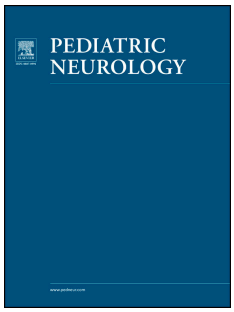

Neonatal arterial ischemic stroke secondary to carotid artery dissection: a case report and systematic literature review

Laura Baggio, Margherita Nosadini, Maria Federica Pelizza, Jacopo Norberto Pin, Anna Zarpellon, Clarissa Tona, Giorgio Perilongo, Paolo Simioni, Irene Toldo, Giacomo Talenti, Stefano Sartori

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TITLE

Neonatal arterial ischemic stroke secondary to carotid artery dissection: a case report and systematic literature review

Running title

Neonatal stroke due to carotid dissection

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ABSTRACT

Background. Carotid artery (CA) dissection is a rare aetiology of neonatal arterial ischemic stroke (NAIS). Diagnosis is challenging due to low level of suspicion and difficult interpretation of neonatal vascular studies.

Aim. To collect data on clinical-radiological presentation, treatment and outcome of NAIS due to CA dissection.

Methods. We describe one novel case and conduct a systematic literature review on NAIS attributed to CA dissection, complying with the PRISMA guidelines.

Results. 8 published cases of NAIS attributed to CA dissection were identified, and analysed with our case. All patients (9/9) were born at term, and 8/9 experienced instrumental/traumatic delivery or urgent caesarean section. None had foetal problems during pregnancy or thrombophilia. Signs and symptoms at presentation (between day of life 0-6) included: seizures (8/9), respiratory distress or irregular breathing (5/9), hyporeactivity, decreased consciousness or irritability (4/9), focal neurological signs (2/9). At MRI, stroke was unilateral in 7/9, extensive in 5/9. CA dissection was documented in 7/9 by neuroimaging or at post-mortem studies, and hypothesised by the treating physicians based on delivery and neuroradiology characteristics in the remaining 2/9. Antithrombotic treatment was used in 2/9. According to available follow-up, 1/8 died at age 7 days, 7/8 had neurologic or epileptic sequelae, and CA recanalisation occurred in 3/4.

Conclusions. NAIS attributed to CA dissection is rarely identified in the literature, often preceded by traumatic/instrumental delivery, presenting with seizures and systemic signs/symptoms, and characterised by extensive MRI lesions and neurologic sequelae. Definite evidence and recommendations on antithrombotic treatment are lacking.

Key words

Arterial ischemic stroke, neonatal, perinatal, carotid artery dissection, carotid occlusion, pediatric

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INTRODUCTION

Perinatal stroke comprises a group of cerebrovascular diseases occurring between 20 weeks of foetal life and 28 days postnatal life. Perinatal stroke can be categorised into arterial or venous, ischaemic or haemorrhagic, and also according to the timing of clinical presentation, into acute symptomatic perinatal strokes and presumed perinatal strokes [1,2]. Acute symptomatic perinatal strokes present shortly after onset, manifesting clinically within 28 days after birth typically with focal seizures; they can be distinguished into neonatal arterial ischaemic stroke (NAIS), neonatal cerebral sinovenous thrombosis and neonatal haemorrhagic stroke. Whereas, presumed perinatal strokes refer to chronic strokes diagnosed in a delayed manner and presumed to have occurred in the perinatal period, typically presenting clinically in infancy as hemiparetic cerebral palsy, pathological early handedness, developmental delay or seizures with imaging confirmation of remote stroke; they include arterial presumed perinatal ischaemic stroke, periventricular venous infarction and presumed perinatal haemorrhagic stroke [1-3] (Figure 1).

