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1. TITLE PAGE:

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Highlights

- Massive infarction appears to be a distinctive subtype of neonatal infarction.
- Neonates with Massive infarction consistently present moderate to severe adverse outcome.
- Early Massive infarction identification would for prompt, specific interventions.

Key words: Neonatal arterial ischaemic stroke, massive infarction volume, oedema, brain midline shift.

Massive Neonatal Arterial Ischemic Stroke

ABSTRACT

Purpose: Massive infarction in adults is a devastating entity characterized by signs of extreme swelling of the brain's parenchyma. We explored whether a similar entity exists in neonates, which we call Massive Neonatal Arterial Ischemic Stroke (M-NAIS), and assess its potential clinical implications.

Methods: Prospective multicentre cohort, comprising 48 neonates with ≥ 35 weeks of gestation age with middle cerebral artery (MCA) NAIS. Diagnoses with MRI were performed within the first 3 days after symptom onset. The presence of signs of a space occupying mass, such as brain midline shift and/or ventricular and/or extra-axial space collapse, was recorded. The volume of the infarct and brain midline shift were determined with semiautomatic procedures. Neurodevelopment was assessed at 24 months of age.

Results: Fifteen (31%) neonates presented MRI signs of a space-occupying mass effect and were considered to have an M-NAIS. The relative volume (infarct volume/total brain volume) of the infarct was in average significantly greater in the M-NAIS subgroup (29% *vs.* 4.9%, p <0.001). M-NAIS patients consistently presented lesions involving the M1 arterial territory of the MCA, and showed more apneic and tonic seizures, which had an earlier onset and lasted longer. Moderate to severe adverse neurodevelopmental outcomes were present in most M-NAIS cases (79% *vs.* 6%, p <0.001).

Conclusions: M-NAIS appears to be a distinctive subtype of neonatal infarction, defined by characteristic neuroimaging signs. Neonates with M-NAIS frequently present a moderate to severe adverse outcome. Early M-NAIS identification would

allow for prompt, specific rehabilitation interventions, and would provide more accurate prognostic information to families.

INTRODUCTION

Neonatal arterial ischemic stroke (NAIS), a major cause of long-standing neuro-disability, is defined as an acute symptomatic focal cerebral infarction localized in an arterial territory diagnosed between birth and 28 days of life that is confirmed by neuroimaging [1].

NAIS has a complicated nature due to the uncertainty about when it occurs, the diversity of risk factors involved, and the heterogeneity of lesion location even within the same arterial territory. There is also wide variability in the size and volume of NAIS-derived lesions. Previous studies have observed that large infarcts are highly predictive of poor outcome [2-6].

In adults, massive middle cerebral artery (MCA) infarction is one of the most devastating forms of ischemic stroke since it is associated with an 80% mortality rate with conservative medical management [7,8]. When CT shows a stroke that involves more than 50% of the MCA territory or a volume greater than 145 cm^3 between 2 and 14 hours from the onset of symptoms, it is defined as a massive or malignant infarct [8-11]. Among the neuroimaging features described, brain midline shift (MLS) and collapsed ventricles are important indicators of malignant infarction, providing prognostic information and determining the treatment needed [12]. Malignant infarction has also been described in children, representing fewer than 2% of cases of pediatric arterial ischemic stroke [13]. We aimed to explore whether an analogous type of arterial ischemic infarction, which we call Massive NAIS (M-NAIS), occurs in neonates. Moreover, we considered which specific clinical and neuroimaging characteristics define this NAIS subtype, and we report its effect on outcomes at 2 years of age.

METHODS

Patients

This is a sub-study of a prospective observational multicentre study including 48 infants with symptomatic NAIS located in the MCA. The study was conducted in six paediatric university hospitals in Spain from January 2010 to December 2017. All consecutive cases with at least 35 weeks of gestation who presented a symptomatic MCA-NAIS within the first 28 days of life were included. Exclusion criteria were: a) MRI suggestive of an old infarction that occurred before birth, b) vascular malformation, c) moderate to severe hypoxic-ischemic encephalopathy (HIE), d) congenital or chromosomal anomalies, e) metabolic (including persistent hypoglycemia) or infectious diseases, and f) complex heart congenital anomalies. For this sub-study, we also excluded those infants with MRI performed more than 8 days after symptom onset. Brain electrical activity of all patients was monitored on admission to the NICU by bichannel amplitude integrated electroencephalography with two channels of raw EEG. Clinical seizures were classified using Volpe's classification but they were considered true neonatal seizures if they were associated with paroxysmal, abnormal, and sustained ictal rhythm in the aEEG [14,15].

