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● *Original Contribution*

CORRELATION OF QUANTITATIVE TEXTURE ANALYSIS OF CRANIAL ULTRASOUND WITH LATER NEUROBEHAVIOR IN PRETERM INFANTS

Violeta Tenorio,*† Elisenda Bonet-Carne,‡ Francesc Figueras,*†§ Francesc Botet,*† Angela Arranz,*† Ivan Amat-Roldan,‡ and Eduard Gratacos*†§

*Neonatal and Maternal–Fetal Medicine Department, ICGON, Hospital Clınic, Universitat de Barcelona, Barcelona, Spain; †Fetal and Perinatal Medicine Research Group, Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; ‡Transmural Biotech SL, Barcelona, Spain; and §Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain

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Abstract—The purpose of the study was to evaluate the association between a quantitative texture analysis of early neonatal brain ultrasound images and later neurobehavior in preterm infants. A prospective cohort study including 120 preterm (<33 wk of gestational age) infants was performed. Cranial ultrasound images taken early after birth were analyzed in six regions of interest using software based on texture analysis. The resulting texture scores were correlated with the Neonatal Behavioural Assessment Scale (NBAS) at term-equivalent age. The ability of texture scores, in combination with clinical data and standard ultrasound findings, to predict the NBAS results was evaluated. Texture scores were significantly associated with all but one NBAS domain and better predicted NBAS results than clinical data and standard ultrasound findings. The best predictive value was obtained by combining texture scores with clinical information and ultrasound standard findings (area under the curve = 0.94). We conclude that texture analysis of neonatal cranial ultrasound-extracted quantitative features that correlate with later neurobehavior has a higher predictive value than the combination of clinical data with abnormalities in conventional cranial ultrasound. (E-mail: egratacos@clinic.ub.es) © 2014 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Prematurity, Cranial ultrasound, Neurobehavior, Texture analysis, Quantitative ultrasound.**

INTRODUCTION

The incidence of premature birth has been progressively increasing since the mid- eighties, and it is known that preterm infants are at high risk of adverse neurodevelopment (Larroque et al. 2008; Marlow et al. 2005; Tucker and McGuire 2004). Approximately 5%–10% of very preterm infants will develop cerebral palsy, and up to 50% of them may have cognitive, behavioral, learning or visual deficits during childhood (Back et al. 2007; Hamrick et al. 2004; Volpe 2003). Prediction of adverse neurodevelopment, especially in the early postnatal period, remains one of the main challenges in current neonatology. The ability to better predict outcome in the infant period could substantially improve parental counseling. Serial cranial ultrasound (CrUS) is currently the standard method used to screen these high-risk patients. Ultrasound is readily available, inexpensive and non-invasive (de Vries and Groenendaal 2002). Abnormalities revealed on CrUS (Paneth 1999) are strong predictors of cerebral palsy and developmental delay (De Vries et al. 2004; Fily et al. 2006; Roth et al. 1994; Stewart et al. 1987; Wood et al. 2005), and conversely, a normal CrUS scan provides considerable confidence that an infant will have normal neuromotor development (Ancel et al. 2006; de Vries et al. 2004; Kuban et al. 2009; Stewart et al. 1987). However, whereas the association of cystic periventricular leukomalacia (PVL) with poor neurologic outcome is well documented (de Vries et al. 2001; Hamrick et al. 2004; O'Shea et al. 2008; Roelants-van Rijn et al. 2001), most infants with cognitive deficits do not manifest this pattern of injury, but a diffuse and more subtle one (Volpe 2003). Furthermore, the identification of brain damage using CrUS is limited partially because of the intrinsic subjectivity linked to clinical assessment. This is further influenced by different approaches to classification of abnormalities (Paneth 1999), differences in

Address correspondence to: Eduard Gratacos, Maternal–Fetal Medicine Department, Hospital Clínic–Maternitat, Sabino de Arana 1, 08028 Barcelona, Spain. E-mail: egratacos@clinic.ub.es

ultrasound machines and acquisition settings and variability in the experience of examiners, which results in a wide variation in the reported incidence of brain damage (Harris et al. 2006). In addition, below a certain threshold, subtle changes in tissue microstructure remain invisible to subjective inspection (Hope and Iles 2004; Hope et al. 2008). In this scenario, the use of quantitative analysis of medical imaging might potentially improve diagnosis robustness and reduce clinical variability.