Figure 1

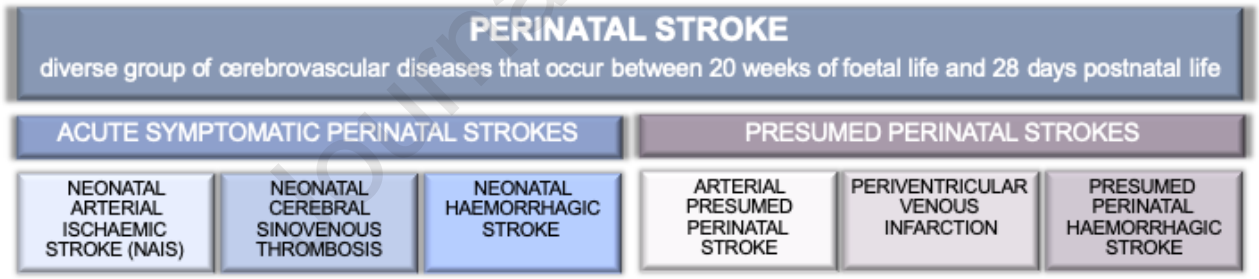

Figure 1. Subtypes of perinatal strokes. According to the timing of clinical presentation and diagnosis, perinatal stroke includes the categories of acute symptomatic perinatal strokes (neonatal arterial ischaemic stroke [NAIS], neonatal cerebral sinovenous thrombosis and neonatal haemorrhagic stroke), manifesting clinically within 28 days after birth typically with focal seizures, and presumed perinatal strokes (arterial presumed perinatal ischaemic stroke, periventricular venous infarction and presumed perinatal haemorrhagic stroke), typically presenting in infancy as hemiparetic cerebral palsy with imaging confirmation of remote stroke [1-3].

NAIS is characterised by a vascular focal brain ischaemic infarction corresponding to one or more arterial territories, and accounts for about 80% of acute neonatal strokes [1,2,4-6]. Despite advances in perinatal care and increased awareness, NAIS still represents an important cause of injury to the developing brain and accounts for a high morbidity rate.

Different risk factors for NAIS have been recognised, including both maternal and neonatal factors, none with a definite causative relation, and aetiology is considered to be multifactorial [2,7]. Thromboembolism arising from the placenta and direct vessel injury occurring during birth or due to an underlying arteriopathy are the two main pathophysiological processes hypothesised in NAIS [3,6,8]. Among the latter, carotid artery dissection is a rarely described aetiology in neonates, also in view of the challenges related to vascular imaging in this age.

In this study we report one novel case of NAIS related to a carotid artery dissection and we review the pertinent literature, in order to identify clinical and neuroradiological features suggestive for NAIS attributed to carotid artery dissection, and collect data on treatment and outcome.

METHODS

We retrospectively analysed data of patients with NAIS diagnosed at our tertiary care centre (Padova, Italy) with the aim of identifying the frequency of NAIS due to carotid artery dissection in our centre, and we describe a novel case of NAIS related to carotid artery dissection (the identity of this case cannot be retrieved from the data provided).

We subsequently conducted a systematic literature review of neonatal cases with NAIS due to carotid artery occlusion/dissection. The search was carried out in Pubmed independently by two researchers (LB and MN), up to date to 15.08.2022, with the search terms ((carotid dissection) or (carotid occlusion)) and (stroke or infarction or ischemia or ischemic) and (neonatal or neonate or newborn or perinatal). Articles in English, Italian, French and Spanish were included.

The available articles were filtered manually for patients in neonatal age (≤28 days) with stroke attributed to carotid artery dissection. Demographics, clinical, radiological and treatment data were collected. Studies on animals, and articles reporting neonatal patients with stroke and carotid occlusion not clearly attributed to dissection by the authors [9-14], or neonatal patients with carotid dissection in the absence of an associated stroke, were excluded [15] (Figure 2). The systematic literature review complies with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Figure 2