Cerebral magnetic resonance imaging

All MRI studies were performed using 1.5 Tesla units (General Electric). MRI was performed at a median age of 3 days (P_{25}-P_{75}: 2.75-6). The acquisition protocol has been described elsewhere [16]. Diffusion-weighted imaging (DWI) data were available in all cases.

Distribution of the site of MCA occlusion and labelling

Infarcts were classified by 2 observers (AGA and GA) blinded to the clinical data, according to the middle cerebral artery segments and branches involved. Differences in

the anatomical location of NAIS were resolved by consensus among the observers, as previously described elsewhere [17].

Two groups of patients were defined according to signs of space-occupying brain swelling: M-NAIS, in which MRI findings of brain MLS and/or ventricular and/or extra-axial space collapse were present, and NonM-NAIS, in which these features were not present (see supplementary Figure 1).

Brain midline shift and lesion volume quantification

1. Brain midline shift

We employed a high-resolution neonatal template [18], previously registered to a standardized neonatal anatomic space [19], in which we delineated the theoretical brain midline and defined 9 different points of interest, distributed along 3 axial planes

(Figure 1), at each of which we measured brain MLS (i.e., the distance [in mm] between the real observed brain midline and the theoretical one) in our neonatal sample. We used non-elastic deformations to register all the high-resolution T1 images to the previously mentioned neonatal template in order to achieve precise alignment without modifying the brain structure of the neonates. We employed ITK-Snap (v3.8.0; http://itksnap.org) [20] to automatically perform this registration process; in some cases, we performed slight manual corrections to improve the accuracy of the registration. Afterwards, brain MLS was measured for each neonate at all 9 points using the 'Line and Ruler' tool available in ITK-Snap. We then computed the mean brain MLS by averaging all the distances obtained.

2. Lesion volume

MRI volumetric segmentation of the lesions was performed independently by 2 researchers (CSO and CN); both of them were blinded to neuroimaging diagnosis and

clinical data. NAIS volume included only primary lesions, and excluded distant changes by pre-Wallerian degeneration [5]. The process was performed through the multimodal analysis of MR images with ITK-Snap software [20]. The entire procedure has been described in detail elsewhere [16]. Total infarct volumes were expressed in cubic centimeters (cm^3), and the relative infarct volume (RIV) in percentages. The latter was obtained in terms of total brain volume, excluding the cerebellum.

In order to examine whether the NAIS in the MCA extended to adjacent territories, each lesion was registered to a three-dimensional map of the arterial territories of the neonatal brain [21]. We considered an adjacent territory to be affected if the lesion spanned at least 10% of its volume.

Outcomes

Serial head circumference (HC) measurements were made up to 24 months, and microcephaly was defined as an HC more than two SD below the mean for gender and age [22].

The Gross Motor Function Classification System (GMFCS) was used to grade functional impairment in infants who have cerebral palsy. Further, the outcome at 24 months was assessed using the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III) [23]. Mild adverse outcome was considered when there was a Bayley-III score between -2 SD and -1 SD (70 to 85) on any of the domains, and/or a GMFCS level I. The moderate-severe adverse outcome was defined as -2 SD (MDI or PDI <70) in any Bayley-III domains, and/or GMFCS level II-V.

Three patients were partially lost during the follow-up as their Bayley Score III (BSITD-III) was not performed; two of them belonged to the NonM-NAIS group and one to the M-NAIS group.

Statistical analysis

All the analyses were performed with SPSS v25.0 (IBM Corp., Armonk, NY). Perinatal, clinical, and imaging data were compared between groups by means of t or χ^2 tests, as appropriate. Bivariate correlations were carried out to analyze relationships between variables. Differences with associated p values below 0.05 were considered statistically significant. In order to assess the clinical relevance of considering the M-NAIS group, receiver operating characteristic (ROC) curves were computed for some of the outcome variables. For each of these variables, cutoff points for lesion volume and brain midline shift were estimated.

