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FOREIGN BODIES CAUSING AND PROLONGING HOSPITALIZATION IN CHILDREN 0–14 AGE: RESULTS FROM THE ESFBI STUDY

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THE INJURY DUE TO THE INGESTION, ASPIRATION OR INHALATION OF FOREIGN BODIES (FB) REMAINS A COMMON PAEDIATRIC PROBLEM WITH SERIOUS AND SOMETIMES FATAL SEQUEL. THE DIAGNOSIS IS OFTEN DELAYED OR OVERLOOKED CAUSING THE ONSET OF COMPLICATIONS, WICH USUALLY REFLECT IN A PROLONGED HOSPITALIZATION. THE ESFBI PROJECT IS A RETROSPECTIVE STUDY IN THE MAJOR EUROPEAN COUNTRIES AIMED AT COLLECTING DATA ON FB INJURIES IN THE UPPER AIRWAYS. DATA WERE GATHERED FROM THE DISCHARGE CARDS IN 17 UNIVERSITY CLINICS IN 2004 AND REFERES TO THE YEARS 2000, 2001, 2002. COLLECTED DATA CONCERNED INJURIES OCCURED TO CHILDREN AGED 0–14 WITH THE ICD9-CM CODES ICD931, ICD932, ICD933, ICD934 AND ICD935. ANALYSIS WAS BASED ON THE PROBABILITY OF HAVING AN HOSPITALIZATION LASTING MORE THEN 3 DAYS. ASSOCIATION OF FB CHARACTERISTICS AND LENGTH OF STAY (LOS) WAS ASSESSED USING A MULTIVARIABLE LOGISTIC REGRESSION MODEL. ALL EFFECTS WERE ADJUSTED BY AGE, GENDER AND ICD9-CM CODE. A MEDIAN LOS OF 2 DAYS (1,2) WAS OBSERVED WITH 24.5% OF THE CHILDREN HAVING A LOS OF AT LEAST 3 DAYS. NO DIFFERENCES WERE FOUND WITH RESPECT TO SEX AND AGED DISTRIBUTION. PROLONGED LOS WAS ASSOCIATED WITH SMALLER FB (MEDIAN DIAMETER OF 7MM) AND OF SEMI-RIGID CONSISTENCE. INORGANC OBJECTS HAD A SMALLER RISK OF PROLENGED LOS (OR 0.62, 0.43–0.89 CI) AS COMPARED WITH ORAGANIC OBJECTS. COMPARED TO NUTS, ONLY COINS WERE SIGNIFICANTLY ASSOCIATED TO A SMALLER RISK OF PROLONGED HOSPITALIZATION (OR 0.29, 0.15–0.57 CI). FB INJURIES ARE CONFIRMED TO POSE A GREAT RISK FOR CHILDREN, AND THEIR EFFECT ARE ALSO SHOWN TO INVOLVE ASPECT OF HEALTH MANAGEMENT, CAUSING IN 24& OF THE CASES A LONGER HOSPITALIZATION.

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COMBINED INHIBITION OF NEURONAL AND INDUCIBLE NOS PROVIDES NEUROPROTECTION AFTER HYPOXIA-ISCHAEMIA IN P3 AND P7 RAT PUPS

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Background, aim: Nitric oxide (NO) contributes to neuronal damage following perinatal hypoxia-ischaemia (HI). We examined the neuroprotective effects of 2-iminobiotin (2-IB), a selective inhibitor of neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthae (iNOS), after HI in P3 and P7 rat pups as model of more immature developmental stages of the human brain.

Methods: P3 and P7 rat pups were subjected to occlusion of the right carotid artery followed by 60 (P3) or 120 min (P7) of hypoxia (FiO2 0.08). Immediately after HI, and 12 and 24 h later, pups received s.c. 10 mg/kg 2-IB or vehicle. Heat-Shock Protein-70 (HSP70) was determined 48 h post-HI using Western blotting. Cytochrome c and nitrotyrosine were determined at 24 h post-HI. At 6 weeks post-HI neuronal damage of hippocampus and cortex was assessed using a 4-point histological scale, the maximal score of normal animals being 33.

