Brief Report

Three-Dimensional Map of Neonatal Arterial Ischemic Stroke Distribution From Early Multimodal Brain Imaging

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Background and Purpose—Although neonatal arterial ischemic stroke (NAIS) location has considerable impact on long-term outcome, a map showing spatial distribution of NAIS is lacking. Our aim was to generate this distribution map, based on early magnetic resonance imaging data.

Methods—Lesions from 34 consecutive neonates with NAIS from a single center were segmented using multimodal magnetic resonance imaging (median age at acquisition =5 days). Lesion masks for all subjects were registered onto a standard neonatal brain and then overlaid to generate a 3D map of NAIS distribution.

Results—The region posterior to the central sulcus is the most frequently affected in neonates, with 24 of the 34 neonates (71%) showing lesions in this region in at least one hemisphere. Moreover, NAIS frequency is markedly higher in the left hemisphere.

Conclusions—This is the first report of an NAIS distribution map. Regions posterior to the central sulcus present increased vulnerability. Our findings suggest that motor areas are not as frequently affected as has been previously reported. By contrast, we find high NAIS vulnerability in functional areas related to language. The distribution of ischemic strokes in neonates seems to be different from that seen in adults. **(*Stroke*. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.014186.)**

Key Words: ischemic stroke ■ multimodality imaging ■ neonatal ischemia

Neonatal arterial ischemic strokes (NAIS) are cerebrovascular arterial events occurring during neonatal life, before 28 days after birth. Newborns, along with the elderly, are at the highest risk of having a stroke.[1] The location of NAIS seems to predict long-term neurological outcome.[2,3] In neonates, the territory of the middle cerebral artery is that most frequently affected by NAIS, with up to 93% of strokes occurring in this region.[3,4] There is a wide range of possible outcomes after an NAIS, with motor and language deficits being the most common. The estimated prevalence of motor deficits in children who have suffered an NAIS is 25% to 50%, while the estimated prevalence of language deficits is 20% to 25%.[5] Despite the importance of the location of NAIS for outcome prediction, a neonate brain map showing their spatial distribution is lacking. By contrast, the distribution of stroke in adults has been extensively studied.[6]

Our aim in this study was to generate a map showing the distribution of NAIS from early magnetic resonance imaging (MRI) data. To achieve this, we segmented lesions from 34 consecutive neonatal patients and overlaid them simultaneously on a standardized newborn brain. To locate each lesion more precisely, a multimodal segmentation methodology was used.

Materials and Methods

Patients

Thirty-four newborns with NAIS (12 females), consecutively admitted to a single tertiary unit (Hospital Sant Joan de Déu-Hospital Clinic, Barcelona) between 2010 and 2016, were included in the study. The inclusion criteria were newborn infants (>36 gestational weeks) with symptomatic NAIS later confirmed by MRI. The medical ethics committee of our institution approved the study, and parents of all the subjects signed an informed consent.

MRI Data Acquisition

MRI was performed on a General Electric 1.5 T Signa Excite scanner at Hospital Sant Joan de Déu using the neonatal head coil following the clinical MRI protocol for neonates with suspected NAIS. Median age at MRI acquisition was 5 days (interquartile range =5). Structural T1, axial and coronal T2, and diffusion acquisition parameters are described in the online-only Data Supplement.

Individual MRI Image Analysis

The lesion segmentation process was performed through the multimodal analysis of MRI images with ITK-Snap software, version 3.0 (http://www.itksnap.org).[7] To simultaneously display images from the different acquisition modalities, the linear transformation *flirt* function of the FSL suite, version 5.0 (http://fsl.fmrib.ox.ac.uk), was used: for each subject, the diffusion, coronal T2, and axial T2

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images were registered to the more anatomically precise T1 image. Then, the region competition preprocessing function of ITK-Snap was applied using 5-tissue clustering, 0.5 region competition force, and 0.5 smoothing force. Once a satisfactory lesion segmentation was attained in the evolution step, it was manually corrected by simultaneously inspecting its features in all the imaging modalities, as well as its 3D visualization. In this step, consensus by 3 experts blind to radiological diagnosis was reached.

