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### SURFACE ELECTROMYOGRAPHY FOR REGISTRATION OF INFANT NEUROMUSCULAR ACTIVITY

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**Aim**: The objective of the present study was to develop a method for surface electromyographic (EMG) registration of muscle activity in infants, with the perspective of assessing neuromuscular function/prognosis in infants with obstetric brachial plexus palsy (OBPP).

**Method**: Fifteen healthy infants, aged 1–4 days, were recruited for the study. EMG signals were registered from the biceps, triceps and palmar portion of thenar muscles on both arms and hands. For this purpose surface electrodes for bipolar recording were developed using two sintered Ag/AgCl pellets that had been cast in silicone rubber. The Moro reflex was used to elicit a standardised motor stimulus. The reflex was elicited 5 times, and during EMG recording the procedure was video taped. To define the onset of muscle activity the running block threshold method was adapted to time signals.

**Results**: The custom-made electrodes performed well and EMG signals of good quality were obtained from the different sites. The onset algorithm worked automatically, giving stable and visually correct registration. The signals could clearly describe the onset of muscle activity during the Moro reflex with a symmetrical pattern in both arms and hands. The extension/abduction phase of the reflex was characterised by predominant activity in the triceps muscle with concomitant low-grade activity in the antagonistic biceps muscle. During the embracing phase, occurring up to 1 second after onset of abduction, the opposite pattern was seen. Thenar activation, causing flexion/opposition of the thumb, was salient only during the embracing phase.

**Conclusion**: Surface EMG can be used in infants to objectively assess the normal motor pattern in muscles innervated by different branches of the brachial plexus. This convenient method shall be applied to evaluate the status and possibly the prognosis in infants with OBPP.

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### THE E292V VARIANT IN ABCA3 IS OVER-REPRESENTED IN NEWBORNS WITH RESPIRATORY DISTRESS SYNDROME (RDS)

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**Background**: ABCA3 is an ATP Binding Cassette protein localized to the limiting membrane of lamellar bodies in alveolar Type II cells. Recessive mutations in ABCA3 disrupt surfactant composition and function and cause lethal respiratory distress in newborns. A valine for glutamic acid substitution at codon 292 (E292V) has been found in unrelated individuals with chronic respiratory insufficiency.

**Objective**: To determine the prevalence of the E292V variant in infants with and without RDS. Design/Methods: We obtained genomic DNA and clinical data from an unselected cohort of newborns with RDS (RDS, n=125, gestational age [GA] 31±5 wks), newborns with RDS referred for evaluation of familial or atypical RDS (REF, n=56, GA 34±5 wks), and normal newborns (noRDS, n=167, GA 39±2 wks). We amplified a 637 base pair product that included codon 292 and subjected amplicons to BsrG1 restriction analysis and agarose gel electrophoresis.

**Results**: Excluding 1 each of concordant twins in the REF and noRDS groups, 3 RDS (2.4%), 5 REF (9.1%), and 2 noRDS (1.2%) infants were heterozygous for E292V (P=0.009). Males and females were equally represented. One infant with E292V in the noRDS group was Black, all others with E292V were White. Symptomatic infants (REF+RDS) with E292V were more mature than those without E292V (35±3 vs 32±5 wks, P=0.007). Duration of mechanical ventilation, and need for supplemental oxygen were not significantly different. Infants with RDS and E292V developed pneumothoraces more frequently (78%) than infants with RDS but without E292V (9%) (P<0.001). Six infants had resolution of symptoms within 1 month of birth; the noRDS individuals with E292V remained asymptomatic.

**Conclusions**: The E292V variant in ABCA3 is significantly more prevalent in infants with RDS than in asymptomatic controls. Patients heterozygous for E292V come to clinical attention by presenting with RDS that is more severe than anticipated for gestational age. E292V may be a genetic influence for the risk and severity of RDS.

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### VARIATION IN THE SURFACTANT PROTEIN B GENE (SFTPB) CONTRIBUTES TO NEWBORN RESPIRATORY DISTRESS (RDS)

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**BACKGROUND**: SFTPB expression (>25% normal) is necessary for the successful fetal-neonatal pulmonary transition.

