that the output of the DASL assay is a reflection of the extended and ligated query oligonucleotide pool. Because this is an indirect measurement of expression that is dependent on competition among the resulting products for labeling in the PCR amplification, changes in hybridization signal may not accurately reflect changes in transcript abundance. Thus, measurement of absolute changes in cancer-specific gene expression during cancer progression requires independent experimental determination. Nevertheless, we found that intensity in the DASL assay generally tracked with RNA expression, with a correlation coefficient (r^2) of 0.8–0.9 in a comparison between the DASL assay and qPCR for fold difference detection among samples *(11)*.

In summary, we have demonstrated that gene expression profiling of RNAs from FFPE samples is possible, despite their extensive degradation, by use of the DASL assay and universal microarrays. The DASL assay combines the advantages of array-based gene expression analysis with those of multiplexed qPCR, thereby offering much higher multiplexing capacity and substantial throughput and cost-saving advantages. It uses 200 ng of total RNA to analyze ~500 genes, 5- to 100-fold less than that required by qPCR, which usually takes 2–50 ng per reaction (per gene) *(9, 18–21)*. In addition, the small size of the targeted gene sequence (~50 nucleotides) and the use of random primers in cDNA synthesis allow detection of RNAs that are otherwise too degraded for conventional microarray analysis. Our results suggest that archival tissue samples may be used to provide sufficient expression information to monitor multiple stages in disease progression as well as response to treatment. The capacity of the DASL assay to monitor hundreds of genes simultaneously in RNAs from FFPE samples may also accelerate the identification of potential biomarkers as prognostic indicators, given that the patient's history is already known for many of these samples. Furthermore, the parallel processing of 96 samples at once, using the Sentrix® Array Matrix fiber optic array platform *(22)*, should permit rapid analyses of expression patterns in hundreds of clinical samples.

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Cerebrospinal Fluid Activin A Measurement in Asphyxiated Full-Term Newborns Predicts Hypoxic Ischemic Encephalopathy, *Pasquale Florio,[1] Stefano Luisi,[1] Matteo Bruschettini,[2] Dariusz Grutzfeld,[3] Anna Dobrzanska,[3] Pierluigi Bruschettini,[2] Felice Petraglia,[1*] and Diego Gazzolo[2]* ([1] Department of Pediatrics, Obstetrics and Reproductive Medicine, University of Siena, Siena, Italy; [2] Department of Pediatrics, Giannina Gaslini Children's University Hospital, Genoa, Italy; [3] Department of Neonatology, Children's Memorial Health Institute, Warsaw, Poland; * address correspondence to this author at: Department of Pediatrics, Obstetrics and Reproductive Medicine, University of Siena, Policlinico "Le Scotte", Viale Bracci, 53100 Siena, Italy; fax 39-0577-233-454, e-mail petraglia@unisi.it)

Hypoxic ischemic encephalopathy (HIE) is an important cause of mortality and morbidity in full-term newborns, and neurologic handicaps develop in ~25–28% of these infants *(1, 2)*. The postasphyxia period is crucial because

brain damage may be at a subclinical stage or its symptoms may be hidden by the effects of sedation, and radiologic assessment may still be unrevealing *(3, 4)*. Because activin A is a growth factor produced in the central nervous system (CNS) *(5, 6)*, mainly after brain injury to modulate neuronal survival against toxicity *(7–14)*, in the present study we investigated whether its concentrations in cerebrospinal fluid (CSF) collected from asphyxiated full-term newborns were higher in those developing HIE and whether this measurement could be useful for the early detection of postasphyxia HIE.

We conducted a longitudinal cohort study, recruiting any infants consecutively admitted (April 1998 through June 2002) to our Neonatal Intensive Care Units (NICUs), who underwent a lumbar puncture in the first 24-h from birth for clinical indications. We expected approximately one third of asphyxiated infants to exhibit moderate/severe HIE; we therefore planned to enroll 30 infants in the asphyxiated group (full-term infants with a gestational age >36 weeks), with at least 8 of them in the HIE subgroup, which would assure a statistical power of 90% to detect differences ≥10% between group means with a significance level of 95%. Considering that <40% of the infants submitted to lumbar puncture in our NICUs have a history of perinatal asphyxia, we expected that ~40–50 nonasphyxiated infants could be enrolled to the control group contemporarily with the 30 infants of the asphyxiated group. The Local Ethics Committees approved the study protocol, and parents of the infants examined gave informed consent.