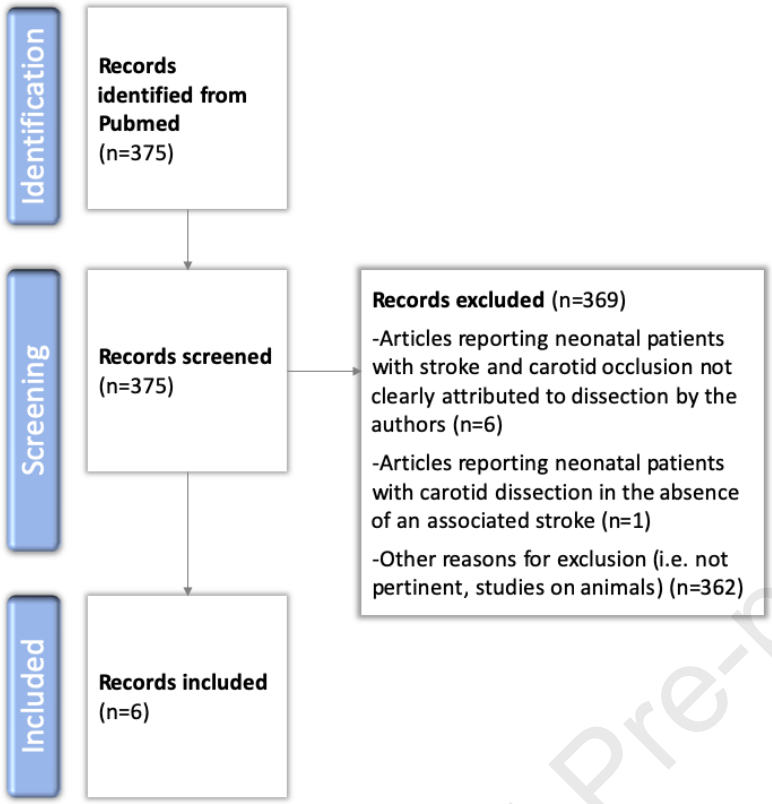

Figure 2. Identification of studies via Pubmed search (PRISMA).

RESULTS

Case presentation

From May 2010 to September 2021, among 49 cases of NAIS diagnosed in our tertiary care centre, carotid artery dissection was diagnosed in 1/49 (2%). This patient is described below.

A 40-gestational-week-old female was born in 2021 after an uneventful pregnancy from an urgent caesarean section due to a pathological cardiotocographic tracing. At birth she was hypotonic, hyporeactive and had respiratory distress. Apgar scores were 8-9-10 (at minutes 1, 5 and 10 respectively) and arterial cord pH was 7.09 with base excess -12,8 mmol/L. She was diagnosed with a mild hypoxic ischemic encephalopathy (Sarnat score 1). At birth, weight was 3970 g (90-97th centile), length 50 cm (10th centile), head circumference 35 cm (50-97th centile).

A transcranial ultrasound showed hyperechogenicity of the left parietal lobe. During her day of life (DOL) 1, she experienced focal electroclinical seizures, thus phenobarbital was started.

Brain magnetic resonance imaging (MRI) with MR angiography on DOL 1 (Figure 3) showed a left middle cerebral artery (MCA) acute cortico-subcortical ischaemic lesion in the insular, parietal, temporal lobes and in the striatum. A focal dissection in the proximal part of the left carotid artery was detected with secondary thrombosis of the left MCA.

Antithrombotic therapy with low molecular weight heparin 150 IU/kg/day was started.

Follow-up brain MRI on DOL 12 showed partial recanalization of the left M1 segment and complete re-canalisation of the left internal carotid artery (ICA).

The supra-aortic vessels and transcranial doppler sonography performed on DOL 15 were suggestive for an intimal flap of the extracranial portion of the left ICA.

At age 1 month, brain MRI showed further MCA recanalisation with mild residual stenosis of the proximal third of the M1 segment. Thus, heparin was discontinued and aspirin 2.5 mg/kg/day was administered for 1 month. Phenobarbital was discontinued at age 4 months due to the absence of seizures.

At age 7 months, the girl has right hemiparetic cerebral palsy with mild developmental delay and is not yet able to sit unsupported.