Ethics

The medical research ethics committee of each institution approved the study, and written consent was obtained from the parents. PIC-150-15.

RESULTS

Of the 48 neonates with NAIS included in the study, 15 (31%) showed signs of space-occupying swelling and met the neuroimaging criteria that we used to define massive infarction (M-NAIS). MRI scans were obtained earlier in infants with M-NAIS *vs.* NonM-NAIS. Median time from symptom onset to imaging was 66 (P_{25}-P_{75}: 41-96) *vs.* 90 (66-155) hours, respectively (p=0.07). Demographic characteristics and clinical signs of all infants are summarized in Table 1.

The most common clinical presentation was clonic seizures (73%). However, the type of clinical seizure was significantly different between the two groups (p=0.027). While in NonM-NAIS hemicorporal clonic seizures were present in 28 cases (85%), in M-NAIS this type of seizure was only present in 7 infants (47%). Another 7 (47%) within this group presented with tonic or apnea seizures. Furthermore, the group with M-NAIS had an earlier clinical onset of seizures (20 hours *vs.* 35 hours in NonM-NAIS, p

<0.001) and they were convulsing for longer until complete seizure remission was achieved (p <0.001, Table 1).

MRI findings

M-NAIS and NonM-NAIS lesion topology and volume

In 36 (75%) neonates the NAIS was unifocal, mainly located on the left side in 22 of them (61%), and multifocal in 12 (25%), being bilateral in 10 (21%) neonates. The infarct distribution of the MCA territory and qualitative MRI findings are presented in Table 2 (Online Resource 2). None of them died nor showed signs of transtentorial herniation or brain stem compression. All 15 neonates with M-NAIS had M1-MCA arterial territory involvement, versus 7 (21%) in the NonM-NAIS group. Patients with M-NAIS both showed significantly greater absolute volume than the group without M-NAIS (102.7cm^3 [Q1: 69.4, Q3: 147.6] *vs.* 17.4cm^3 [8.1,28.9], p <0.001), as well as greater relative infarct volume (29% [19.6,41.7] *vs.* 4.9% [2.3, 8.2]; p <0.001). The brain MLS was greater in the patients with M-NAIS, and brain MLS of the NAIS correlated significantly with infarct volume (r = 0.54, p < 0.001).

According to the 3D map of arterial territories of the neonatal brain [14], 13 patients (87%) with M-NAIS apparently showed a lesion extending to the bordering PCA territory, while this happened in only 9 (27%) with NonM-NAIS (p<0.001,Table 2 in the Online Resource 2).

Massive NAIS and outcome

Twenty-two (46%) of all NAIS had an adverse outcome, with this evolution being more frequent in the M-NAIS group (87% *vs.* 27%, p<0.001). A moderate-severe adverse outcome was present in 11 patients (79%) of the M-NAIS group, as compared with only 2 patients (6%) of the NonM-NAIS group (p<0.001). As seen in Table 3, patients with

M-NAIS had lower BSITD-III scores at two years compared to those with NonM-NAIS in the three different domains (motor domain 75.5±18.3 *vs.* 98.5±10.6, cognitive domain 80.3±22.2 *vs.* 101.1±12 and language domain 75.6±18.3 *vs.* 94.8±12.1; $p<0.001$). Regarding the motor domain, the prevalence of cerebral palsy (spastic monoplegia or hemiplegia) was higher in M-NAIS (80% *vs.* 18%, $p<0.001$).

Infarct volume was associated with the severity of cerebral palsy at 2 years ($\rho=0.585$, $p<0.001$) and inversely related to BSITD-III motor, cognitive, and language scores ($r = -0.69$, $r = -0.60$ and $r = -0.62$, respectively, with $p<0.001$). In addition, higher infarct brain volume correlated with longer seizure duration during the neonatal period ($r= 0.528$, $p<0.001$). ROC analysis revealed that an absolute volume cut-off value of 66.1 cm^3 and a brain MLS of 0.21 mm (AUC volume 0.88, S 0.85, Sp 0.91, PPV 0.79, NPV 0.94) were the values with the maximum predictive accuracy for moderate to severe adverse 2 year outcome (Table 4 in Online Resource 4).