**OBJECTIVE**: To determine if variants in SFTPB contribute to the risk of RDS in newborns.

**METHODS**: Using amplified genomic DNA and high throughput, automated sequencing, we genotyped promoter, all translated exons and intervening introns (8.5 kB) of SFTPB in 3 cohorts: 1) anonymous Guthrie cards from the Missouri Newborn Screening Program (Missouri cohort, n=1,116; 18% Black, 79% White), 2) newborns with RDS (RDS cohort, n=204; 40% Black, 59% White), and 3) newborns without lung disease (Control cohort, n=86, 51% Black, 45% White). We used PHASE V2.1, a Bayesian-based haplotype inference program, to computationally reconstruct race and gestational age-specific haplotypes in the RDS and Control cohorts using variant alleles that were present in >5% of the population.

**RESULTS**: We identified 119 polymorphic sites in SFTPB, including 17 exonic SNPs (10 nonsynonymous) and 5 intronic insertions or deletions. Of the other 97 intronic SNPs, 4 may impact RNA splicing by altering intron-exon junctions. The 121ins2 insertion, the common mutation associated with SP-B deficiency, was identified in 4 heterozygous individuals in the Missouri cohort. Based on Ewens predicted allele frequency, we have identified >99% of the SNPs with predicted frequencies of >0.001 in the Missouri cohort, and 92% in the NICU cohort. Despite the difference in cohort size, we found 17 rare (<4 heterozygous individuals) SNPs in the NICU cohort not detected in the Missouri cohort. There were significant differences in haplotype frequencies between the RDS and Control groups for all race and gestational age cohorts (P=0.01 to 0.05).

**CONCLUSIONS**: Rare variants contribute approximately 50% of genetic variation in the SFTPB. Rare, private variants and haplotypes are overrepresented in patients with RDS. Genetic variation in the SFTPB contributes to risk of RDS in infants.

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### EARLY PATTERNS OF CYTOKINE RESPONSE IN PRETERM INFANTS AND NEURO-COGNITIVE OUTCOME AT 2 YEARS OF AGE

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**Background**: In a cohort study of preterm infants increased plasma concentrations of proinflammatory cytokines were associated with premature rupture of membranes, arterial hypotension and cerebral damage.

**Objective**: To evaluate in a follow-up if early postnatal levels of cytokines in preterm infants predict neuro-cognitive outcome at 2 years of age.

**Methods**: A prospective cohort study of 71 surviving infants <32 gestational weeks. Plasma concentrations of proinflammatory (TNF-alfa, IL-1beta, IFN-gamma, IL-2, IL-6, IL-8, IL-12) and modulatory (IL-4, IL-10) cytokines were analyzed in umbilical cord and at 6, 24 and 72 h age. Intraventricular hemorrhage (IVH) and white matter brain damage (WMD) was assessed with ultrasound. Neuro-cognitive outcome at 24 months corrected age was evaluated using Bayley Scales of Infant Development (Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI)) and a standardized neurological examination (Neurological Optimality Score (NOS)).

**Results**: 64 infants (mean gestational age (GA) 27.1 wks) were assessed at 24 (0.5) months (mean, SD). NOS correlated with both MDI and PDI (r=0.60 p<0.001 and r=0.70 p<0.001 respectively). GA correlated with MDI, PDI and NOS ( r=0.34 p=0.006, r=0.42 p=0.001 and r=0.40, p=0.001 respectively). Male gender had lower NOS ( p=0.03). Cord levels of the proinflammatory cytokineTNF-alfa were inversely correlated with PDI (r=-0.33 p=0.014) and levels of the modulatory cytokine IL-10 at 24 h correlated positively with PDI and NOS (r=0.42 p=0.001 and r=0.32, p=0.015 respectively) after adjustment for GA and gender. Infants with IVH grade III/IV or WMD (n=8) had lower median (range) MDI and NOS, 74 (50–106) and 63 (36–76), respectively, as compared to infants without brain injury (n=56): 88 (50–116) and 71 (58–78), respectively. Differences remained after adjustment for GA, gender and parental education.

