Management and outcomes of newborns at risk for inherited antithrombin deficiency

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Abstract

Background: As levels of antithrombin (AT) are low at birth, diagnosing inherited AT deficiency in newborns is challenging. In Stockholm, Sweden, pregnant women with known AT deficiency are referred to the Karolinska University Hospital, where local guidelines for management of newborns at risk of inherited AT deficiency have been established. Data on pregnancy, obstetric, and neonatal outcomes are recorded in a registry.

Objectives: We aimed to evaluate the current practice at the Karolinska University Hospital for managing delivery of newborns at risk for AT deficiency, the predictive value of AT levels at birth, and the neonatal outcomes of newborns with AT deficiency.

Patients/Methods: This was an observational, retrospective study. All children born to mothers with AT deficiency at the Karolinska University Hospital 2003-2018 were identified from the registry and included in the study. Data were collected from the medical records and the registry. AT activity was measured postnatally and after 6 months of age.

Results: The total study cohort included 41 newborns. There was a significant association between low AT values postnatally and after 6 months of age (P = .001). Half (21/41) of the children were diagnosed with AT deficiency; two suffered from sinus thrombosis, which presented at 10 days of age. Both children with sinus thrombosis were delivered using vacuum extraction.

Conclusions: The current practice of testing newborns can in most cases predict inherited AT deficiency. The risk for thrombosis during the neonatal period is enhanced by the use of instrumental delivery.

KEYWORDS
inherited antithrombin deficiency, newborns, sinus thrombosis, thrombophilia, venous thromboembolism
1 | INTRODUCTION

Thrombotic events in children are rare. According to a Canadian registry, the incidence of venous thromboembolism (VTE) is 5.3 per 10,000 hospital admissions and the overall incidence of VTE is 0.07 per 10,000 children, with the highest risk observed in children younger than 1 year of age. One of the most severe manifestations of VTE in young patients is cerebral sinus venous thrombosis (CSVT). Every year 0.34 to 0.67 per 100,000 children develop CSVT, of whom approximately 27% to 35% are neonates. Outcomes following CSVT vary, from uncomplicated neurological development in approximately 45% of the patients to death in 3% to 12%.2

Inherited antithrombin (AT) deficiency, a rare condition with a prevalence of 0.02% to 0.2%,4,5 significantly increases the risk of VTE. AT deficiency is inherited in an autosomal dominant manner; children of individuals with AT deficiency have 50% risk of inheriting the condition.6,7 There are two time periods during which incidence of VTE peaks in pediatric patients with AT deficiency, the first during the neonatal period and the second during adolescence.8 AT deficiency can be divided into two subtypes: type I is characterized predominantly by a reduction in the levels of AT (quantitative deficiency) and type II is caused by mutations that affect protein function (qualitative deficiency) with normal immunological activity. Type II is the most common in the general population.6 Different functional laboratory assays for measuring AT activity based on either thrombin inhibition or factor Xa inhibition are being used with varying efficacy in recognizing type II defects, therefore complicating the diagnostic procedure.4 The reference intervals for AT during the neonatal period vary, but AT levels are generally considered to be about 50% lower in infants compared to adults.9

In Stockholm, pregnant women with known inherited AT deficiency are generally referred to the Department of Obstetrics, Karolinska University Hospital, where local guidelines on management of newborns at risk of inherited AT deficiency are applied. The children are referred to the Pediatric Coagulation Unit for investigation and follow-up concerning AT deficiency. Due to the rarity of the condition and lack of international guidelines, it is essential to evaluate and update local management practices regularly. Additionally, there is ongoing debate on the optimal diagnostic algorithm and laboratory method for diagnosing inherited AT deficiency. This study aims to assess the efficacy of the current practice in diagnostics and management of newborns at risk of inheriting AT deficiency for research and quality purposes; the neonatal outcomes of children with inherited AT deficiency; as well as the correlation of AT activity in newborns with AT activity at 6 months of age, ie, the predictive value of postnatal AT levels.