Forty percent of M-NAIS had epilepsy *vs*. 15% of NonM-NAIS ($p=0.058$, Table 3). Twice as many M-NAIS patients required antiepileptic treatment during the first two years versus the NonM-NAIS group.

Ten patients (71%) with M-NAIS were microcephalic at two years of age with a mean HC of 45.5 cm, while in those with NonM-NAIS the mean HC was 47.5cm ($p=0.004$, Table 3). We also found an inverse correlation between infarct volume and head circumference ($r =-0.492$, $p<0.001$).

DISCUSSION

The present study shows that in our NAIS population, almost a third of the patients had signs of M-NAIS defined as the presence of the space-occupying brain swelling that we called massive infarction. M-NAIS were different from NonM-NAIS regarding the volume of the infarct, arterial distribution of the infarction in the MCA territory,

extension of the area of lesion to the territory of PCA, and neurological outcome at two years of age.

In adults, the diagnosis of malignant MCA infarction defined by MRI findings of massive oedema of a hemisphere (decrease of extra-axial space and/or deviation from the midline, and/or uni or bilateral ventricular collapse within 48h from the onset of symptoms) allows early detection of those patients who will have a poor prognosis [24]. In the appropriate clinical context, decompressive hemicraniectomy can be considered, as well as drugs to reduce oedema because of the extremely high mortality rate associated with M-NAIS [7,8].

Since none of the neonates with M-NAIS died or were at serious risk of death, the malignant label used for adults may be a confusing term in infants. The absence of mortality in infants affected by M-NAIS may be explained by the intracranial compliance of the infant skull due to open fontanelles and not fused suture lines. Accommodative mechanisms in neonates could explain the non-life threatening nature of increased intracranial pressure, in contrast with the devastating consequences seen in adults. However, the oedema, midline shift, and ventricular collapse associated with M-NAIS may compromise cerebral blood flow and worsen the ischemia in surrounding areas due to mechanical forces, which could explain the unexpected finding that some infarcts extend into the border territory of the PCA. In the periventricular haemorrhagic infarction of prematurity, the presence of a midline deviation is also a sign that has been associated with significant cognitive and/or motor abnormalities [25,26].

Other clinical conditions such as the periventricular hemorrhagic infarction characteristic of prematurity can also be associated with the presence of space occupying brain swelling, which in turn is associated with poor cognitive and/or motor outcome.

The volume of the injured area was approximately 6 times greater in patients with M-NAIS than in patients with NonM-NAIS. In adults, several studies have used DWI data to state the threshold volume values that predict malignant MCA infarction.

In our study, the threshold volume associated with signs of swelling is similar to those reported for malignant infarction in some studies in adults [27,28].

Five of the 10 patients with bilateral infarction showed signs of space-occupying brain swelling (extra-axial space and uni- or bilateral ventricular collapse), but only three had brain MLS, illustrating that this sign might be compensated for in these patients.

As expected, the highest volume infarcts were all located in the M1 arterial territory of the MCA, and 66% were pre-bifurcation (including the basal ganglia).

Signal changes in the thalamus ipsilateral to the infarction were consistently found in the M-NAIS group. Since blood is supplied to the thalamus by other, unaffected arteries, this finding is likely related to the wide impairment of functional connectivity through the corticothalamic and thalamostriatal tracts ("netwok injury") associated with M-NAIS. It has been previously reported that these changes, known as pre Wallerian degeneration, result in volume loss in remote structures [29]. However, the clinical relevance of this kind of thalamic lesions is still unknown.

There were a larger proportion of male patients in our M-NAIS sample (80%) as compared with NonM-NAIS (55%). However, this difference did not attain statistical significance ($p=0.09$), likely due to lack of statistical power. The mechanisms behind these differences between males and females remain unclear, but could involve several factors, such as the epigenetic sexual dimorphism that may underlie sex-based differences in susceptibility and response to adverse perinatal risk factors, [32] the early sex differences in the immune-inflammatory system responses, [33] and the endocrine

factors such as the potential neuroprotective effects of estrogens observed in other ages [34].

The clinical picture of the patient with M-NAIS presents some peculiarities that differ from the picture of NonM-NAIS patients, such as earlier onset of symptoms, frequently with apnea and tonic seizures, and longer duration of seizures. The volume, the structures involved, and the pressure generated by the brain swelling are the most plausible explanation for this earlier onset of symptoms. These characteristics could guide doctors regarding the possible presence of M-NAIS.