Creation of an NAIS Probability 3D Map

The brains of all subjects, along with the corresponding NAIS segmentations, were elastically registered to a neonatal high-resolution brain template[8] previously registered to a standardized neonatal anatomic space[9] using ANTs software (http://www.ants.org). The NAIS probability map was then created by adding all NAIS segmentation masks. Finally, Gaussian smoothing with full width at half maximum =2 mm was applied to the composite map.

Results

The mean weight at birth of the newborns was 3135±471 g, the mean gestational age was 39.3±1.8 weeks, and clinical symptoms started 24 hours (interquartile range =29.75) after birth. The type and frequency of first clinical manifestation are presented in Table I in the online-only Data Supplement. The full brain NAIS distribution map is shown in Figure 1. The region posterior to the central sulcus was affected in 24 out of the 34 cases (71%) in at least one of the hemispheres, whereas the corticospinal tract was involved in 7 out of the 34 cases (21%) studied. Given the uneven incidence of NAIS in the two hemispheres (18 of them were located in the left hemisphere, 11 in the right hemisphere, and the remaining 5 affected both hemispheres), Figure 2 depicts the spatial distribution for each hemisphere separately.

Discussion

To our knowledge, this is the first report of an NAIS distribution map. The region posterior to the central sulcus is the most affected, suggesting an increased vulnerability. In addition, the left hemisphere is more frequently affected than the right, in accordance with previous reports.[2,4] Despite this, both hemispheres show symmetrical involvement patterns. Neonatal MRI enables prediction of motor outcome in NAIS patients by locating the stroke area according to the corticospinal tract,[4] which is affected in only 21% of the cases studied. On the other hand, lesions involving the arcuate fasciculus seem to account for language deficits.[10] The arcuate fasciculus is closer to our high-vulnerability region, involved in up to 71% of cases.