All asphyxiated newborns were delivered by emergency cesarean section because of acute fetal distress as defined by the American College of Obstetricians and Gynecologists *(15)*. Asphyxia was defined according to an Apgar score <3 at 5 min, a pH <7.0 or a base excess of −12 or higher in cord or venous blood taken from newborns within 60 min of birth, or the need for resuscitation at birth and/or for positive pressure ventilation (>3 min) *(15)*.

Infants that fulfilled three or more of the above criteria were included in the asphyxia group and were retrospectively subdivided according to the clinical examination as either (*a*) no/mild HIE with good prognosis or (*b*) moderate/severe HIE with a greater risk of neurologic handicap *(16)*. Controls were 44 healthy term neonates of the same gestational age who were delivered after the cases by either elective cesarean section (n = 12) or vaginal delivery (n = 32). On admission, all patients were checked against routine clinical and laboratory values, and CSF samples were obtained by lumbar puncture for routine examination and activin A assessment in the first 24-h after birth. For ethical reasons, CSF specimens from controls were obtained only from infants from whom CSF samples were collected to identify confirmed or probable meningitis based on perinatal infection risk factors. Samples were excluded from further analysis if there was any evidence of meningeal inflammation. Healthy infants admitted to the study fulfilled all of the following criteria: no signs of fetal distress, pH >7.2 in cord or venous blood, and Apgar scores >7 at 1–5 min. Other exclusion criteria were fetal or neonatal CNS malformations, chromosomal abnormalities, encephalitis, and congenital heart disease.

Real-time cerebral ultrasound scanning (Acuson 128SP5) was performed at the time of CSF sampling, at 72-h after admission, and on discharge from the hospital. In the controls, ultrasound patterns were evaluated before discharge from the hospital and at 72-h after birth.

In the asphyxiated group, the presence within the first 7 days after birth of HIE was classified according to Sarnat and Sarnat *(17)*. Electroencephalographic traces were recorded in the asphyxiated infants within 7 days of birth.

Neurologic examination was performed at the same time as the collection of CSF and daily. Neonatal neurologic conditions were classified qualitatively *(18)*, and each infant was assigned to one of three groups: normal, suspect, or abnormal *(19, 20)*. An infant was considered to be abnormal when one or more of the following neurologic syndromes were present: (*a*) increased/decreased excitability; (*b*) increased/decreased motility; (*c*) increased/decreased tonus; (*d*) asymmetries; (*e*) CNS defects; and (*f*) any combination of the above. When only isolated symptoms were present, the infant was classified as suspect.

CSF samples (150 μL) were centrifuged at 900*g* for 10 min, and supernatants were stored at −70 °C before measurement of activin A by ELISA (Serotec), which was performed in duplicate, as described previously *(21)*, without knowledge of the clinical classification. The assay detection limit was 10 ng/L, and samples were tested in a single run with intra- and interassay CVs of 2.5% [mean (SD), 1.01 (0.02) ng/L; n = 8] and 3.0% [0.92 (0.02) ng/L; n = 6], respectively.

Statistical significance was assessed by one-way ANOVA followed by the Tukey as a post hoc test, and the two-tailed Fisher exact test was used to compare the incidences of abnormal cerebral ultrasound results and neurologic outcome in patient groups. Data are expressed as the mean (SE). $P < 0.05$ was considered significant. Cutoff points for defining "high" CSF activin A concentrations for HIE prediction were chosen by ROC curve analysis *(22)*.

At birth, no significant differences were found between asphyxiated and control groups in weight, gestational age, or gender distribution (Table 1). According to the occurrence of HIE within the first 7 days after birth, asphyxiated infants were subdivided as follows: group A (n = 20), with no/mild HIE with good prognosis; and group B (n = 10), with moderate/severe HIE with a greater risk of neurologic handicap. Apgar scores at 1–5 min, pH, $Pvco_2$, base excess, and respiratory distress syndrome incidence were significantly ($P < 0.001$) different in asphyxiated newborns compared with controls regardless of the severity of HIE. Respiratory distress syndrome incidence (group A, 8 of 20 infants; group B, 5 of 10 infants), clinical and laboratory values, and cerebral ultrasound scans ($P > 0.05$ for all) did not differ between groups A and B.