It is well known that large infarcts are highly predictive of poor outcome; [2-6] hence our results are in line with this observation. Practically all infants with M-NAIS showed adverse outcome, and the vast majority had moderate-severe adverse outcome at two years. Recently, Wiedemann et al. [35] studied 37 term-born infants with NAIS. They calculated the relative stroke volume related with cerebral palsy, and found an optimal threshold of >3.3%. The results of this study contrast strongly with the cut–off volume above which our patients present a greater risk of cerebral palsy (18.7%). This difference could be due to the use of different infarct inclusion criteria and methodology (e.g., they included cerebellum and brainstem in the calculation of the relative stroke volume).

Our study has some limitations. Despite inclusion of a relatively large population of NAIS involving the MCA, and despite a third of our patients presenting M-NAIS, the low number of patients belonging to the M-NAIS group may limit the generalizability of our results. A further limitation is the variation in MRI examination timings between the two groups. Although MRI timing differences were not significant between the two groups, it could have played a role in observing the mass effect of edema on surrounding tissue structures. Moreover, it is important to note that with the available

data, we are unable to determine whether there are different pathophysiological mechanisms that contribute to the poorer outcome shown by the M-NAIS group or whether this is fully explained by infarct volume differences.

The uncertainty about the exact moment of injury in NAIS constitutes an unavoidable limitation for this study as in all studies of neonatal stroke. Brain injury after an ischemic insult evolves through several phases. Cytotoxic oedema resulting from the ischemic injury is progressive in temporal relation to the onset of the insult and reaches a peak within a few days after the injury, and this oedema exerts mechanical forces on the surrounding tissues. However, due to the precociousness of the MRI studies carried out in the first 78 hours after the onset of symptoms, we think that our study to a large extent reflects the time near the peak of oedema [36].

Moreover, midline deviation was measured employing a manual method, and in only 9 points of the brain, likely providing only an estimation of this deviation rather than a highly accurate quantification. However, these estimations proved useful for the objectives of this study, and, in fact we observed brain MLS to be significantly associated with NAIS volume. We followed-up our patients only until two years of age, at which point it is still difficult to establish the extent of cognitive deficits and neuropsychological function, educational achievement, language development, and visuospatial function, as well as behavioral problems. Due to this wide range of functional deficits, studies with larger patient samples and longer-term follow-ups are required.

In conclusion, we have found that the presence of brain MLS, ventricular and/or extra-axial collapse within the first week after onset of symptoms define a variety of NAIS that we have called M-NAIS. M-NAIS involves the M1 territory of MCA and a high volume of injury, in each case above 60 cm^3 and frequently with the injured area

extending to bordering territories of the posterior area of the brain. This variety of NAIS is associated with a high risk of moderate to severe adverse outcome at two years of age. Given the consistently poor outcome of the affected patients, their early identification could help in counselling parents and planning long-term neurodevelopmental follow-up. These patients could be reasonable candidates for future interventions using neuroprotective or neuroregenerative strategies and drugs for successful reperfusion.

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Figure 1. Measurement of the brain midline shift. a) The neonatal template used for reference is depicted along with the 3 axial planes in which we took the measurements (3 points per plane). b) Two examples of brain midline measurement are shown comparing a neonate with no deviation (mean = 0 mm, left) and another neonate with high deviation (mean = 2.57 mm, right).

Table 1. Demographic characteristics and clinical symptoms of all infants with NAIS according to the characterization of M-NAIS.

