Cranial Ultrasound-Based Prediction of Post Hemorrhagic Hydrocephalus Outcome in Premature Neonates with Intraventricular Hemorrhage

Pooneh R. Tabrizi, Rawad Obeid, Awaiz Mansoor, Scott Ensel, Juan J. Cerrolaza, Anna Penn, Marius George Linguraru

Abstract—Premature neonates with intraventricular hemorrhage (IVH) followed by post hemorrhagic hydrocephalus (PHH) are at high risk for brain injury. Cranial ultrasound (CUS) is used for monitoring of premature neonates during the first weeks after birth to identify IVH and follow the progression to PHH. However, the lack of a standardized method forCUS evaluation has led to significant variability in decision making regarding treatment. We propose a quantitative imaging tool for the evaluation of PHH on CUS for premature neonates based on morphological features of the cerebral ventricles. We retrospectively studied 64 extremely premature neonates born less than 29 weeks gestational age, less than 1,500 grams weight at birth, admitted to our center within two weeks of life, and diagnosed with different grades of IVH. We extracted morphological features of the lateral ventricles from CUS imaging using image analysis techniques to compare neonates who needed a temporizing intervention to treat PHH to the ones who did not. From the original set of features, an optimal ranking was obtained based on linear support vector machine. A subset of features was subsequently selected that maximizes the overall accuracy level. Regarding whether or not there was a need for temporizing intervention, we predicted the outcome of PHH with an improved accuracy level of 84%, compared to the 76% rate obtained by linear manual measurement. The proposed imaging tool allowed us to establish a quantitative method for PHH evaluation on CUS in extremely premature neonates with IVH. Further studies will help standardize the evaluation of CUS in those neonates to institute treatments earlier and improve outcomes.

I. INTRODUCTION

Cerebral palsy is a significant neurological by-product of prematurity with about 10,000 infants diagnosed each year in the United States alone [1]. The incidence is highest in extremely preterm neonates born less than 30 weeks gestational age (GA) with an average occurrence of 60 per 1,000 live births, compared to 3 per 1,000 live births in late premature neonates (> 30 weeks GA) [2]. Premature neonates with intraventricular hemorrhage (IVH) followed by hydrocephalus (post – hemorrhagic hydrocephalus, PHH) are at the highest risk of severe palsy and other adverse neurodevelopmental outcomes [3, 4]. IVH originates from the germinal matrix in the caudothalamic groove in the brain and can extend into the ventricular cavities causing impairment of the cerebrospinal fluid (CSF) flow and leading to PHH. PHH can compromise the developing white matter tracts around the ventricles, eventually leading to white matter injury associated with cerebral palsy [5, 6].

Cranial ultrasound (CUS) is a safe and easy imaging test to perform in neonates that allows identifying IVH and evaluating the size of the ventricles as a sign for PHH. Ventricular enlargement on CUS has been shown to correlate with multiple neurodevelopmental outcomes in this population, making it a potential biomarker for cerebral injury [7]. However, the ventricular evaluation is still qualitative based on the sonographer’s experience or quantitative based on two dimensional (2D) visually estimated measurements, such as the ventricular index (VI) [8-10], ventricular angle (VA) [11, 12], frontal and temporal horn ratio (FTHR) [13], and anterior horn width (AHW) [8, 9]. Those methods of ventricular evaluation have not been successful in differentiating PHH that may have benefited from an early intervention to improve outcome [14]. This could be explained by the subjectivity and high inter-rater reliability of those methods. Moreover, 2D visually estimated measurements lack the robustness to efficiently describe the ventricle shape.

In our previous work for children with hydronephrosis [15-17], we showed that quantitative image analysis of renal ultrasound can predict the severity of the condition and the necessity of additional examinations by diuretic nuclear renography. In this work, we create a new quantitative imaging framework to automatically quantify the morphology of the cerebral ventricles in early CUS. We also employ a machine learning framework to analyze the morphological features in order to predict the potential need for temporizing intervention in premature neonates.

II. MATERIALS

This is a retrospective study of extremely premature neonates who were admitted to a neonatal intensive care unit (NICU) at Children’s National Health System between the years of 2011-2014. Inclusion criteria for the study: (1) less than 29 weeks GA, (2) less than 1,500 grams birth weight, and (3) with different grades of IVH. We identified 64 neonates who met these inclusion criteria for the study. All
cases were diagnosed with IVH on CUS within the first week after birth. Mean age at first CUS was 3±3 days. As part of our center’s guidelines, CUS is done on all premature neonates less than 32 weeks GA within 24 hours after admission. If no IVH is noted, CUS is repeated at days 7, 14, and 42 after birth per the American Academy of Neurology practice parameters. In case of IVH, CUS is repeated weekly to monitor for PHH, until IVH and/or PHH is stable or resolved on at least two consecutive scans. If there is progression of PHH on two or more CUS scans, a neurosurgical consult is requested to decide about performing a temporizing or permanent surgical intervention based on the severity of the prior clinical and radiographic criteria, and weighing risks versus benefits. CUS scans are interpreted by a pediatric radiologist and are performed using a GE LOGIQ E9 (GE Healthcare Ultrasound, Waukesha, Wisconsin, USA) medical ultrasound system. Overall, 23% (15/64) of infants with IVH received at least one temporizing intervention to treat PHH during the NICU course (14 received a lumbar puncture and 1 received a ventricular access device). In this work, the goal is to differentiate intervention-needed cases from 49 no intervention-needed cases based on the morphological information extracted of the lateral ventricles from early CUS.