Quantitative ultrasound analysis has long been proposed as a solution to improve the diagnosis of subclinical conditions (Back et al. 2007). Disease processes may alter the normal tissue structure or histology, which might change the reflection of ultrasound waves and, consequently, the ultrasound image rendered (Tunis et al. 2005). Quantitative ultrasound analysis aims to estimate tissue characteristics by extracting specific image features that can be measured consistently (Insana et al. 1989). Image texture analysis is one approach to quantitative ultrasound analysis. Texture methods are often inspired by how the visual system works in the human retina (Silverman et al. 1989), and discriminate textures by decomposing the image into a set of sub-bands (Landy and Bergen 1991). The use of texture quantitative analysis has been investigated for several medical diagnostic applications, including breast cancer, liver disease, fetal lung maturation and carotid atherosclerosis (Acharya et al. 2012; Alacam et al. 2003; Chen et al. 2002; Cobo et al. 2012; Hartman et al. 1991; Kadah et al. 1996; Palacio et al. 2012). With respect to white matter in neonates, several studies have investigated different approaches based on texture analysis to assess neonatal CrUS scans quantitatively (Barr et al. 1996; Stippel et al. 2002; Tenorio et al. 2011; Vansteenkiste et al. 2009). These studies support the idea that neonatal brain damage is associated with specific texture ultrasound patterns, which could be objectively detected by quantitative analysis of CrUS scans. However, the relationship between specific texture patterns in ultrasound quantitative analysis and subsequent neurodevelopment has not yet been assessed.

In the present study, we evaluated the association between quantitative ultrasound texture analysis performed early after birth and later neurobehavior. We studied a cohort of preterm infants born at <33 wk of gestational age. Early CrUS scans (within 7 d of delivery) were analyzed with a texture analysis method, which resulted in quantitative texture scores for each patient. An algorithm was applied to select the combination of early ultrasound texture scores that best predicted neurobehavior at term-equivalent age. We evaluated the predictive value of texture analysis, alone and in combination with clinical data and standard CrUS evaluation.

METHODS

Subjects

The cohort comprised 120 consecutive preterm infants delivered at a gestational age ≤33 wk between September 2007 and May 2010. Exclusion criteria included congenital anomalies, chromosomal or metabolic disorders and meningitis/encephalitis. The study protocol was approved by the ethics committee, and parents provided written consent.

Neurobehavioral assessment

For all infants, functional development was measured at term-equivalent age using the Neonatal Behavioural Assessment Scale (NBAS) (Nugent and Brazelton 2000), which assesses both cortical and subcortical functions by evaluating 35 items; the items are rated on a scale of 1 to 9 (with 9 being the best performance) except for 8 curvilinear scale items, which, according to the manual, are rescored as linear on a 5-, 6- or 8-point scale. Items are grouped into six domains: Habituation (habituation to light, rattle, bell and tactile stimulation of the foot); Motor (general tone, elicited activity, spontaneous activity, motor maturity); Social-Interactive (responses to visual, animate and inanimate auditory stimuli and alertness); Organization of State (irritability, state liability, maximal excitation, reaction time), Regulation of State (self-quieting, hand-to-mouth responses); and Autonomic Nervous System. All evaluations were performed by one of three trained examiners accredited by the Brazelton Institute (Harvard Medical School, Boston, MA, USA); examiners had been tested before this study for reliability and achieved an inter-rater reliability level ≥90%. The examiners were blinded to the study group and perinatal outcomes. Neonates were assessed in the afternoon, between feedings, in a small, semi-dark, quiet room with a temperature between 22°C and 27°C, in the presence of at least one parent. We defined an abnormal Brazelton score as one below the centile 10.

CrUS acquisition and evaluation

All infants underwent at least three scans: one within the first week of life, another at about 1 mo of age and the last one at term-equivalent age. All images were acquired using Siemens Sonoline Antares ultrasound equipment (Siemens Medical Systems, Malvern, PA, USA) with the P10-4 neonatal probe. All settings could be changed if clinically indicated. All exams were performed according to a protocol including five sagittal and six coronal plane images through the anterior fontanel. Images were digitally collected in the original Digital Imaging and Communications in Medicine (DICOM) format and stored in a custom program using a Graphical User