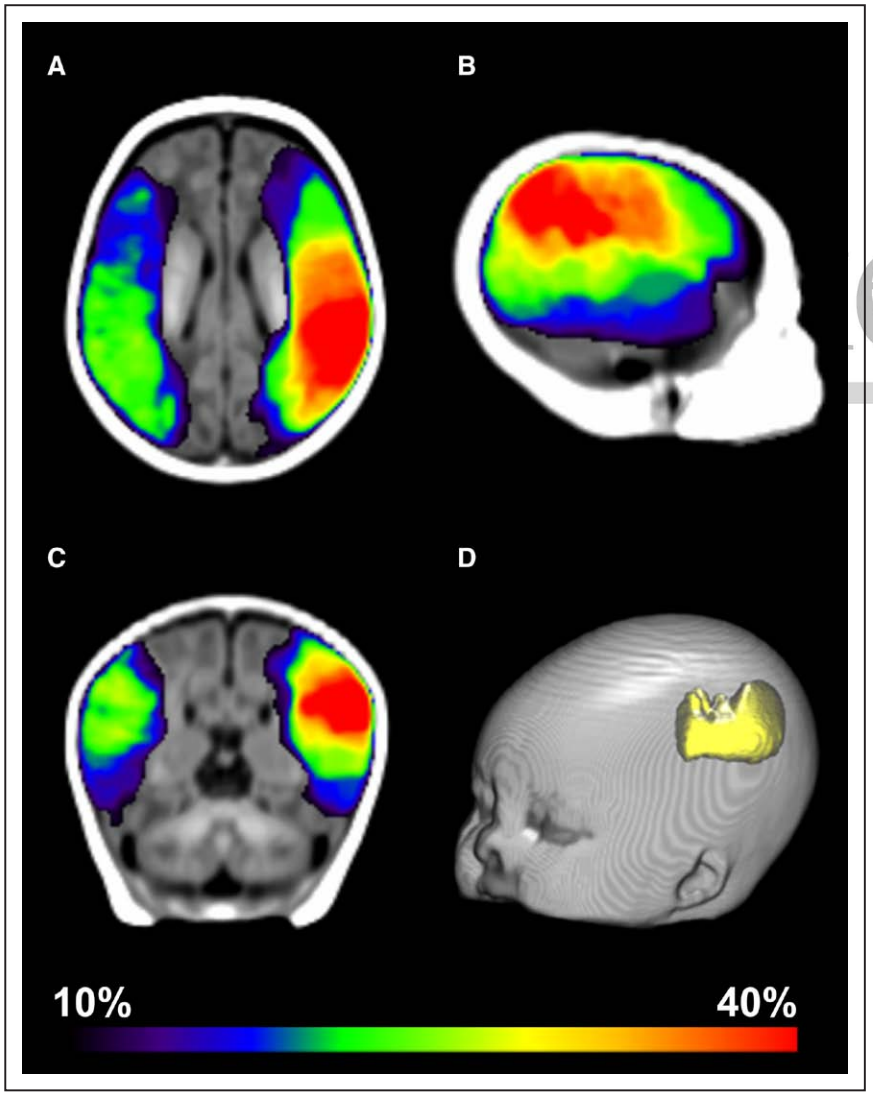

Figure 1. A, Axial; **B**, sagittal; **C**, coronal; and **D**, 3D view of the full brain neonatal arterial ischemic stroke (NAIS) distribution map. For **A** to **C**, only regions where at least 10% of the NAIS overlapped are colored. The highest intensity color means an NAIS overlap of at least 40% of the subjects. For **D**, the region in which at least 50% of the NAIS overlapped in the left hemisphere is depicted in yellow. The image shows a radiological orientation, with the left hemisphere in the right side.