2 | MATERIALS AND METHODS

2.1 | Study design and patient cohort

All pregnant women with known inherited AT deficiency in Stockholm County are primarily referred and followed up by the Department of Obstetrics, Karolinska University Hospital. A national registry for pregnant women with AT deficiency and their children was established in 2016 and includes deliveries from 1990 onward (retro- and prospective). The deliveries of children at risk for inherited AT deficiency are managed according to local guidelines (see below). Children at risk of AT deficiency are followed up by the Pediatric Coagulation Unit at Karolinska University Hospital and are included in the registry following their mothers’ consent. The initial follow-up includes blood sampling for AT measurement at birth and 6 months of age to confirm the diagnosis of AT deficiency. Thereafter, only the children with confirmed diagnosis are subsequently followed up.

This study was conducted as a retrospective observational cohort study. All children born to mothers with AT deficiency between 2003 and 2018 who were included and identified via the national patient registry for women with AT deficiency were eligible for inclusion.

Exclusion criteria were: (a) children with missing data on AT activity both postnatally and after 6 months of age and (b) children who had already turned 18 years of age or who had not reached the age of 6 months and subsequently had not yet undergone the initial recommended follow-up at the Pediatric Coagulation Unit. Data were collected both from the registry and the patients’ medical records, and included mode of delivery, AT values postnatally and after at least 6 months of age, the laboratory method used for the AT measurements, results from brain ultrasound at infancy, and data on thrombotic events (age at onset, site, radiologic method used for diagnosis, treatment, and long-term outcomes). During the time period covered by the study, the AT assay used at the Karolinska University Hospital has changed from factor Xa-based (reference interval at 6 months of age 0.85-1.25 kIU/L) to factor IIa-based (reference interval at 6 months of age 0.80-1.20 kIU/L). The local reference intervals for the neonatal period for both the factor Xa-based and factor IIa-based methods are 0.39-0.87 kIU/L (age < 5 days) and 0.41-0.93 kIU/L (5-30 days).

The registry and the subsequent studies stemming from it have been approved by the Regional Ethical Committee (Stockholm, Sweden).
2.2 | Local guidelines for management of newborns at risk of antithrombin deficiency at the Karolinska University Hospital

Instrumental delivery, such as vacuum extraction, is not recommended in order to avoid any trauma which could activate the coagulation system and increase the risk of thrombosis. If instrumental delivery has been used, in cases of decreased Apgar score or if immediate intravenous vein access is required, acute AT testing is performed. Otherwise, and in cases of unaﬀected infants, AT testing is usually performed in connection with the routine newborn blood sampling for screening of rare metabolic disorders (phenylketonuria [PKU] testing). The general recommendation is that sampling for PKU testing occurs after 48 hours of age, and in cases of infants at risk for AT deficiency sampling is preferably performed prior to discharge. Early discharge should be avoided. It is advised that the newborn and the mother remain at the hospital until breast-feeding is fully functioning to avoid dehydration, which is a risk factor for thrombosis. Before discharge, all newborns with suspected AT deﬁciency and AT activity under 0.5 kIU/L undergo brain ultrasound to screen for CSVT. Parents are instructed to seek medical care early on if the infant starts vomiting, shows decreased will to breastfeed, or in case of any signs of altered mental state, all of which could be an indication of thrombosis or stroke (Table 1). It is recommended that blood sampling for measurement of AT is repeated after 6 months of age to verify the diagnosis.

2.3 | Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 for Windows (SPSS Inc). Mann-Whitney U test was used to compare continuous variables between the group with AT deﬁciency and the group suspected for, but ultimately not diagnosed with, AT deﬁciency. Correlation between AT levels during the newborn period and after 6 months of age was evaluated using the Pearson correlation coefficient. Linear regression was used to illustrate the relationship between these variables, with AT values during the newborn period serving as the independent variable and AT values after 6 months of life as the dependent variable. The statistical signiﬁcance of the association between having subnormal AT values lower than the reference range during the newborn period and after 6 months of age was evaluated using Fisher’s exact test. P values < .05 were considered statistically signiﬁcant.