Figure 3

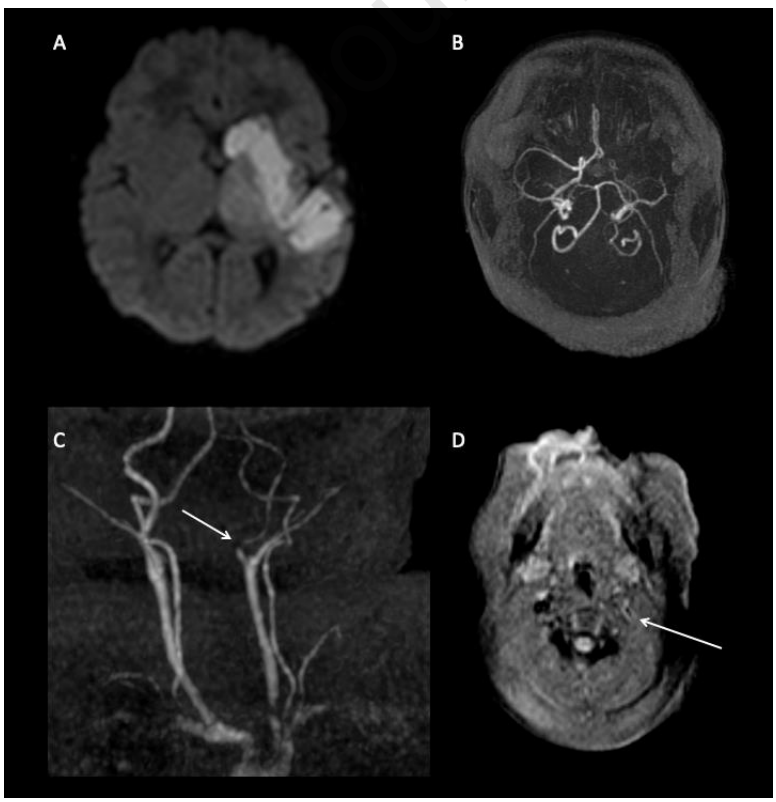

Figure 3

A. Brain MRI at day of life 1: left middle cerebral artery (MCA) acute cortical-subcortical ischemic lesion in the insular, parietal, temporal lobes and in the striatum.

B. MR Time of Flight Angiography demonstrates absence of flow in the left middle cerebral artery (MCA).

C. MR Time of Flight Angiography shows focal flow signal defect (arrow) of the internal carotid artery (ICA) just after the bifurcation, in keeping with dissection.

D. Axial T1 fat-sat showing spontaneous arterial wall hyperintensity (arrow) in the left internal carotid artery (ICA) consistent with intramural hematoma.

Literature review

The literature search yielded a total of 375 results. Among these, 6 articles reporting a total of 8 cases of NAIS attributed to carotid dissection were identified [3, 16-20] (Figure 2). These 8 literature cases were analysed and described together with our novel patient below and in Table 1.

All cases (9/9) were born at term and 8/9 experienced an instrumental or traumatic delivery or an urgent caesarean section; foetal problems during pregnancy were not reported, and maternal problems during pregnancy were reported only in 1/9 case (hypertension); thrombophilia assessment was normal in 9/9.

Signs and symptoms at clinical presentation (ranging between DOL 0 and 6) included: seizures (8/9), respiratory distress or irregular breathing (5/9), hyporeactivity, decreased level of consciousness or irritability (4/9), focal neurological signs (unilateral hypotonia or hypertonia) (2/9).

The first brain parenchymal neuroimaging was cranial ultrasound in 5/9, showing pathological findings in all 5/5, cerebral computed tomography (CT) in 3/9, revealing an ischaemic lesion in 3/3, and brain MRI in 1/9. Brain MRI was carried out in all 9/9 patients, showing an ischaemic lesion in all (left-sided in 4/9, right-sided in 3/9 and bilateral in 2/9), described as extensive in 5/9.

Regarding vascular studies, doppler sonography was carried out in 6/9, detecting absent blood flow in the ICA and/or MCA in 4/6, and MR angiography was done in 9/9 cases, revealing pathological findings in all. Neuroradiology-demonstrated carotid artery dissection was reported in 6/9 patients including our case [16-20], and demonstrated at post-mortem studies in an additional 1/9 case [17]; in in the remaining 2/9 cases, a

carotid artery dissection was hypothesised by the treating physicians based on the delivery modality and the characteristics of the cerebral lesion [3].

In 2/9 patients including our case [3], antithrombotic treatment was used, with aspirin and heparin followed by aspirin, respectively.

One patient died at DOL 7 [17]. Data on outcome were available in 7/8 remaining patients (duration of follow-up: range 0.5-8 years): 6/7 had hemiparetic/unilateral cerebral palsy, 5/7 had developmental delay and 3/7 developed epilepsy.

In patients with available follow-up neuroimaging, carotid recanalisation occurred in 3/4.