	All NAIS (n = 48)	NonM-NAIS (n = 33)	M-NAIS (n = 15)	NonM-NAIS *vs.* M-NAIS *p value*
Perinatal data				
Gestational age, weeks (SD)	39.7 (1.3)	39.8 (1.3)	39.3 (1.2)	p = 0.180
Birth weight, g	3.208 (437)	3.217 (447)	3.190 (427)	p = 0.844
Head circumference, cm	34.5 (1.2)	34.5 (1.3)	34.3 (1.2)	p = 0.474
Male/female	30/18	18/15	12/3	p = 0.091
IUGR (yes/no)	3/45	2/31	1/14	p = 0.936
Vaginal delivery (yes/no)	12/36	11/22	1/14	p = 0.048
Instrumental delivery (yes/no)	10/38	8/25	2/13	p= 0.388
Elective caesarean (yes/no)	3/45	0/33	3/12	p = 0.008
Emergency caesarean (yes/no)	23/25	14/19	9/6	p = 0.259
Apgar score 1 minute	6.7 (2.7)	7.2 (2.5)	5.5 (2.7)	p = 0.030
Apgar score 5 minutes	8.7 (1.6)	9.0 (1.5)	8.1 (1.8)	p = 0.053
Arterial umbilical cord pH	7.20 (0.11)	7.22 (0.09)	7.17 (0.13)	p = 0.206
Advanced resuscitation (yes/no)	6/42	3/30	3/12	p = 0.289
Maternal age, years	32.2 (5.1)	32.0 (5.4)	32.7 (4.6)	p = 0.682
Clinical data				
Clinical onset, hours	30.5 (24.3)	35.0 (26.1)	20.7 (16.2)	p = 0.058
Postnatal days until MRI	5.4 (3.1)	6.1 (3.3)	4.0 (1.8)	p = 0.027
Time between onset of symptoms and MRI acquisition, hours *	78 (53,132)	90 (66,155)	66 (41,96)	p = 0.070
Seizures (yes/no)	47/1	32/1	15/0	p = 0.496
Duration of seizures, days*	1.1 (0.5,2.5)	1.0 (0.1,1.6)	3.2 (1.2, 4.4)	p < 0.001
Type of clinic seizures:				p = 0.027
Clonic	35 (73%)	28 (85%)	7 (47%)	
Tonic	3	0	3	
Apnea	6	3	3	
Apnea + tonic	2	1	1	
Only electric	1	0	1	
Infants needing more than one antiepileptic drug (yes/no)	20/28	11/22	9/6	p = 0.082

NAIS, Symptomatic neonatal arterial ischaemic stroke; M-NAIS, Massive-NAIS; NonM-NAIS, Non-Massive-NAIS; IUGR, Intrauterine growth retardation; SD, Standard deviation.
Significant *p value* <0.05
* Displayed as median (P_{25},P_{75})
T-tests were performed to analyze differences in continuous variables, while dichotomic variables were analyzed by means of $\chi 2$ tests. For each of the variables of interest, mean (SD) or frequencies are displayed.

Table 3. Outcome at 2 years of age in all NAIS.

Outcome	All NAIS (n=48)	NonM-NAIS (n=33)	M-NAIS (n=15)	NonM *vs.* M-NAIS *P value*
Epilepsy (yes/no)	11/37 (22)	5/28 (15)	6/9 (40)	p = 0.058
Antiepileptic treatment (yes/no, %)	10/38 (20)	5/28 (15)	5/10 (33)	p = 0.151
Head circumference at 2 years, cm	46.9 (2.3)	47.5 (2.2)	45.5 (1.9)	p = 0.004
Microcephaly (≤2SD)¶ (yes/no, %)	16/31 (33)	6/27 (18)	10/4 (71)	p < 0.001
Speech therapy (yes/no, %)	20/28 (41)	9/24 (27)	11/4 (73)	p = 0.003
Strabismus (yes/no, %)	5 / 43 (10)	1 / 32 (0,3)	4 / 11 (26)	p = 0.013
Adverse outcome* (yes, %)	22/24 (47)	9/24 (27)	13/1 (93)	p <0.001
Adverse outcome (moderate-severe)† (yes/no, %)	13/33 (28)	2/29 (6)	11/3 (79)	p <0.001
Cerebral palsy enrolment GMFCS>I (yes/ no, %)	11 / 36 (23)	1 / 31 (0,3)	10/ 5 (66)	p < 0.001
Cerebral palsy GMFCS =I (yes/no, %)	18/29 (38)	6/26 (18)	12/3 (80)	p < 0.001
Bayley Score, motor	91.2 (17.2)	98.5 (10.6)	75.5 (18.3)	p < 0.001
Bayley Score, cognitive	94.5 (18.5)	101.1 (12.0)	80.3 (22.2)	p < 0.001
Bayley Score, language	88.5 (16.8)	94.8 (12.1)	75.6 (18.3)	p < 0.001

¶ Microcephaly was defined as an HC more than two SD below the mean for gender and age

* Adverse outcome was defined as a composite variable encompassing mild and moderate-to-severe adverse outcome. Mild adverse outcome was considered when there was a Bayley-III score between -2 SD and -1 SD (70 to 85) on any of the domains, and/or a GMFCS level I.

