SIGNA VITAE 2012; 7(2): 29 - 32

ORIGINAL

Thrombosis in newborns: experience from 31 cases

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ABSTRACT

Thrombosis is the result of congenital or acquired prothrombotic risk factors. The incidence of thrombosis in the paediatric population is highest in newborns, as about 10% of thrombotic events occur in the first four weeks of life. Haemostasis in a newborn, though still developing, is a well balanced mechanism. About 90% of all thrombotic events are due to acquired and the rest to congenital risk factors.

The aim of our study was to estimate the incidence of thrombosis in a population of Slovenian newborns and to study risk factors, location and treatment of thrombotic events.

Inpatient charts of newborns with thrombosis, admitted to a tertiary neonatology centre and paediatric intensive care unit between 2004 and 2011, were studied retrospectively. Family history, location, aetiology and treatment of thrombosis were analysed.

Thirty one newborns, 17 boys (54.8%) and 14 girls (45.2%), with 31 thrombotic events were found. There were 17 cases (54.8%) of arterial and 14 cases (45.2%) of venous thrombosis. A family history of thrombophilia was found in two cases (6.5%). Twenty six cases (83.9%) were contributed to acquired risk factors and five (16.1%) to congenital aetiology. Four cases (12.8%) were treated, two with anticoagulation, one with thrombolysis and one with both. The estimated incidence of thrombosis was 0.17 per 1000 live births. Our data showed a higher incidence of thrombosis in Slovenian newborns and a higher incidence of congenital prothrombotic risk factors than in the data published so far.

Key words: newborn, thrombosis, incidence, risk factor, treatment

Introduction

Neonatal haemostasis is a dynamic process and changes dramatically in the first months of life. (1) It starts to develop as early as the 10th week of gestation when the foetus starts producing all the necessary coagulation factors by itself. Although several coagulation factors are present in very low concentrations and prolonged prothrombin time and activated partial thromboplastin time are usually present in newborns, haemostasis in a normal situation still works as a well balanced mechanism without a higher risk of thrombotic events. At birth, a term newborn has a 30 to 50% lower concentration of vitamin K-dependent procoagulant factors II, VI, IX, X, contact factors XI, XII, precalicrein and high-molecular weight kininogen. On the other hand, the concentration of anticoagulant factors, such as protein C, S, antithrombin and heparin cofactor II, is also lower. The fibrinolytic process is also diminished due to decreased concentration and activity of plasminogen and increased concentration of plasminogen activator inhibitors. The concentration of these factors rises in the next weeks of life and reaches adult values at about 6 months of life.

Generally, a thrombotic event is the result of congenital or acquired prothrombotic risk factors. (2) The incidence of thrombosis in the paediatric population is highest in newborns, as about 10% of thrombotic events occur in the first four weeks of life. (3) A healthy term newborn without prothrombotic risk factors does not risk thrombosis more than an older child. However, as prot-

Table 1. Distribution of thrombotic events.

Site of thrombosis	Number of events
Cerebral artery	13 (42%)
Cerebral vein	4 (13%)
Portal vein	4 (13%)
Limb vein	3 (10%)
Limb artery	2 (6%)
Abdominal aorta	2 (6%)
Other location	3 (10%)

Table 2. Acquired prothrombotic risk factors.

Risk factor	Number of newborns
Central vascular catheter	7 (27%)
Operation	6 (23%)
Sepsis	4 (15%)
Respiratory distress syndrome	4 (15%)
Necrotising enterocolitis	2 (8%)
Birth asphyxia	2 (8%)
Infant of diabetic mother	1 (4%)

Table 3. Congenital prothrombotic risk factors.

Risk factor	Number of newborns
Homozygotic MTHFR mutation	3
Factor V mutation	1
Prothrombin mutation	1
Antithrombin deficiency	1

hrombotic risk factors are more often present in this period of life, the likelihood of thrombosis increases almost fivefold in comparison to the general paediatric population. (4) Around 90% of all thrombotic events are due to acquired and the rest to congenital risk factors. (5) The aim of our study was to estimate the incidence of thrombosis in a population of Slovenian newborns and to study risk factors, location and treatment of thrombotic events.

Materials and Methods

Inpatient charts of newborns with thrombosis, hospitalized in the Department of Neonatology and the Department of Paediatric Surgery and Intensive Care, University Medical Centre Ljubljana, between 2004 and 2011, were studied retrospectively. Risk factors, age at presentation, location of the thrombotic event, aetiology and the treatment of thrombosis were analysed. Thirty one newborns, 17 boys (54.8%) and 14 girls (45.2%; male vs. female ratio 1.3) with 31 thrombotic events were found; their birth weight was from 620 to 4210 g (median 3380 g), their gestational age from 24 to 40 weeks (mean 36 weeks). Four newborns (12.9%) were small for their gestational age and seven (26.9%) were premature.

Results

The estimated incidence (data from two out of four tertiary centres in the 2 million Slovenian population) of thrombosis was 0.17 per 1000 live births. The median age at presentation was two days (range 0 to 28 days). There were 17 cases (55%) of arterial and 14 cases (45%) of venous thrombosis (arterial vs. venous ratio 1.2). The distribution of thrombotic events is summarised in table 1. Twenty six thrombotic events (84%) were attributed to acquired risk factors (table 2) and in five cases (16%) congenital aetiology was found (table 3). A family history of thrombophilia was positive in two cases (6%); in a mother of one child, deficiency of antithrombin was found, and antiphospholipid syndrome was found in another. Four newborns (13%) were treated, two with anticoagulation (low molecular weight heparin - LMWH), one with thrombolysis (alteplase) and one with both.

Discussion

Based on our data, the estimated incidence of thrombosis in Slovenian newborns was 0.17 per 1000 live births annually. The reported incidence of thrombosis in the neonatal period is 5.1 per 100.000 live births annually, (6) therefore the incidence we found is more than 3 times higher. In view of the fact that we included only two out of four Slovenian tertiary medical centres, covering about half of Slovenia's

population, the real incidence could be even higher. This could be due to a higher incidence of congenital prothrombotic risk factors in our population; on the other hand, the diagnostic facilities to identify newborns with thrombosis may be more sensitive or thrombotic events during therapeutic procedures more frequent. Further studies covering the whole population are needed to explain our result. The great majority of thrombotic events in our study were due to acquired risk factors, which is in accordance with previously published data. The most commonly acquired risk factor in our group was a central vascular catheter, which is known to be the most common cause of thrombosis in the newborn. (7) A catheter has a more or less thrombogenic composition, it mechanically injures vascular endothelium and changes blood flow by itself and by infused substances. Other risk factors such as polycythemia, perinatal asphyxia, respiratory distress syndrome, congenital heart disease, necrotizing enterocolitis, dehydration, sepsis, renal disease (e.g. congenital nephrotic syndrome and neonatal haemolytic-uremic syndrome) are also described and besides these, environmental factors such as immobilization, surgery, trauma, extracorporeal membrane oxygenation should be considered. In our group, four (13%) newborns were small for gestational age and seven (27%) were premature, but according to the studies performed so far no uniform conclusions about the role of intrauterine growth restriction or prematurity as risk factors were made. (8-11)

Congenital aetiology of thrombosis in our study was about five times rarer than acquired aetiology. However, the incidence of congenital aetiology was higher than in previously published data. (6,7) The most common congenital prothrombotic risk factors, such as mutation of the factor V gene (G169A), prothrombin gene (G20210A), antithrombin deficiency, protein C or protein S deficiency, C6775T homozygous mutation of the methylenetetrahydrofolate reductase (MTHFR) gene and the mutation of lipoprotein(a) gene, which are most commonly described in other studies, were also found in our group. Despite the fact that the presence of more than one risk factor is needed for a thrombotic event in the newborn period, as most children with a single congenital prothrombotic risk factor do not develop thrombosis until adulthood, (12) we did not find coexistence of risk factors, either congenital or acquired. A step by step laboratory diagnostic approach in a newborn with thrombosis of possible congenital aetiology, which is generally recommended, was used in all our patients according to the family history, epidemiological data and clinical presentation. Protein C, protein S and antithrombin activity are usually measured as a first step and lipoprotein(a), homocysteine, factor VIII and XII concentration as a second. The maternal antiphospholipid syndrome and transplacentally transferred antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein I) can also act as a cofactor in the development of neonatal thrombosis; the determination of these antibodies in the mother and, if she proves positive in the newborn, is essential. At the same time, the search for known gene defects, such as the G1691A mutation of factor V, the G20210A mutation of prothrombin and the homozygous C677T mutation of MTHFR gene, should be performed. If all these tests prove negative it is suggested that the diagnostic procedure should be expanded to even rarer causes, such as congenital dysfibrinogenemia and congenital dysplasminogenemia. (13)

Our study shows a slight but not important predominance of arterial versus venous thrombosis. This observation corresponds well to the published data, where arterial thromboses make up about 50% of all neonatal thrombotic episodes. (14) The most common location of thrombosis in our study was the cerebral artery, which was present in almost half of the newborns from the group. This location is also described as predominant in the literature, followed by the aorta, the left atrium, the renal, the mesenteric artery and limb arteries. (14) The distribution of thrombosis location in our group was slightly different, but it is difficult to compare our data to other studies due to the low number of cases studied. The most common location of venous thrombosis in our group was the cerebral vein, which is in contrast to locations described in the literature, where the most common locations are deep veins of the extremities, followed by pulmonary, renal, hepatic veins, the upper and lower vena cava, the right atrium, the portal, mesenteric, cerebral and retinal veins. (14)

Due to the lack of randomized controlled trials (RCT), recommendations for antithrombotic therapy in newborns are based on recommendations for adult patients and expert opinions of paediatric haematologists and neonatologists. These recommendations suggest the use of LMWH or unfractionated heparin for the treatment of neonatal thrombosis. (15) For symptomatic newborns with severe or several concomitant congenital prothrombotic risk factors prolonged anticoagulant therapy for up to 6 months is recommended. These newborns should also receive prophylactic LMWH in risky situations (e.g. indwelling central vascular catheters). Moreover, due to the lack of RCTs in this age group, thrombolysis is not recommended except if major arteries are occluded or if viability of an organ or limb is endangered. (16) If this is the case, ten days of thrombolytic therapy without further anticoagulant therapy is usually sufficient. In our group of patients, thrombolysis was used once for abdominal aorta thrombosis and once for femoral vein thrombosis after an operation for aortic coarctation. Only in this case was further anticoagulation therapy used.

Conclusions

Our data showed a higher estimated incidence of thrombosis in Slovenian newborns and a higher incidence of congenital prothrombotic risk factors than in the published data.

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