3 | RESULTS

3.1 | Study cohort

Of the 38 women with known AT deﬁciency giving birth at Karolinska University Hospital during the study period, all but one consented to be included in the registry and their children were eligible for inclusion in the study. The 37 mothers had in total 72 pregnancies, of which three resulted in intrauterine fetal death (IUID). Of the 69 newborns, 28 were excluded (18 due to missing data, 9 because they were already ≥ 18 years old, and 1 child had not yet turned 6 months old). The total study group comprised 41 newborns, 21 of whom were diagnosed with AT deﬁciency (data on diagnosis missing on 4 children). Two children were judged not to have AT deﬁciency without further testing based on one normal value (0.65 and 0.74 kIU/L, lower reference interval 0.39 kIU/L), which is against the recommended clinical practice.

TABLE 1 Local guidelines for management of newborns with mothers who have known inherited AT deficiency, Karolinska University Hospital, Stockholm, Sweden

| Heredity for AT deficiency during the perinatal period |
|------------------------------------------------------|
| If the newborn has antithrombin deficiency, there is an increased risk of thrombosis including stroke. The following guidelines for the delivery and management of the child are recommended |
| 1. If possible, avoid instrumental delivery such as forceps or vacuum extraction to avoid bleeding that could trigger the coagulation system and lead to secondary thrombosis |
| 2. Early measurement of antithrombin level is recommended in cases of instrumental delivery or a distressed child with impaired Apgar score and/or need for intravenous access |
| 3. In cases of an unaffected child and normal delivery, the antithrombin level of the child is tested in connection with the PKU test. Early discharge is discouraged |
| 4. Brain ultrasound is recommended before discharge with a distressed child as soon as possible. If the antithrombin level of the child is above 0.5 kIE/L, ultrasound can be omitted |
| 5. Breastfeeding should be successful before discharge to avoid dehydration, which could lead to increased thrombosis risk |
| 6. Parents are instructed to contact the hospital if there are difficulties in breastfeeding, vomiting, lethargy, or decreased general condition which could indicate stroke or thrombosis |
| 7. Inform the pediatric coagulation center of the antithrombin level if the child is well; with distressed child contact the coagulation consultant immediately to discuss further investigation and treatment including antithrombin substitution |

Diagnosis of AT deﬁciency was established by AT measurement after 6 months of age in all but two cases. In those two cases, the patients had been diagnosed with neonatal CSVT and were diagnosed with AT deﬁciency at the time of the event, ie, before 6 months of age. In both cases the diagnosis of AT deﬁciency was later veriﬁed by additional sampling.

Data on mode of delivery was missing in six children. Twenty-five children (out of the 35 children for which data were available) were born via non-assisted, normal vaginal delivery (VD), two were born via vacuum extraction (by VD), seven were born by caesarean section (CS), and one by CS with vacuum extraction (Table 2).

There were no statistically signiﬁcant diﬀerences in gestational age, birth weight, or Apgar scores between the children who were diagnosed with AT deﬁciency and those who were not. The mean gestational age for those with and without AT deﬁciency was 39.6 weeks (SD 1.5) and 38.7 weeks (SD 1.3), respectively (P = .451). The median birth weights were 3305 (range
Measurements of antithrombin

AT values at birth were measured during the first 4 days of life in 27 newborns and between 4 to 10 days of life in 3 additional newborns, exact whereas the date of early postnatal testing was missing for 1 more child. In total 31 children were tested during the postnatal period. AT was measured after 6 months of age in 34 cases (excluding 1 child who was tested again shortly before reaching the age of 6 months). Twenty-four children were tested at both time points (and one child was tested postnatally and at 5 months of age), while only one blood sampling was available for 16 children. The reasons for these deviations from the recommendation are not mentioned in the patients’ medical records. Children who were later diagnosed with AT deficiency had lower values already as newborns as compared with those who did not have AT deficiency (mean AT as newborn was 0.34 and 0.59 kIU/L, respectively; Table 3). After 6 months of age, the mean AT in children with AT deficiency was 0.64 kIU/L (normal lower limit 0.80-0.85 kIU/L).