Table 1. Published cases of NAIS attributed to carotid artery dissection retrieved from the literature review, (n=8) and our case (n=1)

Reference	Sex, GA and weight at birth Apgar score UCBGA	Delivery	Risk factors	Timing and type of clinical presentation	Neuroimaging (timing)	Carotid artery occlusion	Neuroradiologic demonstration of dissection	Vascular territory involved by the stroke	Antithrombotic treatment	Age at last follow-up Neurological outcome Epilepsy Vascular studies
Mann 1993	M, 42 gw 3300 g Apgar s. 1-9	Urgent C-section after vacuum delivery attempt	Stained meconium	DOL 6: seizures and right hemiparesis involving the face, arm and leg	DUS (DOL 9): tapering of the left ICA immediately distal to the bifurcation, with undetectable flow 5 mm distal to the bifurcation MRI (N/A): infarct in the left MCA distribution with absent signal void in the left ICA MRA (N/A): occlusion of the left ICA just superior to the CA bifurcation, with a positive string sign; decreased calibre of the left MCA	Left ICA (DUS, MRA)	Yes: string sign (DUS, MRA)	Left MCA	None	10 m Outcome and epilepsy N/A MRA (10 m): left ICA recanalization, persistent attenuation of the left MCA MRI (10 m): encephalomalacia in the left MCA stroke region
Lequin 2004	F, at term 3240 g Apgar s. 5-7 pH 7.16 BE 10.9	Instrumental (vacuum and forceps extraction)	None	DOL 0-2: irregular breathing due to pneumothorax DOL 3: hypertonia and convulsions (PB, MDZ)	CUS (DOL 3): slit ventricles and a slightly increased basal ganglia echogenicity, no midline shift MRI (DOL 4): infarctions in the territory of left MCA and ACA, and right ACA and pial segments of the right MCA, caused by a complete occlusion of the ICA on the left and a partial occlusion on the right, best seen on the T2 weighted spin echo (SE) images. MRA (DOL 4): loss of signal in left carotid artery at petrous level (C2); the right carotid artery shows signal loss at supraclinoid level (C4) DUS: no sign of dissection at the C1 level Postmortem confirmation of brain infarction due to dissection with ICAs thrombosis	Left ICA, complete Right ICA, partial (MRA)	No (postmortem demonstration)	Left MCA + ACA Right MCA (extensive)	None	Died at DOL 7
Lequin 2004	M, 41 gw 4900 g Apgar s. 9-10	Vaginal	Prolonged rupture of membranes Stained meconium	DOL 0 (2 h): right cervical lump, respiratory distress, irritability	CUS (DOL 4): right basal ganglia hyperechogenicity with some mass effect DUS (DOL 4): thrrombus distal to the right carotid bulb (C1) due to dissection at this level, collateral vessels CT (DOL 4): infarction in the area of the right MCA MRI (DOL 13): early right hemisphere atrophy due to right ICA occlusion MRA (DOL 13): narrowing of the right CA due to dissection and thrombosis	Right ICA	Yes: narrowing of the right CA (DUS, MRA)	Right MCA	None	4 y Left spastic hemiplegia, language delay, special schooling Epilepsy under control with CBZ
Hamida 2014	M, 38 gw 4600 g Apgar s. 7-9	Instrumental	Poorly followed pregnancy, maternal hypertension Difficult extraction with right humeral fracture and right brachial palsy, shoulder dystocia	DOL 0: mild respiratory distress, weak sucking reflex, Moro reflex asymmetry (right brachial palsy) DOL 1: generalised convulsive seizures (PB, VPA)	CT (DOL 1): hypodense areas in the right occipital and capsulo-lenticulo-caudate regions and left fronto-temporo-parietal regions, in keeping with ischaemic cerebrovascular accidents, with haemorrhagic changes on the left DUS (DOL 1): extensive thrombosis affecting the left CCA and its two branches and partially the right ICA; vertebral arteries patent in their cervical tract MRI (N/A): signal hyperintensity at the level of the right posterior territories, right ICA and left superficial sylvian region MRA (N/A): dissection of the left CCA and its two external and internal branches. An anomaly of signal at the level of the third portion of the right vertebral artery evoked a dissection at its level but the partial thrombus of the right CCA was not visualized on this exam.	Left CCA, ICA, ECA, complete Right ICA, partial (DUS, MRA)	Yes (MRA)	Right PCA + MCA Left MCA	None	11 m Microcephaly, motor delay (not yet sitting unsupported), right upper limb paresis No epilepsy DUS (1 m): recanalization of the carotids