**Conclusion**: An early inflammatory response in preterm infants is associated with perinatal brain injury and might be prognostic for adverse neuro-cognitive outcome at 2 years of age.

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### UPDATE ON ENZYME REPLACEMENT THERAPY (ERT) WITH RECOMBINANT HUMAN ARYLSULFATASE B (RHASB) FOR MPS VI (MAROTEAUX-LAMY)

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MPS VI is a rare, life-threatening lysosomal storage disease with no effective treatment. ERT with rhASB has shown promising results in 2 clinical studies. The objective of this Phase 3 study was to confirm efficacy and safety. 39 patients were enrolled in a randomized, double-blind, placebo-controlled study for 24 weeks. The primary endpoint was the distance walked in 12 minutes (12MWT), while secondary endpoints were the number of stairs climbed in 3 minutes (3MSC), and the level of urinary glycosaminoglycans (GAGs). After 24 weeks, all patients received drug in a 24 week open label extension period. For the Week 1–24 period, the 19 patients receiving rhASB demonstrated a significant mean improvement of 92 meters (m) in the 12MWT as compared to the 20 patients receiving placebo (p=0.025). For the weeks 25 to 48 period, the placebo group, now receiving rhASB, showed a mean increase of 65 m relative to Week 24 (p=0.007). The original rhASB group continuing on treatment during this period improved their mean walk distance an additional 36 m (p=0.15). For the 3MSC, the rhASB group demonstrated a mean improvement of 5.7 stairs/minute after 24 weeks as compared to the placebo group (p=0.053). Relative to 12MWT, similar improvements in 3MSC were observed for each group from Week 24 to Week 48. Upon receiving rhASB, both the rhASB and placebo groups had rapid declines in urinary GAGs (p<0.001). Infusions were generally well tolerated: 98% of possible infusions were received. The majority of adverse events were mild to moderate in severity. All but one patient developed IgG antibodies to rhASB, but these antibodies were not associated with infusion-associated reactions or lack of clinical benefit. rhASB improves physical mobility and endurance, reduces GAGs, and has an acceptable safety profile. Sponsor: BioMarin Pharmaceutical Inc.

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### VARIATION IN THE REPORTING OF CEREBRAL ULTRASOUND SCANS IN NEW ZEALAND NICUS

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**BACKGROUND**: Rates of germinal matrix/intraventricular haemorrhage(GM/IVH) and white matter damage reported to the Australian and New Zealand Neonatal Netwrok (ANZNN) vary between neonatal intensive care units (NICUs).

**AIMS**: To determine whether the capture and reporting of cerebral ultrasound scans influenced the reported variation between NICUs.

**METHODS**: Two hundred and twenty five infants with birth weight <1500g and gestation <32 weeks were randomly selected from the six Level III intensive care units in New Zealand; 44 from each unit. All early scans (4 to 14 days) and all late scans (4 to 8 weeks) were copied using digital photography, identification was removed, and the copied images were independently read by three experts using a standardised approach.

**RESULTS**: One third of the scans were incomplete and one third were of poor quality. The rate of both incomplete and poor quality scans differed between NICUs (p <0.001). However there was little variation in the reporting of GM/IVH between the reviewers and the ANZNN for all NICUs (weighted kappa statistics 0.75 to 0.95). For late scans variation was greater (kappa 0.45 to 0.51) and for all NICUs reviewers reported 6 to 20 % more cystic changes and ventricular dilatation than was orginally reported to the ANZNN.

**CONCLUSION**: The high level of agreement between the reviewers' reports and the reports to the ANZNN for early scans suggests that the reported varaiton in incidence of GM/IVH is unlikely to be due to the differences in scanning and reporting. However the poorer agreement for late scans suggests that some of the reported varation in cerebral white matter changes may be due to variation in interpretation of scans.