### TABLE 2 Characteristics of study group

|                     | Total n (%) | AT deficiency diagnosis n (%) | No AT deficiency diagnosis n (%) |
|---------------------|-------------|------------------------------|---------------------------------|
| **Gender**          |             |                              |                                 |
| Female              | 21 (51.2)   | 10 (47.6)                    | 8 (38.0)                        |
| Male                | 20 (48.8)   | 11 (55.0)                    | 8 (40.0)                        |
| Total               | 41 (100)    | 21 (51.2)                    | 16 (39.0)                       |
| **Mode of delivery**|             |                              |                                 |
| Vaginal delivery    | 25 (71.4)   | 15 (78.9)                    | 10 (62.5)                       |
| Vacuum extraction   | 3 (8.6)     | 2 (10.5)                     | 1 (6.3)                         |
| Caesarean section   | 7 (20.0)    | 2 (10.5)                     | 5 (31.2)                        |
| Total               | 35 (100)    | 19 (100)                     | 16 (100)                        |
| **Ultrasound result**|            |                              |                                 |
| Normal              | 21 (60.0)   | 15 (71.4)                    | 4 (25.0)                        |
| Abnormal            | 1 (2.8)     | 1 (4.8)                      | 0                               |
| Not performed       | 13 (37.1)   | 3 (14.3)                     | 8 (75.0)                        |
| Total               | 35 (100)    | 19 (100)                     | 12 (100)                        |

Abbreviations: AT, antithrombin; n, number of cases.

a Data on AT deficiency diagnosis missing in four children.

b Data on mode of delivery missing in six children.

c One was delivered by caesarean section and vacuum extraction.

d Cranial ultrasound performed during the first 10 days of life. Data on ultrasound missing in six children.

e Data on AT deficiency diagnosis missing in two children.

### TABLE 3 Values of antithrombin during the neonatal period (at birth) and after 6 months of age

|                      | Total Mean (SD), median (range) | AT deficiency diagnosis Mean (SD), median (range) | No AT deficiency diagnosis Mean (SD), median (range) |
|----------------------|---------------------------------|-----------------------------------------------|-----------------------------------------------|
| AT values (kIU/L)     |                                 |                                              |                                              |
| At birth (n = 27)a    | 0.44 (0.15), 0.38 (0.27-0.81)   | 0.34 (0.05), 0.33 (0.30-0.46)                 | 0.59 (0.12), 0.56 (0.42-0.81)                 |
| Measured day 0-4 of life (n = 24) | 0.44 (0.13), 0.40 (0.27-0.74)   | 0.34 (0.05), 0.33 (0.30-0.46)                 | 0.57 (0.10), 0.55 (0.42-0.74)                 |
| Measured day 5-10 of life (n = 3) | 0.51 (0.26), 0.38 (0.33-0.81)   | 0.36 (0.04), 0.36 (0.33-0.38)                 | 0.81b                                          |
| After 6 months (n = 34) | 0.84 (0.26), 0.72 (0.49-1.30)   | 0.64 (0.11), 0.62 (0.49-0.96)c               | 1.13 (0.08), 1.12 (0.97-1.30)                 |

Abbreviations: AT, antithrombin; kIU/L, kilo international unit/liter; n, number of cases; SD, standard deviation.

a Four children with missing diagnosis on antithrombin deficiency diagnosis were excluded.

b n = 1.