At CSF sampling, periventricular hyperechogenicity

was observed in 16 of 30 asphyxiated infants (group A, n = 11; group B, n = 5; $P > 0.05$), but no significant ultrasound differences were found between the two asphyxiated subgroups. At 72 h, ultrasound was negative in all but six group B infants (middle cerebral artery infarction, n = 2; intraventricular hemorrhage, n = 2; intraventricular hemorrhage with ventricular dilatation, n = 2). In the controls, ultrasound patterns were negative for any CNS diseases.

Twenty of 30 asphyxiated infants were classified as suspect at neurologic examination on admission (hypohypertonia, n = 10; hyperexcitability, n = 10), but because of their severe clinical conditions, the effects of sedative drugs, and intervention by NICUs, neurologic examination was inconclusive, especially during the first 24-h after insult.

Activin A was measurable in all samples examined: its mean (SE) concentrations were significantly higher in group A [0.9 (0.04) μg/L; $P < 0.001$] and group B [1.88 (0.14) μg/L; $P < 0.001$] than in controls [0.43 (0.020) μg/L] and were significantly ($P < 0.001$) higher in group B than in group A (Fig. 1). The sensitivity and specificity of activin A as a diagnostic test were 100% [95% confidence interval ($CI_{95\%}$), 69.0–100%] and 100% ($CI_{95\%}$, 94.3–100%), respectively (cutoff >1.3 μg/L; area under the ROC curve, 1.00; $CI_{95\%}$, 0.951–1.00). Ten of 74 patients developed HIE, making the overall prevalence of the disease in our population 13.5% ($CI_{95\%}$, 0–34.6%). This was the predicted probability of developing HIE before activin A measurement (pre-test probability). At activin A concentrations >1.3 μg/L, the probability of developing HIE (positive predictive value) was as high as 100%, but if concentrations were unaltered, that probability (100 − negative predictive value) was 0% (Fig. 1).

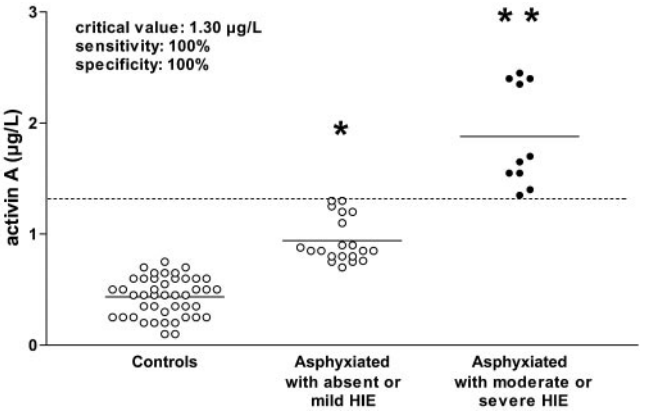

Fig. 1. CSF concentrations of activin A were significantly higher in asphyxiated full-term newborns than in healthy controls, mainly in those developing moderate or severe HIE.

Horizontal solid lines represent the mean of each group. The *horizontal dashed line* indicates the cutoff point (critical value) with the best separation between infants who developed severe HIE and those who did not or in controls. *, $P < 0.001$ vs controls; **, $P < 0.001$ vs asphyxiated infants with absent or mild HIE.

The present study demonstrates that full-term asphyxiated infants have higher CSF activin A concentrations than healthy newborns, suggesting that hypoxia/asphyxia may trigger activin A secretion. Furthermore, concentrations were higher in the asphyxiated infants who developed severe HIE than in those who did not or in controls, supporting the notion that increased activin A in the CSF is reasonably a direct expression of increased

Table 1. Clinical and laboratory values at birth in asphyxiated newborns with absent or mild HIE (group A) or with moderate or severe HIE (group B), and in healthy newborns (group C).