Piris-Borregas 2015	F, at term 4194 g Apgar s. 9-10 pH 7.22	Instrumental (forceps)	Stained meconium	DOL 2: seizures (PB)	CT (DOL 2): extensive hypodensity in the territory of the left MCA and PCA MRI (DOL 3): infarction in the left MCA territory: left basal ganglia and cerebral hemisphere MRA (DOL 3): absent flow in the left CCA and left ICA	Left CCA and ICA (MRA)	Yes (MRA)	Left MCA (extensive)	None	4 y Right hemiparesis No epilepsy (no ASM)
Fluss 2016	M, 39 gw 3250 g Apgar s. 10-10	Instrumental (forceps)	Shoulder dystocia	DOL 1: right-sided hypotonia and focal convulsions	CT (DOL 2), MRI (DOL 12): extensive ischemic stroke involving both the superficial and deep territories of the left MCA MRA (DOL 15): occlusion of the left ICA, presumably related to arterial wall injury upon obstetrical trauma although not formally confirmed by imaging	Left ICA (MRA)	No	Left MCA (extensive)	None	8 y Right-sided spastic cerebral palsy, behavioural issues, mild intellectual disability Refractory epilepsy
Fluss 2016	F, 40 gw 4560 g Apgar s. 7-9-10 pH 7.12	Vaginal	Shoulder dystocia, macrosomia	DOL 0: respiratory distress and focal seizures (apnoea, right hand clonia)	CUS (N/A): diffuse hyperechogenicity on the right hemisphere MRI (DOL 5): major right hemispheric infarction with absent flow in the right ICA but sparing of the deep MCA territory; right PCA territory involvement MRA (DOL 5): absent right ICA flow, with visible flow along the right MCA CT (DOL 11): confirmed carotid occlusion at the cervical level	Right ICA (MRA, CT angiography)	No	Right MCA + ACA (extensive)	ASA for 3 months (no side effects)	14 m Left hemiparesis, left hemianopsia, microcephaly No epilepsy MRA (3 m): persistence of right ICA occlusion MRI (14 m): atrophy of the whole superficial MCA territory, partially sparing the deep MCA territory
Benavente-Fernández 2019	M, 39+4 gw 3550 g Apgar s. 6-8	Urgent C-section after vacuum delivery attempt	None	DOL 2: decreased level of consciousness, hypertonia, bulging fontanelle, electrical focal seizures (PB, LEV, lidocaine)	CUS (DOL 2): large triangular wedge-shaped echogenic area in the right hemisphere with collapsed right ventricular system and sulci, causing mass effect and left midline shift DUS: no flow signal in the right MCA and in the right ICA MRI (DOL 4): extensive ischemic injury in the right MCA territory MRA (DOL 4): confirmed the US suspicion of dissection and thrombosis of the right ICA (carotid dissection with findings of irregular stenosis, “string sign”)	Right ICA (DUS)	Yes: string sign (MRA)	Right MCA (extensive)	None	6 m Infantile spasms (ASM)
Our case	F, 40+4 gw 3940 g Apgar s. 8-9-10 pH 7.09 BE -12.8	Urgent C-section	Pathological cardiotocographic tracing, maternal fever	At birth: hyporeactivity, hypotonia, respiratory distress DOL 1: focal seizures	CUS (DOL 1): hyperechogenicity of the left parietal lobe MRI (DOL 1): left MCA acute cortico-subcortical ischaemic lesion in the insular, parietal, temporal lobes and in the striatum MRA (DOL 1): focal dissection in the proximal part of the left ICA, secondary thrombosis of the left MCA DUS (DOL 15): intimal flap of the extracranial portion of the left ICA	Left ICA + MCA (MRA)	Yes (MRA, DUS)	Left MCA	LMWH, then ASA (no side effects)	7 m Right hemiparesis No epilepsy (no ASM) MRI (DOL 12 partial recanalization of the left M1 segment and complete left ICA recanalisation

Legend: ACA: anterior cerebral artery; ASA: acetylsalicylic acid; ASM: antiseizure medications; BE: base excess; CA: carotid artery; CCA: common carotid artery; C-section: caesarean section; CT: cerebral computed tomography; CUS: cerebral ultrasound; DOL: day of life; DUS: doppler ultrasound; ECA: external carotid artery; F: female; GA: gestational age; gw: gestational weeks; ICA: internal carotid artery; LEV: levetiracetam; m: months; M: male; MCA: median cerebral artery; MDZ: midazolam; MRA: cerebral magnetic resonance angiography; MRI: cerebral magnetic resonance imaging; N/A: not available; PB: phenobarbital; PCA: posterior cerebral artery; UCBGA: umbilical cord blood gas analysis; VPA: valproic acid; y: years.

Discussion

Neonatal arterial ischemic stroke (NAIS) secondary to carotid artery dissection is a rare clinical entity associated with direct vessel injury. We have described one novel case of NAIS due to carotid artery dissection and carried out a systematic review of the pertinent literature, identifying 8 additional published cases [3,16-20].

Our main results, derived from pooling together the literature patients and our novel case, show that most patients experienced an instrumental or traumatic delivery or an urgent caesarean section, and the great majority presented with seizures accompanied by systemic signs/symptoms such as respiratory distress, hyporeactivity, decreased consciousness or irritability. Neuroradiology was characterised in most cases by extensive ischemic brain lesions, mostly unilateral, with documented carotid artery dissection in the majority of cases, by neuroimaging or at post-mortem confirmation. Antithrombotic therapy was used in the minority, and outcome was characterised by severe neurological sequelae.

The low frequency of carotid artery dissection among NAIS cases in our centre (2%, n=1 case), and the very limited number of published cases of NAIS attributed to carotid artery dissection identified by our literature review (n=8 published cases), confirm that carotid artery dissection is a rare aetiology of NAIS.

It is well established that the detection of vascular lesions in general is infrequent in NAIS, with intraluminal thrombi in cerebral arteries, evidence for vessel wall injuries, or arteriopathy being seldom documented on angiographic sequences in neonatal age [3,8]. In a previous work collating novel and literature cases [3], patients with NAIS and documented carotid occlusion due to any cause were identified in less than 0.5% (n=16; of these, 6/16 cases were attributed to traumatic arterial injury) [3,16-18]. The frequency of MR angiography abnormalities in patients with NAIS was higher (35%, 29/81) in a recent monocentric retrospective analysis conducted by the International Pediatric Stroke Study, although it should be noticed that this included both pathological and not clearly pathological anatomical variants, with presumed ICA dissection in only 2/29 [21].

The radiological diagnosis of carotid artery dissection is based on the evidence of an intimal flap, vessel wall hematoma, double lumen and geometric changes at follow-up [22,23]. There are several reasons explaining the difficulties identifying these findings, and vascular lesions in general, in neonates. First of all, neonatal circulation assessment is challenging because of its anatomy, the smaller and/or more tortuous vessels and

the lower blood flow velocities compared with older children and adults. Secondly, stroke in newborns is characterised by peculiar elements such as quick thrombus resolution, thus the affected artery is often patent and cerebral vessels exhibit normal anatomy at the time of first acute imaging [3,8,24]. Further challenges in neonatal imaging may be represented by scanner unavailability or unsuitability for a neonate who is clinically unstable, or the absence of an expert team for critical ill neonates [9,25].

Moreover, angiographic sequences are often not routinely performed in stroke study protocols, especially at the cervical level [3], despite its importance has been previously highlighted [8]. For all these reasons, the use of cranial ultrasound and doppler sonography is supported as a useful, inexpensive, noninvasive and easily available tool for a first evaluation in newborns with concern for stroke, possibly to be identified also based on proposed prediction models [25]; MRI could be then performed for an essential more detailed definition [20].

As regards the general characteristics of our cohort, the high rate of instrumental or traumatic delivery is noteworthy. To date, the role of instrumental delivery as a risk factor for NAIS is uncertain. However, by analogy with childhood ischemic stroke, it could be reasonably supposed that mechanical stretching during traumatic delivery may cause or favour a direct arterial injury, especially in the presence of macrosomia and shoulder dystocia [3]. Furthermore, no foetal problems (and rare maternal problems) were reported during pregnancy, and thrombophilia screening was normal in our cohort, further supporting the hypothesis that stroke might have resulted from an insult occurring in the perinatal frame [8,26].

Similar to the previously mentioned cohort of NAIS due to carotid occlusion [3], and differently to more common NAIS aetiologies in which neonates mostly experience isolated seizures [27,28], most of our patients presented with seizures accompanied by other nonspecific signs and generalised illness (respiratory distress, hyporeactivity, depressed consciousness, irritability, hypotonia).

Indeed, it has been observed that occlusion of a large vessel such as carotid artery may cause a less transient vascular occlusion than thromboembolic mechanism, and this could be responsible for more extensive lesions, more frequently associated with encephalopathy or generalised signs/symptoms beside seizures, as opposite to isolated focal seizures as a more common presentation in other aetiologies of NAIS [3].

As previously reported in literature, we could find no side prevalence of the NAIS and no specific MRI lesion pattern, with possible involvement of different areas and of both superficial and deep territories [3].

All the patients of our series developed important neurological deficits such as unilateral cerebral palsy associated with a severe intellectual disability. When considering NAIS due to other (more frequent) aetiologies, disabilities in motor, learning, behaviour, language, and mental health are otherwise reported in different grades of severity, in relation with the infarction dimensions [2,4,26,29]. As regards epilepsy, it was reported at follow-up in nearly half of patients in our literature cohort, similarly to what reported for other types of arterial ischemic stroke, which is considered the most frequent stroke category associated with structural epilepsy development (50% of presumed perinatal AIS and 71% of NAIS), probably because of the involvement of the cerebral cortex.

To date, only supportive treatment is recommended for neonates with a first episode of NAIS, especially because of the low recurrence rate, except in cases with a documented thrombophilia or complex congenital heart disease [2,30], and thrombolysis and mechanical thrombectomy are rarely considered in neonates due to the lack of evidence and the small artery size in this age [2]. However, the potential utility of early antithrombotic treatment in NAIS due to a direct vascular lesion like dissection has been hypothesised [3,9,21], similar to recommendations for paediatric and adult stroke due to arteriopathy and in particular arterial wall injury such as dissection [2,30], but definite evidence and recommendations in neonatal age are lacking. Therefore, the best treatment strategy in NAIS attributed to carotid artery dissection represents a knowledge gap due to the lack of evidence on the efficacy/safety profile and of definite recommendations, and a challenging decision for the treating physician which appears to be often taken on a case-by-case basis.

Limitations. The main limitations of our study include the heterogeneous data availability for the literature patients included due to the retrospective study design, and the limited number of cases identified, hindering definite conclusions. Furthermore, data collected refer to a large literature timeframe, during which knowledge on perinatal stroke, its diagnosis and management have improved substantially. Finally, as mentioned earlier, it should also be acknowledged that in our literature cohort carotid artery dissection was not documented at neuroimaging in all cases, and in 2/9 it was hypothesised by the authors of the articles included in the literature review based on the extension of the neuroradiological characteristics and the presence of risk factors.

Conclusions. Despite the above-mentioned limitations, in the present study we sought to collect data on NAIS attributed to carotid artery dissection, potentially useful for its characterisation and understanding.

Indeed, poor understanding of the underlying primary mechanism in stroke represents an important limitation for prevention, recognition and acute management.

Our study confirms the rarity of NAIS secondary to carotid artery dissection, the possible association with instrumental or traumatic delivery in the absence of maternal or foetal risk factors, the characteristic presentation with seizures associated with systemic signs/symptoms, the relatively large parenchymal lesions and the severe neurological sequelae. These factors may aid a timely clinical suspicion of this rare entity. More importantly, despite the intrinsic challenges in this age, neurovascular imaging remains be essential to identify the aetiologic mechanism in NAIS, including large or medium vessel occlusion, vascular anomalies such as tortuosity or malformation, and craniocervical arteriopathy including dissection [6].

Our study confirms and highlights a knowledge gap in the best treatment strategy for NAIS secondary to carotid artery dissection as regards the potential indication for antithrombotic treatment, whose efficacy and safety in this clinical setting is still to be properly assessed in larger studies.

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Author contribution

Laura Baggio carried out the literature review and drafted the paper.

Margherita Nosadini carried out the literature review and contributed to the last version of the manuscript.

Stefano Sartori provided senior support for the article conceptualisation and contributed to the last version of the manuscript.

Giacomo Talenti provided neuroradiological guidance.

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Highlights

- Neonatal arterial ischaemic stroke due to carotid artery dissection (NAIS-CAD) is rare
- Instrumental/traumatic delivery or urgent caesarean section often precede NAIS-CAD
- Most frequent clinical presentation of NAIS-CAD is with seizures and systemic signs/symptoms
- Neuroradiology is characterised in most cases by extensive ischaemic brain lesions
- Neurovascular imaging should be carried out in all patients with NAIS
- Definite evidence and recommendations on antithrombotic treatment for NAIS-CAD are lacking

Conflict of interest

The authors report no disclosures and no conflict of interest.