†

Moderate-severe adverse outcome was defined as -2 SD (MDI or PDI <70) in any Bayley-III domains, and/or CP (GMFCS level II-V).

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Seizures (yes/no)	47/1	32/1	15/0	p = 0.496
Duration of seizures, days*	1.1 (0.5,2.5)	1.0 (0.1,1.6)	3.2 (1.2, 4.4)	p < 0.001
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NAIS, Symptomatic neonatal arterial ischaemic stroke; M-NAIS, Massive-NAIS; NonM-NAIS, Non-Massive-NAIS; IUGR, Intrauterine growth retardation; SD, Standard deviation.

Significant *p value* <0.05

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Table 2. MRI territory distribution and volume of NAIS.

RM-Arterial distribution	**All NAIS**	**NonM-NAIS (n = 33)**	**M-NAIS (n = 15)**	**NonM- *vs.* M_NAIS** *p value*
Unifocal	**36**	**27**	**9**	
Left / right hemisphere	22/14	17/10	5/4	p = 0.693
MCA – M1 pre- bifurcation	7	1	6	p < 0.001
MCA – M1 post-bifurcation	9	6	3	
MCA – M2 segment	8	8	0	
MCA – M3 segment	3	3	0	
MCA – M4 segment	6	6	0	
Perforants arteries	3	3	0	
Multifocal	**12**	**6**	**6**	
Bilateral/unilateral	10/2	5/1	5/1	p = 1
pWD Thalamus◊ (yes/no)	32/16	17/16	15/0	p < 0.001
PLIC involvement (yes/no)	23/25	10/23	13/2	p < 0.001
Volume				
Absolute volume (cm^3) *	26.2 (13.2, 67.8)	17.4 (8.1,28.9)	102.7 (69.4, 147.6)	p < 0.001
Relative volume supratentorial brain*	7.4 (3.7,19.1)	4.9 (2.3, 8.2)	29 (19.6, 41.7)	p < 0.001
MRI findings of massive NAIS				
Midline shift brain (mm)*	0 (0,0.2)	0 (0, 0.1)	0.24 (0, 1.6)	p = 0.001
Observed midline shift, n (%)	9 (19%)	0	9 (60%)	
Ventricular collapse	-	0	11 (73%)	-
Collapse of extra-axial space	-	0	14 (93%)	-
More than one sign			11 (73%)	-
PCA involvement >10%† (yes/no)	22/26	9/24	13/2	p<0.001
ACA involvement >10% (yes/no)	7/41	4/29	3/12	p=0.473

MCA, midline cerebral artery; pWD, pre-Wallerian degeneration; PLIC, posterior limb of internal capsule; PCA, posterior cerebral artery; ACA, anterior cerebral artery.

◊ Signal changes in ipsilateral thalamus

* Displayed as median (p25, p75)

† Infarct extension adjacent to PCA.

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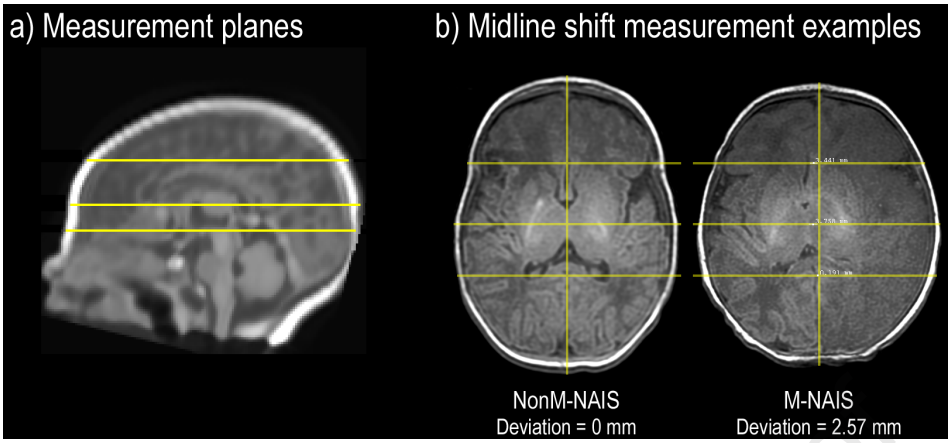
Table 4. Receiver operating characteristic curve analysis of volume (cm^3), brain midline shift (mm) of NAIS and neurological findings between NonM-NAIS *vs.* M-NAIS.

