. The *limits of agreement* (LA), expressed as percent predicted, equal 2 standard deviations of differences between 2 measurements. *Coefficient of variation* (CoV) describes the repeatability of a single measurement by relating the standard deviation to the mean. *Intraclass correlation* (ICC) describes how well pairs of results correlate (= 1-(SD differences between measurements/2)^2/(SD of the measurements)^2).

Results: Within occasion repeatability (all groups n=94): CoV 13%; ICC 0.97;LA 20%. There were no effects of age or health status; and no important difference between groups. Between occasion repeatability: Healthy (n=72): CoV 11%; ICC 0.75; LA 32%. Coughers (n=57); CoV 17%; ICC 0.56; LA 49%. Wheezers (n=95): CoV 16%; ICC 0.66; LA 53%.

Conclusion: Within occasion repeatability is independent of health status. The changes in RINT expected following bronchodilator[1] or methacholine challenge[2] are greater than within-occasion repeatability (LA). Between-occasion repeatability seems poor, especially in previous wheezers. For clinical purposes, the measurement of R_{int} cannot be recommended at the moment for following individuals' progress. The method is suitable for bronchodilator responsiveness and challenge testing, and for research purposes where change in groups of subjects is being measured.

1. McKenzie et al. *Eur Resp J* 2001;16(8).
2. Phagoo et al. *Eur Resp J* 1996;**9**:1374–80.