c The AT value of 0.96 kIU/L in one child was later found to be lower using a different assay; the child was diagnosed with AT deficiency.
In three cases, the measurement of AT levels in infants after 6 months of age was performed using a different laboratory method than the method used for measurement of AT in the mothers. Two of the children had normal AT activity on both occasions. In the third case, AT values on the first day of life were subnormal (0.33 kIU/L) but were normal at the age of 9 days (0.51 kIU/L). Both measurements were performed using the activated factor X (FXa) method (reference interval 0.41-0.93 kIU/L). When the measurements were repeated after 6 months of age using an activated factor II (FIIa)-based method, the value was normal (0.96 kIU/L, reference interval 0.80-1.20 kIU/L; Figure 1, indicated by an arrow). This child was born prematurely at week 32 + 2 through emergency CS. Apgar scores were 3, 6, and 8 after 1, 5, and 10 minutes, respectively. The child was admitted to the neonatal intensive care unit due to prematurity, asphyxia, and acute respiratory distress syndrome. As the AT measurement after 6 months of age was performed with a different assay than the one used to diagnose AT deficiency in the mother, the mother was also tested with the FIIa method at the same time as the child. The mother had normal AT when using the FIIa method, suggesting that this assay could not recognize the AT deficiency in the family. A fourth analysis of the child's AT activity 1 month after the previous normal measurement showed AT activity below the reference interval (0.64 kIU/L; reference interval 0.85-1.25 kIU/L) with the FXa assay and normal values using the FIIa-based assay. The child was thereby diagnosed with type II AT deficiency. The child's mother was tested using the FXa method at the same time as the fourth measurement of the child, which showed reduced AT activity even in her case.

There was a significant correlation between AT values during the first 10 days of life and after 6 months of age in the 24 children with AT measurements at both time points (Pearson correlation coefficient $r = .84, P$-value: $\leq .001$; Figure 1). AT values at birth were measured by the FXa-based method in all cases (data on method missing in three cases). Normal AT activity during the first 4 days of life was associated with normal AT activity after the age of 6 months ($P = .001$). In two cases AT values at birth were normal (0.45 and 0.46 kIU/L; reference interval 0.39-0.81 kIU/L) and subnormal after 6 months (0.71 and 0.73 kIU/L; reference interval 0.85-1.25 kIU/L). All four measurements were performed using an FXa assay. In a third case, AT levels were subnormal at birth and normal after 6 months of age. This was the same newborn in whom AT deficiency was diagnosed by using the FXa method (see above).

### 3.3 | Neonatal thrombosis and perinatal management

Ultrasound screening for CSVT was performed in 22/35 children (data missing for 6 patients), 18 of whom (82%) had AT activity under 0.5 kIU/L at the first AT screening. Of the 13 children who did not undergo ultrasound screening 2 had AT activity under and 11 had AT activity over 0.5 kIU/L at the first AT screening (Table 2). Thrombosis (CSVT) occurred in 2/21 (9.5%) infants with AT deficiency. The first child with CSVT was a female with a birth weight of 2645 g born week 36 + 3 by vacuum extraction. Apgar scores were 7, 10, and 10 points after 1, 5, and 10 minutes, respectively. The AT activity was below the reference interval (0.39 kIU/L). The second child was a male with a birth weight of 2625 g born week 36 + 2 by vacuum extraction. Apgar scores were 7, 10, and 10 points after 1, 5, and 10 minutes, respectively. The AT activity was below the reference interval (0.39 kIU/L).
value on the first day of life was 0.32 kIU/L using the FXa method. At the age of 10 days the child showed symptoms of lethargy and reluctance to breastfeed and had seizures. Ultrasound and computed tomography (CT) were performed and showed intraventricular hemorrhage, and bleeding in the basal ganglia and the thalamus area. The patient was treated with anticonvulsants and fresh frozen plasma. Magnetic resonance imaging (MRI) of the brain was performed at the age of 3 weeks and showed CSVT and posthemorrhage hydrocephalus. The treatment was then switched to heparin and AT concentrate (Atenativ®) until the age of 4 months. At 7 weeks of life, the patient developed thrombosis in the superior vena cava in connection with sepsis and was treated with thrombolysis for 3 days. The patient developed late sequelae in the form of tetraplegia, epilepsy, and cerebral palsy.