III. METHODS

In Fig.1, an overview of our method is illustrated. As a first step, all CUS studies for every neonate were reviewed by one neurologist (RO) to identify the first CUS performed in our institution after birth. Once the CUS is identified, a slice in the coronal plane at the level of the foramen of Monro was selected for evaluation. The shape of the frontal horns of the lateral ventricles was manually segmented using the ITK-SNAP software [18]. The segmentation procedure takes less than one minute for each case. In Fig. 2, one sample of a CUS slice in a coronal view with manual segmentation of both ventricles is shown.

Once the ventricles have been localized, morphological quantitative parameters were extracted from both left and right lateral ventricles, which could be divided into the following two categories (examples of the extracted quantitative parameters are illustrated in Fig. 3):

**Manual morphological parameters:** VI and FTHR were manually measured by a neurologist (RO). VI is defined as the distance between the falx and the lateral wall of the anterior horn in the coronal plane [9]. FTHR is determined as half of the sum of the frontal and temporal horn width divided by the broadest skull diameter at the level of the foramen of Monro [13]. We used those parameters to compare their performance to predict outcome versus our automated morphological analysis described in the next section.

**Automated morphological parameters:** In total, we considered 70 morphological parameters. We chose to consider 8 of these parameters based on measurements from the previous hydrocephalous studies [8-13], of which include VI, FTHR, VA, and AHW from each ventricle. VI and FTHR are defined as the previous section (Manual morphological parameters), but were instead calculated automatically using image processing techniques. VA is the angle made by the anterior or superior margins of the frontal horn at the level of the foramina of Monro [12]. AHW is calculated as the diagonal width of the anterior horn measured at its widest point in the coronal plane [9].

A portion of the remaining 62 parameters are inspired from our presented work for the shape analysis of the kidney and collecting system for pediatric hydronephrosis [15-17] including: (1) size descriptors, such as eccentricity, (2) geometry shape descriptors, such as the ventricle medial axis along with the Hu set of five invariant moments, and (3) curvature descriptors, such as the average, entropy, and maximum values of the ventricle curvatures.

The rest of the parameters are newly extracted to efficiently describe the anatomy of both lateral cerebral ventricles and to capture the dissimilarity between them. These features include: (1) asymmetry between the lateral ventricles, (2) the lengths and ratios of the axes of the circumscribed ellipses enveloping the ventricles, (3) the angle between the two ventricles, (4) the statistics of ventricle thickness in the vertical direction, and (5) the ventricle area. To compensate for inter-patient variability, we normalized these features by the size of the manually determined bounding box encompassing the brain. Also, instead of verifying morphological parameters obtained for each ventricle separately, predictive parameters were determined from the overall maximum and minimum along with the ratio between the left and right ventricle variables.

**Feature selection and classification:** 70 extracted morphological features were ranked based on their importance in classification using the supervised feature selection method based on linear support vector machine (SVM) proposed by Brank et al. [19]. The goal of the classification is to recognize probability thresholds based on the highest maximization of detecting intervention-needed cases to ensure that cases with severe IVH progression are not missed.

The predictive model of temporizing intervention was created and evaluated using two popular classifiers: logistic regression analysis (LOG) and linear SVM [15,19]. The parameter optimization was achieved via grid search with a cross-validation strategy [20] applied for training and testing purposes.
Figure 2. Slice selection of 2D cranial ultrasound with segmentation. a) Selected slice in the coronal view containing the lateral ventricles, b) manual segmentation of two ventricles.

Figure 3. Illustration of morphological parameters: ventricular angle (VA), ventricular index (VI), anterior horn width (AHW), medial axis of ventricle, major and minor axes of the circumscribed ellipse, asymmetry between two centroids and head width.

Since the number of cases in the two classes (15 intervention-needed and 49 no intervention-needed neonates) are different, 15 iterations were performed for cross validation. In each iteration, 14 intervention-needed and 14 no intervention-needed cases were randomly selected and used for training. The test step was done using the remaining one intervention-needed and 35 no intervention-needed cases. Iterations were repeated until each intervention-needed case was tested once. For each iteration, receiver operating characteristic curve analysis was used to determine the probability threshold with the highest sensitivity. After cross-validation, the optimal set of features for each classifier (LOG and SVM) was identified using evaluation of the overall accuracy level based on different number of features (see the Results section).

