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SCIENTIFIC LETTERS

Thrombosis in the intensive care unit: Our experience in 10 years☆

Trombosis en cuidados críticos neonatales: nuestra experiencia en 10 años

Dear Editor:

In recent years there has been an increase in the frequency of diagnosis of neonatal thrombosis associated with the increased use of imaging tests[1] and the increased survival of patients with complex conditions. The incidence is of 5 per 100,000 live births and 5 per 1000 patients admitted to an intensive care unit.[2] Central catheterization is a risk factor found in 90% of episodes.[3] At present, the treatment of thrombosis in newborns is based on adult guidelines[4] and therefore a subject of controversy, with considerable heterogeneity in its management in clinical practice.

We describe the cases of 29 patients with thrombosis managed between 2008 and 2017 in a tertiary level neonatal intensive care unit (excluding postsurgical cardiac patients or patients treated with extracorporeal membrane oxygenation, which was delivered in a different unit of the hospital).

Table 1 presents the epidemiological characteristics and risk factors of the patients included in the study. The clinical manifestations that preceded diagnosis were heterogeneous, and 38.4% of the patients were asymptomatic. The diagnosis was based on the findings of Doppler ultrasound in 26 cases, and on the findings of magnetic resonance imaging (MRI) or computed tomography (CT) scans in the remaining 3. Table 2 presents the location of the thrombus, risk factors, treatment and outcome for each case.

A total of 6 patients died (20%): 2 (cases 11 and 13) as a direct result of thrombosis in the right atrium, with a clinical presentation compatible with pulmonary embolism. A third patient (case 23) died of hypoxic-ischaemic encephalopathy with multiple organ failure in the context of right renal vein thrombosis, with no other relevant findings in the autopsy. The remaining patients died of causes secondary to other diseases, such as pulmonary haemorrhage (case 29) or withholding of life-sustaining treatment in the context of other diseases (cases 15 and 28).

Of the 4 patients that had life- or organ-threatening thrombosis (cases 6, 10, 12 and 14), 2 died. Only 1 had a favourable outcome after treatment with bemiparin of a small atrial thrombus, which resolved in 8 weeks. The patient with bilateral renal artery thrombosis (case 6) was initially treated with fibrinolytic drugs, but the treatment had to be discontinued due to haemorrhage of the choroid plexus, after which she developed end-stage renal disease.

Five patients underwent an evaluation of thrombophilia, and abnormalities were found in 2 (factor V Leiden and factor II and XII, cases 6 and 26).

In the management of neonatal thrombosis, the morbidity and mortality are determined to a great extent by the location of the thrombus. The outcome depends on the optimal diagnosis and management, and therefore in patients at risk, if there is suspicion based on the clinical presentation or laboratory results (persistent thrombocytopenia), imaging tests should be requested at an early stage (Doppler ultrasound, CT angiogram or magnetic resonance angiogram), and an angiogram should be performed in cases with an uncertain diagnosis. We recommend against the D-dimer test in newborns.

The treatment of neonatal thrombosis poses dilemmas that are a source of controversy due to the risk of bleeding in this population, and there is considerable variability in its management between health providers and facilities. The clinical practice guidelines on antithrombotic therapy in newborns and children[4] indicate that in cases of life- or organ-threatening thrombosis, and in the absence of absolute contraindications (surgery or central nervous system ischaemia, active bleeding, invasive procedures or seizures in the past 48–72 h), initiation of thrombolytic therapy should be considered taking into account the size and location of the thrombus (such as: diameter > 2 cm and/or mobile right atrial thrombosis). The risk–benefit assessment should be individualised. There are different schemes for thrombolytic therapy with recombinant tissue plasminogen activator (rtPA), and at present there is no evidence supporting the superiority of any of them.[4]

If there is no risk of patient or organ death or thrombolytic therapy is contraindicated, treatment with an anticoagulant agent treatment should be initiated (low-molecular weight or unfractionated heparin)[3] in patients who are symptomatic (hypertension, change in limb colour, persistent tachycardia, ...), while in patients who are asymptomatic and in whom thrombosis was a chance

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Table 1 Patient characteristics and risk factors.

		Total ($N = 29$)
Gestational age (weeks, median)		37 (33.5–39)
Birth weight (g, median)		2.915 (2.252–3.265)
Sex (female)		15
Median age in days at diagnosis		7 (3–14)
Maternal risk factors	Gestational diabetes	7
	Preeclampsia	1
	Chorioamnionitis	4
	Oligoamnios	3
	Maternal thrombophilia	2
	PROM	2
	IUGR	2
Delivery risk factors	Urgent caesarean delivery	8
	Meconium aspiration syndrome	3
	Instrumental delivery	1
Neonatal risk factors	Catheter	29
	Sepsis	17
	Respiratory distress syndrome	11
	Neonatal asphyxia	7
	Pulmonary hypertension	6
	Heart disease	5
	Erythrocytosis	5
	Hypothermia	4
	Corticoid therapy	4
	Other diseases	4
	Previous surgery	3
	Right-sided heart failure	2
	Enterocolitis	2
	Catheterization	2
	Thrombophilia	2
	Central catheter	29
	Central line malposition	8

IUGR, intrauterine growth restriction; PROM, premature rupture of membranes.

finding, the decision whether to maintain a watchful waiting approach should be made on a case-by-case basis.

We recommend that the follow-up of patients with thrombosis, especially in cases with a related family history, of great severity (purpura fulminans) or in the absence of risk factors, include an investigation of thrombophilia.[2]

Although the reported evidence on the subject is limited, given the high morbidity and mortality associated with thrombosis in critical locations (50% of our sample) and that the reviewed literature offers encouraging data regarding the use of fibrinolytic agents (even in patients born preterm),[5,6] early use of thrombolytic therapy should be considered in life- or organ-threatening cases as long as the hospital has the necessary resources and experienced staff, always with an individualised risk–benefit assessment.

Our study was retrospective, and it is important to take into account the limitations intrinsic to this type of design.

Table 2 Risk factors, location, treatment and outcome.

Patient	Sex/gestational age/birth weight	Catheter	Malposition	Risk factors	Thrombus location	Treatment/day initiated	Resolution of thrombosis	Complications	Sequelae/ death
1	M/41/4550	UVC	No	Heart defect (pulmonary atresia), surgery	Right femoral artery	LMWH/6	Lost to follow-up	Thrombocytopenia due to heparin → anticoagulants	No
2	M/40/-	UAC UVC	No Yes	Asphyxia, PHT, RDS	Aorta and iliac artery	LMWH/4	Yes	No	No
3	M/38/3870	UVC	Yes	Hyperinsulinism, asphyxia, sepsis, corticoids, maternal DM	Abdominal aorta	LMWH/19	Lost to followup	–	–
4	F/41/3420	Percutaneous	No	Heart defect (Fallot), PDA stent catheterization, asphyxia, sepsis, corticoids, maternal DM	Iliac and right femoral arteries	LMWH/16	Partial, collateral vessels	No	No
5	M/39/3900	UVC	No	Sepsis, PHT	Iliac and femoral arteries	LMWH/7	Yes	No	No
6	F/37/2940	Percutaneous	No	Madre: maternal MODY diabetes and factor V Leiden thrombophilia, RDS, sepsis	Bilateral renal artery	LMWH/UFH/rTPA/2	No	Choroid plexus bleeding	Renal failure
7	F/34/2460	Percutaneous	No	Maternal DM prenatal: adrenal haemorrhage and thrombosis in the left hilum, erythrocytosis	Renal vein	LMWH/0	Yes	No	No

Table 2 (*Continued*)

Patient	Sex/gestational age/birth weight	Catheter	Malposition	Risk factors	Thrombus location	Treatment/day initiated	Resolution of thrombosis	Complications	Sequelae/ death
8	M/40/3300	Percutaneous	No	Asphyxia, RDS, sepsis, corticoids	Cerebral sinuses	LMWH/20	Yes, partial	Severe gastrointestinal bleeding: transfusion, octreotide and temporary discontinuation of heparin	No
9	M/30/1320	UAC, UVC, percutaneous	No	Sepsis	Superior vena cava	LMWH/22	Lost to follow-up	Thrombocytopenia	No
10	F/39/3720	UVC, percutaneous	Yes No	Hyperinsulinism, corticoids	RA 12 × 13 mm	LMWH/12	Yes, discontinuation of heparin in 8 weeks	No	No
11	F/38/3020	UVC UAC, percutaneous	Yes (portal) No	Asphyxia, hypothermia, RDS, corticoids	Cerebral sinuses	LMWH/10	No new imaging tests	No	No
12	F/26/740	UVC, percutaneous	Yes (RA)	NRFS	RA 7 × 8 mm	LMWH/3	No	Probable PE	Death due to PE
13	F/35/2230	UVC UAC, percutaneous	Yes (RA) No No	Asphyxia, hypothermia, sepsis, oligoamnios, IUGR	Cerebral sinuses	LMWH/17	Yes	No	No
14	F/28/1140	UVC, percutaneous	Yes (RA) No	Sepsis	RA 19 × 10 mm	Watchful waiting (intraventricular haemorrhage grade III)	–	Probable PE	Death due to PE
15	M/38/2890	UVC, percutaneous	No No	Maternal DM Sepsis	Cerebral sinuses	LMWH/9	Yes, partial	No	No Withholding of treatment (ventilator-dependent nemaline myopathy)

Table 2 (*Continued*)

Patient	Sex/gestational age/birth weight	Catheter	Malposition	Risk factors	Thrombus location	Treatment/day initiated	Resolution of thrombosis	Complications	Sequelae/ death
16	F/40/2940	UVC, UAC, percuta-neous	Yes No No	Asphyxia, hypother-mia	Portal	LMWH/8	Yes	No	No
17	F/36/2550	UVC, per-cutaneous	No No	Sepsis, ery-throcytosis Steinert disease,	Cerebral sinuses	LMWH/14	Yes	No	No
18	F/39/3290	UVC, per-cutaneous	No No	congenital surfactant deficiency, left ventricular hypertro-phy, right-side heart failure RDS, sepsis	Portal and umbilical	LMWH/11	Yes, partial	No	No
19	M/34/2450	UVC, UAC	No	Heart defect (transposi-tion of great vessels), Rashkind atrial septostomy RDS	Right femoral vein	Watchful waiting, favourable outcome	Lost to follow-up	–	–
20	F/38/2600	Percutaneous	No	–	Renal vein	Watchful waiting, progression of thrombosis	Yes		Renal atrophy
21	F/36/3080	UVC, per-cutaneous	No No	Dehydration, sepsis	Umbilical vein	Watchful waiting	Lost to follow-up	–	–
22	M/39/3040	CVC	No	Oligoamnios, sepsis	Inferior vena cava	UFH→LMWH/1	Yes	No	Renal atrophy
23	M/33/2990	UVC	No	Maternal DM, preeclamp-sia RDS, sepsis, corticoids	Right renal vein	Watchful waiting, coagulopa-thy	–	–	Renal failure, multipole organ failure, CA, death
24	M/37/2370	UVC	No	Maternal DM, PROM, erythrocytosis	Umbilical vein	Watchful waiting, asymptomatic	Yes	–	No

Table 2 (*Continued*)

Patient	Sex/gestational age/birth weight	Catheter	Malposition	Risk factors	Thrombus location	Treatment/day initiated	Resolution of thrombosis	Complications	Sequelae/ death
25	M/31/1532	UVC	No	Heart defect (ASD), RDS, erythrocytosis, sepsis, NEC, gastrointestinal surgery	Brachiocephalic and jugular arteries	LMWH/120	No, collateral vessels	No	No
26	M/31/2320	Percutaneous	No	Severe oligoamnios, RDS	Bilateral renal vein	LMWH/4	Yes, partial, renal disease	No	Yes, grade 2 CKD grade II
27	M/37/2135	UVC, percutaneous	No Yes	Sepsis, NEC, IUGR	Portal	LMWH/14	Yes	No	Cavernomatosis and PHT
28	F/40/3190	UVC UAC, percutaneous	Yes (portal) No Yes	PROM, asphyxia, hypothermia, RDS, sepsis	Portal	LMWH/7	–	No	No Withholding of treatment
29	F/31/1790	UVC, percutaneous	No No	RDS, sepsis, erythrocytosis	Portal	Watchful waiting, coagulopathy	–	–	Refractory pulmonary haemorrhage - hypoxaemia, CA, death (familial intrahepatic cholestasis type 2)

ASD, atrial septal defect; CA, cardiac arrest; CKD, chronic kidney disease; DM, diabetes mellitus; IUGR, intrauterine growth restriction; LMWH: low molecular weight heparin (150 IU/kg/day; monitored by measurement of anti-factor Xa levels [target, 0.35–0.7 IU/mL], first at 4 days and after weekly or every 15 days depending on measured levels); NEC, necrotising enterocolitis; NRFS, non-reassuring foetal status; PHT, pulmonary hypertension; PROM, premature rupture of membranes; rTPA, recombinant tissue plasminogen activator (0.1–0.5 mg/kg/h twice daily for 7 days); PE, pulmonary embolism; RA, right atrium; RDS, respiratory distress syndrome; UAC, umbilical artery catheter; UFH, unfractionated heparin (14–28 IU/kg/h); UVC, umbilical vein catheter.

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Does the incidence of congenital pulmonary malformations vary? 11 years of experience☆

¿Varía la incidencia de las malformaciones pulmonares congénitas?: 11 años de experiencia

Dear Editor:

Congenital lung malformations (CLMs) constitute a heterogeneous group of lung anomalies involving the airways, parenchyma and blood vessels. Historically, they have been considered infrequent, as their annual incidence has been documented to be of 1 case per 10,000–35,000 pregnancies[1] or about 30–42 cases per 100,000 inhabitants in the general population. There are also authors that assert that their diagnosis has improved considerably with the introduction of routine prenatal ultrasound examinations,[2] but few studies have analysed how their incidence has actually been changing in recent times.

In order to establish the incidence of CLMs in the autonomous community of Cantabria (Spain), we conducted a retrospective descriptive study of all cases of CLM managed in the Department of Paediatrics of the Hospital Universitario Marqués de Valdecilla in Santander, (Cantabria, Spain), specifically in the Units of Paediatric Pulmonology and Paediatric Surgery, in the period between January 2007 and December 2017. Our hospital is the tertiary care hospital that manages all complicated pregnancies in Cantabria, and we identified the patients using information obtained from the Department of Admissions and Clinical Records. In addition, we obtained data on the number of births during this period from the Instituto Cántabro de Estadística (Statistical Institute of Cantabria) and the Instituto Nacional de Estadística (National Institute of Statistics).

A total of 16 cases of CLM were diagnosed during the period under study, corresponding to 9 female patients and 7 male patients. The diagnosis was prenatal in 15 cases (93.7%), with the defect identified in the ultrasound examination performed at 22 weeks' gestation. All of these patients were evaluated with a chest radiograph and a chest ultrasound examination within 24 h from birth, and these imaging tests confirmed the presence of a CLM in the patients whose second trimester ultrasound examination had been positive. In the remaining patient, treated in 2007, the CLM was diagnosed at age 4 months by means of a chest radiograph and a computed tomography angiogram.

Table 1 presents the data on the annual incidence of CLM. The mean annual incidence was of 2.05 cases per 10,000 births (standard deviation, 3.26) and the median was 1.98 cases (interquartile range, 6.79), calculated with data through December 2016. We could not calculate the incidence for 2017 because at the time of this writing there is no published data on the number of births in Cantabria during this year. We ought to highlight the considerable variability between years, as 2 cases were diagnosed in a total of 31,137 children born between 2007 and 2012, compared to 12 cases diagnosed in a total of 17,710 children born between 2013 and 2016.

These data are consistent with the findings of a study by Stocker et al.,[3] who also found a significant interannual variability and reported an incidence of 1.27 cases per 10,000 births between 1994 and 1998 and an incidence that was nearly triple of 4.15 cases per 10,000 births between 2008 and 2012. Given the increase in the number of CLMs in recent years, we need to consider whether this results from an actual increase in incidence or improvements in diagnostic techniques. Stocker et al.[3] favour the hypothesis of an increased incidence, which is also supported by data in the EUROCAT registry, which shows an increase of 6.5% in some

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