Results: In both P3 and P7 rat pups, 2-IB reduced HSP70 production after HI by 50%. The increase in cytochrome c was also 50% reduced by 2-IB treatment ($P<0.05$). No changes in nitrotyrosine levels were observed in any group at 24h post-HI. Brain histology score of the ipsilateral hemisphere rose significantly from 27 ± 2 (P3, vehicle) to 29 ± 2 (P3, 2-IB) and from 5 ± 5 (P7, vehicle) to 13 ± 9 (P7, 2-IB).

Conclusion: selective inhibition of nNOS and iNOS post-HI provides both short-term (HSP70, cytochrome c) as well as long-term neuroprotection (histology) in both the P3 and the P7 rat without affecting nitrotyrosine levels.

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NITROTYROSINE, ACTIVATED CASPASE-3, AND CD-68 IN THE SPINAL CORD OF ASPHYXIATED FULLTERM NEONATES

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Aim: previous studies have demonstrated nitric oxide toxicity in neonatal hypoxic-ischemic brain injury. Although neonatal hypoxic-ischemic injury of the spinal cord has been reported, pathways of spinal cord injury have not been studied in detail, but may well be relevant for neuroprotective strategies. In the present study, we examined the presence of nitrotyrosine (indicating nitric oxide toxicity), activated caspase-3 (indicating apoptosis), and activated microglia and macrophages (CD-68) in spinal cord tissue of asphyxiated fullterm neonates. Parental informed consent was obtained, and studies were approved by the Ethics Committee of the University Medical Center Utrecht.

Patients, methods: studies were performed in 18 fullterm neonates who died within the first week of life after perinatal asphyxia. All has severe hypoxic-ischemic encephalopathy and multiple organ failure. Histological examinations were performed at three levels of the spinal cord, and included in addition to hematoxylin-eosin (HE) staining for nitrotyrosine, activated caspase-3 and CD-68. Staining was scored on a 3-point scale from 0 (none) to 3 (massive).

Results: nitrotyrosine (score >= 1) was present in 5/18, activated caspase 3 (score >= 1) was present in 8/18 (white matter), 4/18 (motor neurons), and CD-68 (score >= 1) in 3/18 (white and gray matter). Nitrotyrosine staining correlated positively with caspase-3 ($P< 0.05$). Nitrotyrosine was most prominent in the neonates who died within 24 hours after birth, as was activated caspase-3. CD-68 was demonstrated only after 24 hours. Routine HE staining did not show abnormalities.

Conclusion: HE staining was normal, but activated caspase-3, nitrotyrosine and CD-68 could be demonstrated in spinal cord tissue of some asphyxiated fullterm neonates. Neuroprotective strategies for asphyxiated fullterm neonates should also aim at the spinal cord. This study was funded by the 'Dr.W.M. Phelps-Stichting voor Spastici', Bussum, the Netherlands.

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BIOLOGICAL MARKERS OF OXIDATIVE STRESS IN PROGRESSIVE MUSCULAR DYSTROPHIES: A PRELIMINARY STUDY

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Background/Aims. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are fatal degenerative disorders of muscle resulting from mutations in the gene coding for dystrophin. The exact mechanisms through which the absence or an abnormal dystrophin result in muscle degeneration are still uncertain. Oxidative-damage may play a key role in these processes as the neuronal isoform of nitric oxide (NO) synthase, is associated with dystrophin-glycoprotein complex (DGC). Dystrophin abnormalities may lead to an impaired NO production with inadequate NO-mediated protection against ischemia and damaging actions of the reactive oxygen free radical species (ROS). The aim of the study was to evaluate plasma levels of isoprostanes, a sensitive biological marker of oxidative stress, in patients affected by DMD and BMD.

Methods. Twenty nine patients with age ranging from 14 months to 30 years entered the study. In all patients clinical diagnosis was confirmed by molecular analysis. Isoprostanes were assayed in all patients by collecting blood samples with butylated hydroxytoluene to prevent oxidation during processing.

Results. When globally evaluated, serum levels of isoprostanes were found significantly higher in patients than the normal ranges. In particular, wheel-chaired patients with Duchenne muscular dystrophy with ages ranging from 12 years to 16 years, seemed to have the highest plasma levels of isoprostanes.

