Clinical Data of Neonatal Systemic Thrombosis

Paola Saracco, MD, PhD[1], Rossana Bagna, MD, PhD[2], Chiara Gentilomo, MD, PhD[3], Mariella Magarotto, MD, PhD[4], Alice Viano, MD[5], Federica Magnetti, MD[2], Paola Giordano, MD, PhD[6], Matteo Luciani, MD, PhD[7], Angelo Claudio Molinari, MD, PhD[8], Agnese Suppiej, MD, PhD[9], Luca Antonio Ramenghi, MD, PhD[10], and Paolo Simioni, MD, PhD[11], on behalf of the Neonatal Working Group of the Registro Italiano Trombosi Infantili (RITI)*

Objective To evaluate clinical data and associated risk conditions of noncerebral systemic venous thromboembolism (VT), arterial thromboembolism (AT), and intracardiac thromboembolism (ICT) in neonates.

Study design Data analysis of first systemic thromboembolism occurring in 75 live neonates (0-28 days), enrolled in the Italian Registry of Pediatric Thrombosis from neonatology centers between January 2007 and July 2013.

Results Among 75 events, 41 (55%) were VT, 22 (29%) AT, and 12 (16%) ICT; males represented 65%, and 71% were preterm. In 19 (25%), thromboembolism was diagnosed on the first day of life. In this "early onset" group, prenatal-associated risk conditions (maternal/placental disease) were reported in 70% and inherited thrombophilia in 33%. Postnatal risk factors were present in 73%; infections and central vascular catheters in 56% and 54% VT, respectively, and in 67% ICT vs 27% AT (<.05). Overall mortality rate was 15% and significant thromboembolism-related sequelae were reported in 16% of discharged patients.

Conclusions This report from the Registro Italiano Trombosi Infantili, although limited by representing an uncontrolled case series, can be used to develop future clinical trials on appropriate management and prevention of neonatal thrombosis, focusing on obstetrical surveillance and monitoring of critically ill neonates with vascular access. A thrombosis risk prediction rule specific for the neonatal population should be developed through prospective controlled studies. *(J Pediatr 2016;171:60-6)*.

Thromboembolism in hospitalized newborns and children is a rapidly increasing condition[1-5] associated with high morbidity. Neonatal data from infants with thromboembolism are critically needed in order for clinicians to develop appropriate management guidelines as well as prevention strategies. National and international registries[6-8] were implemented in various countries, targeting epidemiology and risk factors and developing clinical trials for improving outcomes of thromboembolism. In Italy, no published data on epidemiology of pediatric thromboembolisms were available. In 2008, a multicenter research network of Italian investigators, supported by the main national Pediatric Scientific Associations, developed through a secure web database a national prospective registry of pediatric thromboembolism called the Italian Registry of Pediatric Thrombosis (Registro Italiano Trombosi Infantili [RITI]). Primary aims were to enroll most cases of thromboembolism and to collect data on risk factors, treatments, and acute/long-term patient outcome, including perceived quality of life and information on social cost of pediatric thromboembolism. The data entered onto the registry were stratified by age and site of thromboembolism and divided into 4 categories of thromboembolism: systemic, arterial, venous, and cerebral thromboembolism because of arterial ischemic stroke, or sinovenous thrombosis. RITI was launched in March 2010, and a total of 700 thromboembolism events were entered through December 2014. The present report shows first data analysis of noncerebral systemic venous (VT) and arterial thromboembolism (AT) in newborns, focusing on clinical characteristics, site distribution, and associated conditions. Further data analysis focusing on treatment management, its safety and efficacy, and long-term outcome will be part of a separate report. Data analysis on neonatal cerebral sinovenous thrombosis and perinatal arterial ischemic stroke is still ongoing.

APLA	Antiphospholipid antibodies
AT	Arterial thromboembolism
CVL	Central vascular line
GA	Gestational age
ICT	Intracardiac thromboembolism
NICU	Neonatal intensive care unit
PC	Protein C
PS	Protein S
RITI	Registro Italiano Trombosi Infantili
TPN	Total parenteral nutrition
VT	Venous thromboembolism

From the [1]Pediatric Hematology, Department of Pediatrics, [2]Neonatal Intensive Care Unit, Department of Obstetrics and Neonatology, University Hospital Città della Salute e della Scienza, Torino, Italy; [3]Department of Pediatrics, Dell'Angelo Hospital, Venezia, Italy; [4]Neonatal Intensive Care Unit, Pediatrics, University Hospital of Padova, Padova, Italy; [5]Department of Pediatric Sciences, University Hospital Città della Salute e della Scienza, Torino, Italy; [6]Pediatric Hematology and Oncology, University of Bari, Bari, Italy; [7]Department of Hematology and Oncology and Transfusional Medicine, IRCCS Pediatric Hospital Bambin Gesù, Roma, Italy; [8]Thrombosis and Hemostasis Unit, Giannina Gaslini Children Hospital, Genova, Italy; [9]Child Neurology Unit, Pediatric University Hospital of Padova, Padova, Italy; [10]Neonatal Intensive Care Unit, Giannina Gaslini Children Hospital, Genova, Italy; and [11]Department of Medicine, Coagulation Diseases Unit, University of Padova Medical School, Padova, Italy

*List of additional members of the Working Group of the RTI is available at www.jpeds.com (**Appendix**).

The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2015.12.035

Methods

The recruitment is event-based. Data entered include identification of the investigator, documentation of informed consent, and anonymized patient data. The Registry is structured as a multiple choice questionnaire but also allows free text entries for further information; a centralized quality control procedure assessed all the events and, when needed, a member of the steering committee contacted the recruiting physicians about missing or inconsistent data.

Data retrieved from the close-ended questions include sex, gestational age (GA), Apgar score, family history of thrombosis (defined as occurrence of thromboembolism in first degree relatives aged less than 40 years), conditions (maternal, neonatal) associated with an established risk for thrombosis; presence of a central vascular line (CVL); infections (included meningitis, abscess, pneumonia, pyelonephritis, bacteriemia, fungemia, and sepsis); imaging techniques; treatment and outcomes; thrombophilia testing (performed in local laboratories): antithrombin, protein C (PC), or protein S (PS) plasma activity; factor V Leiden, prothrombin G20210A, and MTHFR C677T mutations; antiphospholipid antibodies (APLA) (lupus anticoagulant, anticardiolipin IgG and IgM, antibeta-2-glicoprotein IgG and IgM); lipoprotein(a); and plasma homocysteine levels. Normal value ranges of local laboratories was the basis for diagnosis of a deficiency; in case of no availability of local normal values, published reference ranges for neonatal age were used.[9-12] Deficiency of PC, PS, and antithrombin was considered as inherited if: (1) confirmed in subsequent age (at least after 6 months of age); or (2) found in 1 of the parents; or (3) after identification of a causative gene mutation.

The current report includes neonates (birth to 28 days) with a symptomatic or asymptomatic venous and arterial systemic thromboembolism confirmed by an imaging technique, diagnosed between January 2007 and July 2013, and enrolled in RITI. Age at time of thromboembolism diagnosis was corrected for GA: birth to 40 weeks GA +28 days. Events diagnosed after neonatal age and reported as presumed perinatal events were excluded from the present analysis; further exclusion criteria were inconsistency of data and impossibility to contact the referring physician. To extrapolate epidemiologic data, additional information as number of live births and number of admissions to neonatal intensive care unit (NICU) between January 2007 up to December 2013 was provided by 2 investigation centers (Torino center: P.S., R.B.; Padova center: M.M., C.G.) recruiting in the Registry all cases of thromboembolism consecutively diagnosed at their site in the 7-year period.

The study was conducted according to Helsinki declaration and parents gave informed consent to enrollment (www.trombosinfantili.it/consenso informato).

Fisher exact test or χ^2 was used to evaluate differences between groups. The significance level of P value was set at 0.05.

Results

Between January 2007 and July 2013, we recruited 21 neonates with systemic neonatal thromboembolisms from the Torino center (18 in neonates born at the center and 3 in babies transferred from other hospitals), and from Padova center, 18. During this period, the total number of live births at these 2 centers was 53 211 and 27 443, respectively, with 3561 (6.7%) and 2693 (9.8%) NICU admissions, accounting for an incidence of systemic neonatal thromboembolisms of 3.4 and 6.5/10 000 live births and of 5.8 and 6.6/1000 NICU admissions, respectively.

The following results on clinical data refer to 75 neonatal systemic thromboembolisms recorded in RITI up to July 2013: 41 (55%) VT, 22 (29%) AT, and 12 (16%) intracardiac thromboembolism (ICT). All events were first systemic thromboembolism occurring in 75 born live neonates. Cases were enrolled from 24 centers in Italy, most NICU centers.

General characteristics, imaging diagnosis, and outcome at discharge are summarized in **Table I**. Ethnicity was Caucasian in 97%. Males represented 65% (n = 49) of the cohort with no significant difference among type of thromboembolisms; median GA was 34 weeks (range 23-41 weeks); overall, preterm newborns represented 71% (77% AT, 68% VT, and 66% ICT). In 19/75 (25%), thromboembolism was diagnosed on first day of life ("early onset" thromboembolism): 8/42 VT (19%), 9/22 AT (41%), and 2/12 ICT (16%); 14/19 (74%) were in males and all but one (ICT) were in preterm. Overall, AT had earlier onset compared with VT (P = .07) and to ICT (P = .01). Among 41 VT, renal vein thrombosis (8/41:19%, and 8/75:11%) was diagnosed in 3/8 (37.5%) of cases at birth, with median birth age of 1 day (range 0-8 days); all renal vein thrombosis (8/8) occurred in males and in term newborns in 5/8 (62%).

Site locations of 75 events, including "early onset" thromboembolism and CVL-related thromboembolism, are described in **Table II**. Events were associated with symptoms leading to diagnostic imaging examination in 57 cases (76%): all cases of AT, 31/41 (75%) of VT, and 4/12 (33%) of ICT. Incidental diagnosis during imaging for concurrent disease (cardiac, infection) was reported for the remaining 18 cases (24%): 8 ICT, 4 portal VT, and 6 lower venous system VT. Symptoms alerting for AT were pallor, limb hypothermia (70%), absent pulse (60%), and mimics of aorta coarctation (9%). The most frequent symptoms for VT were edema (50%), limb dyschromia (34%), hematuria (17%), palpable abdominal mass (10%), and CVL malfunction (7%). Only 4 ICT were symptomatic (2 with respiratory distress and 2 with arrhythmia).

Risk Associated Conditions

Maternal and neonatal associated conditions are described in **Table III**. At least 1 prothrombotic condition was present in 76% of newborns with thromboembolism at time of