IV. RESULTS

Following the procedure described in the method section, the overall accuracy level was calculated for each classifier based on different feature numbers, as shown in Fig. 4. A set of 10 and 5 features were selected for SVM and LOG, respectively, whose descriptions are reported in Table I.

The performance of each classifier was evaluated using the specificity, sensitivity, and accuracy measurements, whose numerical values are listed in Table II. In this table, the predictability of our automatic measurements was compared with two clinical manual parameters (VI and FTHR) measured by a neurologist (RO). The best performance was obtained using our quantitative imaging-based prediction model (our method), which achieved accuracy, sensitivity and specificity of 0.84, 1, and 0.68, respectively. These results were an improvement over using only clinical manual measurements.

TABLE I. SELECTION OF MORPHOLOGICAL DESCRIPTORS BETWEEN LEFT VENTRICLE (LV) AND RIGHT VENTRICLE (RV) USED AS PREDICTIVE PARAMETERS FOR SVM (MARKED WITH (*) AND LOG (MARKED WITH (^))

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1*^</td>
<td>Maximum value of medial axis lengths</td>
</tr>
<tr>
<td>P2*^</td>
<td>Asymmetry of centroids between LV and RV</td>
</tr>
<tr>
<td>P3*^</td>
<td>Maximum value of AHWs</td>
</tr>
<tr>
<td>p4*</td>
<td>Maximum value of the normalized ventricle areas based on the area of the circumscribed ellipses</td>
</tr>
<tr>
<td>p5*</td>
<td>Minimum value of the normalized ventricle areas based on the area of the circumscribed ellipses</td>
</tr>
<tr>
<td>P6*</td>
<td>Angle between LV and RV</td>
</tr>
<tr>
<td>P7*</td>
<td>Ratio of VIs, LV to RV</td>
</tr>
<tr>
<td>p8*</td>
<td>Maximum value of the major axis length of the circumscribed ellipses</td>
</tr>
<tr>
<td>p9*^</td>
<td>Ratio of entropies of the ventricle thicknesses, LV to RV</td>
</tr>
<tr>
<td>P10*^</td>
<td>Maximum value of the axes ratio of the circumscribed ellipses, LV to RV</td>
</tr>
</tbody>
</table>

The best number of features = 5

Best number of features = 10

Figure 4. The overall accuracy level of our method versus the different number of features for each classifier.

TABLE II. COMPARISON BETWEEN THE PREDICTABILITY OF OUR METHOD AND THE CLINICAL MANUAL MEASUREMENTS (VI AND FTHR) USING TWO CLASSIFIERS BASED ON THE BEST NUMBER OF FEATURES: AVERAGES OF SENSITIVITY, SPECIFICITY, AND ACCURACY LEVEL ARE PRESENTED.

<table>
<thead>
<tr>
<th>Our Method</th>
<th>Classifier</th>
<th>#Features</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVM</td>
<td>10</td>
<td>1.00</td>
<td>0.68</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>LOG</td>
<td>5</td>
<td>1.00</td>
<td>0.64</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Clinical Manual Measurements (VI and FTHR)</td>
<td>Classifier</td>
<td>#Features</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Accuracy</td>
</tr>
<tr>
<td>LOG (based on VI)</td>
<td>1</td>
<td>1.00</td>
<td>0.53</td>
<td>0.76</td>
<td></td>
</tr>
<tr>
<td>LOG (based on FTHR)</td>
<td>1</td>
<td>1.00</td>
<td>0.5</td>
<td>0.75</td>
<td></td>
</tr>
</tbody>
</table>
V. DISCUSSION AND CONCLUSION

We presented a new CUS-based quantitative imaging tool to predict temporizing intervention for PHH. Our model used novel and comprehensive feature combinations able to relate the PHH outcome using early CUS scan, which outperforms approaches using the limited parameters available by clinical manual measurements (VI and FTHR).

Including the previously defined parameters for PHH (VI, VA, ASW, and FTHR) [8-13], we considered a total of 70 morphological parameters, which were calculated automatically from the 2D CUS images via image analysis techniques. The morphological parameters describe the shape of the left and right frontal horns of the lateral ventricles and dissimilarity between them. A selection of these features was performed using a machine learning (i.e., linear SVM) classifier to maximize the predictive sensitivity to identify neonates who will require intervention in the future. The accuracy level of our model is 0.84 with sensitivity of 1 and specificity of 0.68 using the SVM classifier. These preliminary results demonstrate how quantitative image analysis of cerebral ventricles from early CUS could be useful to noninvasively predict the progression to severe PHH in premature neonates with IVH. This approach has the potential to help identify neonates who are at risk sooner and decide early preventive treatment. In future work, we expect to increase the number of cases for evaluation and automate the segmentation procedure of the ventricles.

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REFERENCES