Discussion/Conclusions. ROS are ubiquitously produced during normal aerobic cellular metabolism, with the possibility of initiating damage to lipids, protein, and nucleic acids. A protective role against ROS actions in muscle fibres is played by the DGC. In this context, pathogenetic defects in the DGC mainly have two biochemical consequences: an impaired NO(*) production, which determines a scarce protection of muscle cells against ischemia, and an increased cellular susceptibility to metabolic stress. This pathogenetic model has been called the 'two-hit' hypothesis. In the present study we first reported on the preliminary data regarding the evaluation of isoprostanes plasma level, a sensitive oxidative stress marker, in a series of patients with progressive muscular dystrophies. Isoprostanes resulted higher than the normal range values. In particular, the most severely affected DMD patients showed the highest levels of oxidative stress marker. Unfortunately, the present sample size was nor sufficiently large in number to allow correlation studies between isoprostanes levels and specific clinical/bichemical findings such as the type of muscular distrophy (DMD or BMD) and serum CPK levels. Nevertheless, our ongoing study and previous experimental studies seem to suggest that the increased markers of oxidative stress we found might be the plasmatic expression of the degenerative processes occurring in muscles. Of course, the possibility that oxidative stress might be induced by myoglobin (a Fe-containing protein) released in the blood of these patients, cannot be ruled out at this stage.

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IS SIGHING A RESETTING MECHANISM OF THE AUTONOMIC NERVOUS SYSTEM?

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Sighs are important components of normal breathing. They occur isolated or associated with respiratory pauses. Functional residual capacity and lung compliance increase after sighs. Sighs have been shown to be part of an arousal reaction in infants and to induce heart rate modifications. We investigated the influence of sighs on the autonomic balance in infants.

METHODS: 107 sighs (a single breath of at least twice the amplitude of the preceding breaths, not followed by an apnea) from 23 term infants were selected. The selection was made in conditions known not to interfere with spontaneous HR variability (quiet sleep,absence of movements, apnea or false detections of QRS during the 2 preceding and following minutes. Spectral analysis of RR variability was performed on the 2 minutes preceding and the 2 minutes following the sigh. To study the role of the ANS in the development of a sigh, spectral analysis of the period just before the sigh and of the 2 preceding minutes were compared.

RESULTS: The 2 minutes following the sigh were characterized by an increased RR interval ($p 0.001$), an increased total power ($p <0.01$),an increased LF ($p0.01$), unchanged HF, increased HF/LF ($p <0.001$), increased LF normalized ($p< 0.001$),decreased HF normalized ($p<0.001$). When comparing the interval sigh minus 4 to 2 minutes with the interval sigh minus 2 to 0 minutes, the opposite evolution of autonomic balance was observed.

DISCUSSION:The results of the spectral analysis indicate that sighs are followed by an increase in orthosympatic tone and a decrease in parasympatic tone. On the opposite, the period preceding sighs is caracterized by a decrease in orthosympatic tone and an increase in parasympatic tone.

CONCLUSION: These results indicate that sighs could play a resetting role for the autonomic nervous system during quiet sleep in normal infants.

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CD 64 AS A DIAGNOSTIC MARKER FOR NEONATAL INFECTION

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Background CD64 (Fcgamma-receptor I) is a high-affinity receptor for the Fc-portion of immunoglobulin molecules, normally expressed only by monocytes and to a very low extent by neutrophils. During infection the cytokine-induced activation of neutrophils results in changes in the expression of leucocyte-differentiation antigens with an increase in CD64 levels above the normal cut-off of 6136 antibody-phycoerythrin molecules bound/cell. The aim of this study was to evaluate the diagnostic utility of CD64 expression on neutrophil surface to identify neonatal infection.

Study Design Up to now we have studied 44 term infants (1–18 day old) as they were probably infected (with clinical signs and symptoms of infection, n = 22) or potentially infected (without clinical features of infection but with risk factors, n = 22). Infection was confirmed with positive blood culture and/or positive chest radiography and/or abnormal CRP level in 22 neonates (15 were symptomatic, 7 were asymptomatic).

Results Expression of CD64 was significantly enhanced in the group of infected neonates (median level 7004; range 749 to 19078) compared with the group of not infected ($p = 0,001$, median level 3085; range 1104 to 9024). The sensitivity and specificity of CD64 was 45% and 91%, respectively. Positive predictive value resulted 83 % and negative predictive value 63 %.

Conclusions These preliminary data show that, through a single sample, increased expression of CD64 is a quite good specific marker (91%) of neonatal infection. In contrast its diagnostic sensitivity is low (45 %).

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