The second thrombotic event occurred in a full-term boy with a birth weight of 3460 g, who was also delivered with vacuum extraction. Apgar scores at birth were 8, 9, and 10 after 1, 5, and 10 minutes respectively. AT value at day 9 of life was 0.33 kIU/L using the FXa method. No brain ultrasound was performed at birth. After 10 days of life, the patient developed right-sided seizures. CT and MRI showed massive CSVT and multiple secondary parenchymal bleedings. The patient was treated with heparin and AT concentrate. Follow-up CT at 3 weeks of life showed partial regression of the thrombosis. MR angiography at 5 months of age showed complete resolution of the clot, with only some secondary changes seen in the right temporal lobe. The patient did not suffer from any residual sequela.

A third infant with AT deficiency was treated with AT concentrate prophylactically. This male was born in week 36 + 4 by CS due to breech position. His birth weight was 2550 g and he had Apgar scores 6, 7, and 10 after 1, 5, and 10 minutes respectively. AT value at day 9 of life was 0.32 kIU/L. His brain ultrasound at birth was normal. After 2 days, he showed signs of indolence and was treated with AT concentrate as a precaution. He recovered fully without any verified thrombosis. No AT values were measured during the newborn period; however, later testing showed decreased AT values and the boy was eventually diagnosed with AT deficiency.

4 | DISCUSSION

AT deficiency is a rare condition in the general population. Early diagnosis is difficult as newborns have naturally low AT activity; AT level may be additionally low due to coagulopathy, increased consumption, or compromised liver function in critically ill newborns. Furthermore, the potential of functional laboratory assays in recognizing different types of AT deficiency type II varies. Due to the rarity of this condition, management of newborns with inherited AT deficiency is largely based on clinical experience and local routines. Our study shows that the current local guidelines on management of newborns at risk for inheriting AT deficiency at Karolinska University Hospital are effective. Furthermore, we demonstrated the prognostic value of low AT values in newborns in identifying children later diagnosed with AT deficiency. The neonatal blood sampling may coincide with the blood sampling for the Swedish newborn screening test if this is performed before discharge, because it is important that the initial AT measurement for well newborns is completed before discharge. We believe that the early initial testing of AT levels (while still in the maternity clinic) minimizes the risk for misunderstanding and errors.

A recent large multicenter study from Spain and Belgium by de la Morena-Barrio et al recruited 968 patients of all ages with AT deficiency. They found 73 patients with a thrombotic event, 15 of whom were neonates. The neonates had unusual sites of thrombosis, including cerebral veins, renal veins, and upper extremities; severe outcomes; and often provoking factors such as assisted delivery (forceps or vacuum extraction). Vacuum extraction, forceps delivery, and emergency CS are associated with up to 60% of CSVT events in newborns. In our study, both children with CSVT had been delivered via vacuum extraction, which was against the local recommendations and confirms the results presented in the aforementioned studies. It is therefore paramount to avoid instrumental delivery when the newborn is at risk of inherited AT deficiency.

Due to the phenomenon called "developmental hemostasis," the levels of coagulation factors and inhibitors in healthy newborns differ from those of older children and adults. In cases of ill newborns, liver function may be affected, causing additionally decreased coagulation factors and inhibitors, including AT. Therefore, diagnosis of AT deficiency at the Karolinska University Hospital is established only after 6 months of age using the AT values from two separate blood samplings, except for children with both thrombosis and low AT levels. As expected, approximately half of the children in our study were diagnosed with AT deficiency. The newborns diagnosed with AT deficiency had lower values at birth compared with the group not diagnosed with AT deficiency. Of note, among the children diagnosed with AT deficiency at 6 months of age, none had AT values exceeding 0.50 kIU/L at birth, a level at which brain ultrasound before discharge is not considered necessary according to the local guidelines. This supports the current management of newborns with risk for AT deficiency. In spite of normal AT activity at birth, new testing should nonetheless be performed after 6 months of age. Two cases from our study showed normal AT levels at birth; however, both children were found to have reduced AT activity after 6 months of age and were therefore diagnosed with AT deficiency. Thus, the postnatal testing can reliably diagnose or rule out AT deficiency in most, but not in all, cases. An alternative approach would be to test AT levels only after 6 months of age in asymptomatic children without instrumental delivery; in these cases, we emphasize the importance of information to the families on typical and atypical symptoms of thrombosis that can present after discharge.