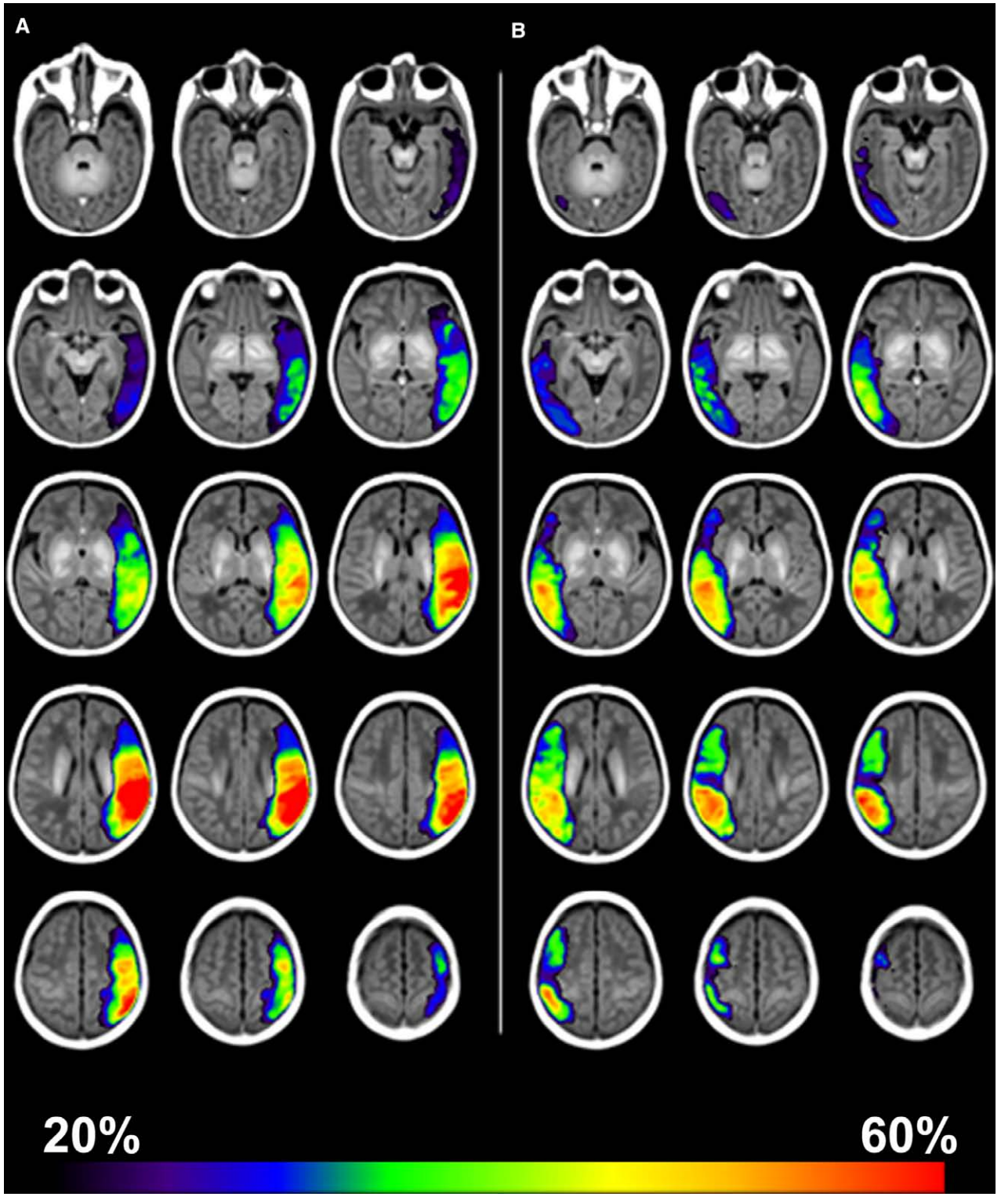

Figure 2. Multislice axial view of the neonatal arterial ischemic stroke (NAIS) distribution map for (**A**) the left hemisphere and (**B**) the right hemisphere. For **A** and **B**, those regions in which at least 20% of the NAIS overlapped are colored. The highest intensity color indicates that at least 60% of the NAIS overlapped in that location. The image shows a radiological orientation, with the left hemisphere in the right side.

Furthermore, in a study of 7-year-old children who suffered an NAIS in the middle cerebral artery, a lesion frequency map at pediatric age showed a different spatial distribution between children with and without cerebral palsy. Those without cerebral palsy had more focal and posterior lesions,[11] similar to the spatial distribution reported in this study.

Our findings suggest that motor areas are not as frequently affected as has been previously reported in neonates, which is

in accordance with recent studies finding between 24% and 26% motor disability in symptomatic neonatal stroke.[2,4] More recently, Chabrier et al[12] found language deficits in half of the sample used in the study of Dinomais et al,[11] and these were more prevalent than motor deficits. Overall, motor impairments after an NAIS may be overrepresented in the literature. By contrast, impairments in other functions, such as language, may be underestimated. This could be because of biases in the studies including only presumed NAIS. These lesions are typically identified by motor impairment, while language deficits, being more subtle, could remain unnoticed or associated to other causes.

Finally, our NAIS map follows a different pattern from stroke distribution maps in adults.[6] The NAIS distribution reported here suggests that branches originating from the posterior trunk of the middle cerebral artery are more commonly affected by emboli than those from the anterior trunk in neonates. Although the reasons for this are not known, anatomic factors could play a role. The posterior trunk of the middle cerebral artery is larger, and branches leading to the parietal regions posterior to central sulcus follow a straighter course, probably making it more likely for emboli to travel to this region.[13]

The present study has some noteworthy strengths. First, we used an ecological symptomatic NAIS sample of patients recruited from a single center. In addition, we included consecutive confirmed NAIS cases without location or volume constraints. Finally, we used a novel segmentation technique, not previously used in a neonatal population with NAIS, which allowed us to locate infarcts in a more precise manner from early MRI data. On the other hand, recruiting patients from a single hospital, together with the relatively low incidence of NAIS, limited our ability to gather a larger sample.

In conclusion, we have generated, for the first time, an NAIS distribution map. The distribution of arterial ischemic strokes in neonates seems to be different from the distribution in the adult population, affecting mostly areas related to language.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

A 3D map of neonatal arterial ischemic stroke distribution from early multimodal brain imaging

MRI acquisition protocol:

Structural T1: TR = 12.64 ms, TE = 5.75 ms, voxel size = 0.4 × 0.4 × 1.0 mm^3, FOV = 20 cm; diffusion-weighted images: TR = 8300 ms, TE = 94.1 ms, voxel size = 0.8 × 0.8 × 5.0 mm3, FOV = 20 cm, b=1000; axial T2: TR = 3000 ms, TE = 11 ms, voxel size = 0.31 × 0.31 × 6.0 mm3, FOV = 16 cm; coronal T2: TR = 4560 ms, TE = 65 ms, voxel size = 0.31 × 0.31 × 4.0 mm3, FOV = 16 cm. The flip angle for T1 was 20^o, while it was 90^o for the rest.

Table I. First clinical manifestation presented by the neonates.

Clinical presentation	Number of neonates	%
Focal clonic seizures	21	61.8
Multifocal clonic seizures	3	8.8
Apnea*	7	20.6
Apnea/lethargy*	2	5.9
Apnea/hypotonia*	1	2.9

* The 10 neonates that presented apnea as the first clinical manifestation later presented apneic events simultaneously with epileptic spells on continuous aEEG monitoring.