Variable	n	Cutoff-point (cm^3) Absolute volume	Cutoff - point (mm) midline shift	AUC (CI) volume	Sens., (95% CI)	Spec., (95% CI)	PPV (95%CI)	NPV (95%CI)
Cerebral palsy (GMFCS II-V)	47	66.1	0.209	0.89 (0.77,1)*	0.91 (0.59,1)	0.86 (0.71,0.95)	0.67 (0.46,0.82)	0.97 (0.83,1)
Adverse outcome	45	44.0	0.209	0.77 (0.63,0.92)*	0.59 (0.36,0.79)	0.96 (0.78,1)	0.93 (0.65,0.99)	0.71 (0.59,0.80)
Mild adverse outcome	45	44.0	0.020	0.44 (0.23,0.65)	0.22 (0.03,0.60)	0.67 (0.49,0.81)	0.14 (0.04,0.38)	0.77 (0.69,0.84)
Moderate-severe adverse outcome	45	66.1	0.209	0.88 (0.75,1)*	0.85 (0.55,0.98)	0.91 (0.75,0.98)	0.79 (0.55,0.92)	0.94 (0.80,0.98)
Speech Therapy	48	47.1	0.044	0.70 (0.55,0.86)*	0.55 (0.32,0.77)	0.86 (0.67,0.96)	0.73 (0.51,0.88)	0.73 (0.62,0.82)
Epilepsy	48	104.5	0.715	0.65 (0.46,0.85)	0.55 (0.23,0.83)	0.76 (0.59,0.88)	0.40 (0.23,0.59)	0.85 (0.74,0.92)
Microcephaly at 2 years of age	47	66.1	0.072	0.75 (0.59,0.91)	0.63 (0.35,0.85)	0.87 (0.70,0.96)	0.71 (0.48,0.87)	0.82 (0.70,0.90)

CI, confidence interval; Sens, sensitivity; Spec, specificity; NPV, negative predictive value; PPV, positive predictive value; AUC, area under the curve. Mild adverse outcome (CP and/or BSID-III Score <85), Moderate-severe outcome (CP and/or BSID-III Score <70).*$p<0.05$.



Highlights

- Massive infarction appears to be a distinctive subtype of neonatal infarction.
- Neonates with Massive infarction consistently present moderate to severe adverse outcome.
- Early Massive infarction identification would for prompt, specific interventions.

Contributors' Statement Page:

The concept for the study came from Dr Arca and Dr García-Alix. The data were collected by Drs García-Alix, Arnaez, and Arca. The MR images were analysed by Drs García-Alix, Arca, and Agut. Volume was calculated by Drs Stephan-Otto and Nuñez. Statistical analysis was conducted by Dr Núñez. The manuscript was written by Drs Arca, Christian Nuñez, Christian Stephan-Otto and García-Alix. All authors reviewed and approved the final manuscript as submitted and agree to be accountable for all aspects of the work. **Conflict of Interest Disclosures:** The authors report no conflict of interest.

Supplementary Figure 1. Representative diffusion sequences from M-NAIS and NonM-NAIS. **M-NAIS (first column):** a) Axial diffusion-weighted brain magnetic resonance image (DWI-MRI) showing acute right middle cerebral artery infarction (M1 pre-bifurcation) presenting with mass effect, midline shift and ventricular collapse obtained 3 days after onset of M-NAIS symptoms, b) DWI-MRI shows the hyperintense ischemic lesion in the territory of the left M-NAIS with partial MLS of the temporo-occipital cortex and pre-Wallerian degeneration (thalamus and peduncles of mesencephalon). **NonM-NAIS (second column):** c) DWI-MRI showing a hyperintensity area in the MCA territory (M2), d) DWI-MRI showing NAIS-M1 post-bifurcation in the second patient also obtained 3 days after onset of M-NAIS symptoms.