Both children with CSVT showed symptoms of distress first after 10 days of life and initially underwent brain CT. In the first case, the CT only showed intracerebral hemorrhage and the diagnosis of CSVT was established after 3 weeks of life by MRI, which delayed initiation of treatment with anticoagulants and led to permanent injuries. MRI has higher sensitivity in detecting CSVT and is
the generally recommended radiologic modality to diagnose CSVT in newborns.\textsuperscript{11,12} The recommended radiologic modality used merely as screening for CSVT in neonates according to the guidelines at Karolinska University Hospital is brain ultrasound. It has been suggested that 48% of CSVT in newborns can be detected via power Doppler ultrasound.\textsuperscript{13} Intraventricular hemorrhage, absent or decreased blood flow in the sinuses, and white matter changes on ultrasound should raise suspicion of CSVT.\textsuperscript{14} Of the three patients treated with AT concentrate in our study, two had ultrasound performed during the neonatal period. One result was pathological, showing intracranial bleeding but not the underlying thrombosis, whereas the other ultrasound was normal, but the child was treated prophylactically due to symptoms. It is unclear whether the child had indeed developed CSVT, which was not detected during the ultrasound investigation and resolved after the prophylactic AT concentrate. Due to small number of patients we cannot draw conclusions on the benefit or effectiveness of ultrasound as a screening method. It is included in the local guidelines as it is non-invasive, simple, and widely available for CSVT screening, and because delayed diagnosis can lead to severe post-thrombotic sequelae. Nevertheless, normal findings can give a false sense of security which needs to be addressed by explaining the limitations of the screening method to the families and the importance of close observation for any signs of discomfort or symptoms in the child.

AT measurements in three children were performed using different methods than the type used for AT analysis in their mothers. AT deficiency was diagnosed at 6 months of age in only one child by using a different method than the one used at birth. AT activity was initially low according to the FXa method (birth) and then normal by both the FXa (9 days of age) and the FIIa (6 months of age) methods and finally low according to the FIIa method. During the first test the child was critically ill and probably received transfusions of blood components thereafter, which could explain the normalization of the AT measurements. The third test was performed when the child reached 6 months of age using the FIIa method and failed to detect AT deficiency, which was later verified by the FXa-based method. This example demonstrates the difficulties in diagnosing type II defects.\textsuperscript{15} Previous studies have suggested that more than one laboratory assay should be used to eliminate the risk of missing individuals with AT deficiency regardless of their mutation causing the deficiency.\textsuperscript{16} We suggest that the same laboratory assay previously used to establish the diagnosis in the mother is used for the child or alternatively that both the child and the mother with known AT deficiency are tested at the same time using the same method.

The main limitation in this study was the relatively small study group of 41 children approximately half of whom had AT deficiency. Furthermore, as this was a retrospective study, data were not available for all patients. Several children were excluded due to lack of antithrombin measurements. Further, three children were born via vacuum extraction, which is against the recommendations. Whether this was due to obstetric complications is unclear. The reason behind the deviations from the recommendations is unknown. Miscommunication on the mothers’ thrombophilia and subsequent noncompliance with recommendations for its management could explain the missing data. After establishing the diagnosis of AT deficiency for the young children and informing the parents, we believe that it is important to even plan the follow-up so that the children themselves will get proper information about the risk for thrombosis at adulthood.