	Group A (n = 20)	Group B (n = 10)	Group C (n = 44)
Gestational age >36 weeks, n	20	10	44
Gender, M/F	16/14	6/4	23/21
Birth weight,[a] g	3328 (234)	3244 (334)	3252 (418)
Apgar score <3 at 1 min, n	20/20[b]	10/10[b]	0/44
Apgar score <3 at 5 min, n	20/20[b]	10/10[b]	0/44
ARDS,[c] yes/total	8/20[b]	5/10[b]	4/44
Erythrocyte count,[a] 10^6/mm^3	3.91 (0.1)	3.88 (0.1)	3.9 (0.07)
Hemoglobin,[a] g/L	134 (0.3)	136 (0.9)	136 (0.4)
Hematocrit,[a] %	40.3 (0.4)	40.4 (0.5)	41.1 (0.2)
Venous blood pH[a]	7.03 (0.01)[b]	7.00 (0.02)[b]	7.36 (0.06)
$Pvco_2$,[a] mmHg	69.6 (1.8)[b]	66.3 (4.9)[b]	41.3 (0.5)
Pvo_2,[a] mmHg	21.1 (0.9)[b]	19.1 (1.7)[b]	40.7 (0.6)
Base excess[a]	−13.5 (0.2)[b]	−13.1 (0.3)[b]	−0.2 (1.1)
Na^+,[a] mmol/L	139 (0.5)	139 (1.26)	140 (0.4)
K^+,[a] mmol/L	4.2 (0.2)	4.3 (0.1)	4.1 (0.1)
Ca^{2+},[a] mmol/L	1.11 (0.04)	1.12 (0.03)	1.14 (0.02)
Plasma glucose,[a] mmol/L	4.2 (0.2)	4.2 (0.4)	4.3 (0.07)
Urea,[a] mg/L	352 (18)	353 (9)	342 (8)
Creatinine,[a] mg/L	8.7 (1.3)	8.5 (0.9)	7.9 (3.6)

[a] Mean (SE).
[b] $P < 0.0001$ vs controls.
[c] ARDS, acute respiratory distress syndrome.

production in the CNS. Indeed, activin A induction represents a common response to acute neuronal damage of various origins in vitro *(5–14)* and was very similar to the response observed after hypoxic-ischemic injury. The role of such an increased secretion warrants considerations because it was proposed that the up-regulation of activin A in brain injury might serve as a neuroprotective factor: activin A enhances the survival of midbrain and hippocampal neurons *(11, 12)*; decrease ischemic brain injury in infant rats *(8)*; and shields striatal and midbrain neurons against neurotoxic damage *(12, 14)*. However, increased activin A concentrations have been reported in amniotic fluid of a patient who subsequently died from intrauterine fetal hypoxia *(23)* and in the plasma of hypoxic preterm newborns *(21)*, suggesting a role for activin A in the events cascade leading to hypoxic ischemic brain damage. Indeed, activin A release forms part of the CNS response to challenges involved in modulating inflammatory processes in the brain *(24, 25)*, the main mechanisms involved in brain damage attributable to hypoxia/asphyxia *(4)*, and it prevents apoptosis *(26)* and inhibits caspase *(27)*, two important pathways of neuronal death *(28)*. Its oversecretion in CSF may therefore serve to reduce cell death after brain insults.

Finally, CSF activin A concentrations were higher in the infants who developed severe HIE than in those who did not or in controls at a stage when ultrasound and other diagnostic procedures were still silent and were unable to indicate which infants would develop HIE. Conversely, already at this stage newborns with activin A above the threshold defined by the ROC curve analysis had a probability of developing HIE as high as 100%, supporting the notion that activin A assessment could provide additional information to physicians at an early stage, thereby permitting earlier adoption of therapeutic strategies.

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Within-Person, Among-Finger Variability of Capillary Blood Glucose Measurements, *Mary M. Kimberly,[1*] Samuel P. Caudill,[1] Hubert W. Vesper,[1] Steven F. Ethridge,[2] Enada Archibold,[1] Kimberly H. Porter,[3] and Gary L. Myers[1]* ([1] Clinical Chemistry Branch, Division of Laboratory Sciences, National Center for Environmental Health, [2] Behavioral and Clinical Surveillance Branch, Division of HIV and AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA; and [3] International Medical Press, Atlanta, GA; * address correspondence to this author at: Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention,