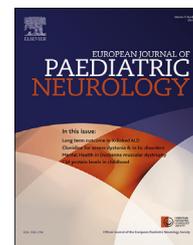




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Official Journal of the European Paediatric Neurology Society



## Letter to the Editor

# Extracerebral thrombosis in symptomatic neonatal arterial ischemic stroke



We read with great interest the recent publication by Fluss et al. presenting 16 cases (5 personal and 11 from the literature) of perinatal arterial ischemic stroke with documented carotid occlusion.<sup>1</sup> The main etiological hypothesis addresses the role of the materno-fetal vascular interface as the origin of thrombi that reach the infant cerebral arterial circulation throughout the physiologically patent foramen ovale and ductus arteriosus.<sup>1–3</sup> Moreover, regarding cases reported by Fluss et al., further proposed mechanisms for stroke occurring acutely after birth are direct vessel injury during the birth process itself and intrinsic arteriopathy.<sup>2–4</sup>

As part of an ongoing project designed to investigate risk factors of perinatal stroke, we searched for thrombi in a cohort of 42 consecutive infants born at >35 weeks of gestation with the diagnosis of symptomatic arterial ischemic stroke within the first 28 days of life, in three tertiary hospitals from October 2006 to December 2012. Symptomatic neonatal arterial ischemic stroke was defined according to clinical and radiographic criteria: (1) seizures, recurrent apnoea or acute neurological deficit, and (2) MRI confirmation of acute focal brain infarction(s) within arterial territories. Infants with arterial stroke and major congenital anomalies, meningitis, sepsis, congenital infections, ECMO, or metabolic diseases were not included. Thrombophilia workup was performed in all mother–infant pairs, including protein C, protein S, antithrombin III, coagulation factor V G1691A, factor II G20210A, methylenetetrahydrofolate reductase C677T, lipoprotein(a), homocysteine, and antiphospholipid antibodies.

Investigation of extracerebral thrombosis included echocardiography and Doppler ultrasound for abdominal vasculature (renal, cava, suprahepatic, and aorta) and cervical vessels (jugular and carotid). Seventeen out of 42 infants (40%) were screened at the three sites. Thirty-nine of 42 infants (93%) had at least one ultrasound test carried out to look for extracerebral thrombi. These were 37/42 (88%) heart cavities, 31/42 (74%) abdominal vessels, and 18/42 (43%) cervical vessels.

Extracerebral thrombi were found in one of 17 infants who underwent full screening; this patient had thrombi at different sites (heart, carotid artery and vena cava). We also

found two infants with thrombi between those who were partially screened: one had a thrombus in the vena cava, and another one had a carotid thrombus. The three infants had arterial strokes involving middle cerebral artery, and none of them or their mothers exhibited thrombophilia. Two infants were born at term and another was born at 36 weeks of gestation—all three by caesarean section. One of the three infants (the one who had an isolated thrombus in the vena cava) underwent umbilical catheterization.

The possibility of vascular damage or blood clots outside the cerebral vasculature associated with cerebral thromboembolic events in the neonate is not systematically pursued in practice. Hence, the percentage of babies with perinatal stroke who may have thrombi outside the cerebral vasculature is unknown. Further, the fact that neonatal vessels may recanalize rapidly<sup>9</sup> may lead to underestimation of the prevalence of intrinsic thromboembolism in the pathogenesis of neonatal arterial stroke. Fluss et al. noted that only 0.5% of patients in the four largest studies of NAIS showed documented carotid occlusion.<sup>4–8</sup> However, none of these studies screened newborns for extracranial thrombi except for Chabrier et al., which recommended performing echocardiography as well as cervical and cranial vessel imaging.<sup>4</sup> In our study, apart from thrombus in the cervical vessels in two of the 18 infants (11%) who underwent cervical imaging, we made the previously unreported finding of thrombi in abdominal vessels in 2 out of the 31 neonates (6%) who underwent abdominal imaging. Similarly to what Chabrier et al. found, complete workup for extracerebral thrombi in our study was carried out in only a minority of patients. Nevertheless, our data support the observation that most cases of NAIS are not attributable to a thromboembolism of intrinsic origin.<sup>4</sup> Furthermore, we provide additional evidence of the conclusion of Fluss et al. that a small, but not negligible number of infants with NAIS present thrombi in extracranial vessels,<sup>4</sup> opening up the possibility of a thromboembolic event originating in extracerebral sites.

The systematic search for extracerebral thrombi, including imaging of heart cavities, cervical and abdominal vessels, should be included in the pathogenic workup in the neonatal arterial ischemic stroke. This search can provide useful information about possible underlying pathophysiology and could have implications when considering anticoagulant therapy. In light of the available data, we now include, as part

DOI of original article: <http://dx.doi.org/10.1016/j.ejpn.2016.03.003>.

of the MRI study of infants with arterial ischemic stroke, non-contrast magnetic resonance angiography (MRA) of both the intracranial and extracranial supra-aortic arteries as a time-of-flight (TOF-MRA) technique.

### Conflicts of interest

None.

### Acknowledgments

The authors thank Dra. Cilla for her helpful comments on the manuscript. This work was supported by the Carlos III Health Institute (PI08/1366).

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1090-3798/\$ – see front matter

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<http://dx.doi.org/10.1016/j.ejpn.2017.05.004>