We conclude that subnormal AT values at birth predict inherited AT deficiency in the majority of cases. The timing for the blood samplings (prior to discharge from the hospital and after 6 months) should be incorporated in the written guidelines to minimize errors. Based on this study, we recommend use of the same AT assay in all family members who are tested. Due to the small number of patients we cannot draw conclusions on the benefit or effectiveness of ultrasound as a screening method. Whether children at risk for inherited AT deficiency and traumatic delivery or other signs of distress should receive AT concentrate prophylactically to avoid thrombus formation is not clear and the data is not sufficient to make a recommendation.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Rozia Chaireti co-designed the study, contributed to data analysis and interpretation and wrote the manuscript along with Susanna Ranta. Ida Trönnhagen gathered most of the data and contributed to data analysis and interpretation. Katarina Bremme co-designed the study, gathered data, and contributed to data analysis and interpretation. Susanna Ranta designed the study, contributed to data analysis and interpretation, and wrote the manuscript along with Rozia Chaireti. All authors revised the manuscript.

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REFERENCES

1. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children – first analyses of the Canadian registry of VTE. Blood. 1994;83:1251-1257.
2. Alvis-Miranda HR, Milena Castellar-Leones S, Alcala-Cerra G, Rafael M-S. Cerebral sinus venous thrombosis. J Neurosci Rural Pract. 2013;4:427-438.
3. Berfelò FJ, Kersbergen KJ, van Ommen CH, et al. Neonatal cerebral sinus venous thrombosis from symptom to outcome. Stroke. 2010;41:1382-1388.
4. Khor B, Van Cott EM. Laboratory tests for antithrombin deficiency. Am J Hematol. 2010;85:947-950.
5. Qi X, De Stefano V, Wang J, et al. Prevalence of inherited antithrombin, protein C, and protein S deficiencies in portal vein system thrombosis and Budd-Chiari syndrome: A systematic review and meta-analysis of observational studies. J Gastroenterol Hepatol. 2013;28:432-442.
6. Patnaik MM, Moll S. Inherited antithrombin deficiency: a review. Haemophilia. 2008;14:1229-1239.
7. Kumar R, Chan AK, Dawson JE, Forman-Kay JD, Kahr WH, Williams S. Clinical presentation and molecular basis of congenital
antithrombin deficiency in children: a cohort study. Br J Haematol. 2014;166:130-139.
8. de la Morena-Barrio B, Orlando C, de la Morena-Barrio ME, Vicente V, Jochmans K, Corral J. Incidence and features of thrombosis in children with inherited antithrombin deficiency. Haematologica. 2019;104:2512-2518.
9. Saracco P, Parodi E, Fabris C, Cecinati V, Molinari AC, Giordano P. Management and investigation of neonatal thromboembolic events: genetic and acquired risk factors. Thromb Res. 2009;123:805-809.
10. Jayakody Arachchillage DR, Gaspar M, Makhecha S, Laffan M. Use of antithrombin concentrate for acquired antithrombin deficiency in acutely unwell children receiving unfractionated heparin. Semin Thromb Hemost. 2019;45:859-864.
11. Canedo-Antelo M, Baleato-Gonzalez S, Mosqueira AJ, et al. Radiologic clues to cerebral venous thrombosis. Radiographics. 2019;39:1611-1628.
12. Grabowski EF, Buonanno FS, Krishnamoorthy K. Prothrombotic risk factors in the evaluation and management of perinatal stroke. Semin Perinatol. 2007;31:243-249.
13. Grunt S, Wingeier K, Wehrli E, et al. Cerebral sinus venous thrombosis in Swiss children. Dev Med Child Neurol. 2010;52:1145-1150.
14. Kersbergen KJ, Groenendaal F, Benders MJ, de Vries LS. Neonatal cerebral sinovenous thrombosis: neuroimaging and long-term follow-up. J Child Neurol. 2011;26:1111-1120.
15. Javela K, Engelbarth S, Hiltunen L, Mustonen P, Puurunen M. Great discrepancy in antithrombin activity measured using five commercially available functional assays. Thromb Res. 2013;132:132-137.
16. Kristensen SR, Rasmussen B, Pedersen S, Bathum L. Detecting antithrombin deficiency may be a difficult task—more than one test is necessary. J Thromb Haemost. 2007;5:617-618.

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