Clinical diversity of cerebral sinovenous thrombosis and arterial ischemic stroke in the neonate: a surveillance study.

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Abstract

Background

Incidence, risk factors, clinical presentation, onset of symptoms and age at diagnosis differ between arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) in the neonate. Distinguishing these two entities early and clinically can be of eminent importance.

Methods

Active surveillance for AIS and CSVT was performed in 345 German pediatric hospitals. Reported cases were validated with questionnaires. Only cases confirmed by cerebral MRI were included in our analysis. Both groups of patients (AIS and CSVT) were compared with regard to age at diagnose, pattern of clinical symptoms and risk factors.

Results

Data on 144 AIS and 51 CSVT neonatal cases were collected from 2015 to 2017. The relative risk of AIS was 2.8 [95% CI 2.1; 3.9] times higher compared to CSVT. CSVT patients were more likely to be born premature (CSVT 14/48, 29.2%; AIS 19/140, 13.2%; $p = 0.02$), to have signs of perinatal acidosis (e.g. umbilical artery pH ≤ 7.1 30.2% CSVT vs. 13.5% AIS $p = 0.01$). Generalized seizures and lethargy were more likely to occur in infants with CSVT ($p < 0.0001$). Age at onset of symptoms and at time of diagnoses was shifted to older ages in CSVT ($p < 0.0001$).

Conclusion

The risk for AIS is about three times higher than for CSVT in neonates. A higher proportion of critically ill infants in CSVT and a later onset of symptoms may indicate that perinatal and postnatal risk factors are more important for CSVT than for AIS. The data point to the need for awareness of CSVT in critical ill infants.

Background

Perinatal stroke comprises a miscellaneous group of cerebrovascular diseases, occurring from 28 weeks' of fetal life through 28th postnatal day [1, 2] with an incidence of 1 in 1600-2300 births [3]. Arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT) are the most frequent forms of stroke and usually become acutely symptomatic within the neonatal period.

Although many cases of perinatal stroke experience normal neurological outcome or only mild disabilities, a substantial proportion of cases yields in hemiparetic cerebral palsy, epilepsy and cognitive deficiencies accounting for impaired quality of life [3]. Initial clinical differentiation of AIS and CSVT can be a challenging task. Therefore, comparison of AIS and CSVT with respect to risk factors, onset and clinical presentation is of interest to improve precision of clinical diagnosis and to guide appropriate imaging techniques to confirm

suspected diagnosis. A better understanding of causation of clinical presentation and risk factors for these two entities would be of great value to standardize the clinical approach in the intensive care nursery. In addition, better identification of clinical differences might support the understanding of underlying etiologies needed for patient selection for future therapy. So far, there is no population-based study comprising these two types of acute perinatal stroke. While most studies focus on one type only, we had the unique opportunity to compare two common types with a population-based dataset with contemporaneous and uniform case ascertainment in the neonatal period.

Methods

Case ascertainment

From January 1, 2015 to December 31, 2017 all 345 pediatric hospitals in Germany were asked to report any case of AIS or CSVT in infants less than 28 days of life on a monthly basis. Active surveillance (null option possible) was carried out by the German Pediatric Surveillance Unit (ESPED) monitoring rare diseases in childhood [4]. Identification of a case prompted a study specific questionnaire filled out by the responsible physician to provide detailed case information. Based on these questionnaires, the study group, including a pediatric neurologist (LG) and three neonatologists (MK, MD., UF) validated the respective case definitions for AIS and CSVT.

Case definition

The case definition included any case of AIS or CSVT diagnosed within 28 days after birth by cerebral ultrasound, MRI- or CT-scan. Cases without MRI confirmation (n=24) were excluded from our study to minimize misclassification of AIS and CSVT. For further characterization the questionnaire addressed multiple topics including gestational age, sex, underlying diseases, potential risk factors, time of diagnosis, observed clinical symptoms and applied imaging techniques describing extent of the injury.

Statistical Analysis

We performed an available case analysis without excluding files with missing data to avoid loss of efficiency. All relevant variables were reported in 90% of the cases. Categorical variables were presented as absolute numbers and percentage of the available population. Continuous variables were given as median with the interquartile range (IQR). For comparison appropriate statistical tests were applied.

Age at diagnosis was calculated as time gap in days between birth and date of confirmation of the diagnosis, for age at onset of symptoms as time gap in days between birth and reported date of onset of symptoms. To investigate differences in duration from birth until onset of symptoms and until confirmation of diagnosis we applied survival analyses using the product limit estimator and log-rank-test.

Neonates born prior to 37^{+0} weeks of gestation were considered to be premature. Small for gestational age (SGA) and large for gestational age (LGA) were defined by birthweight below 10^{th} percentile and birthweight above 90^{th} percentile. We used a 5-minute-Apgar below 7 [5, 6] and an umbilical artery blood pH below 7.1 as indicator for perinatal asphyxia [7]. A list of additional possible symptoms was offered in the questionnaire

with the option for multiple answers. If no clinical information was reported we assumed absence of risk factor.

Relative risk of AIS and CSVT was calculated by using the number of live births in the three year period provided by the German Federal Statistical office (n=2,314,617) [8].

Due to anonymous reporting in ESPED the need for parental consent was waived. Ethical approval was obtained by the ethics committee of the Medical Faculty of the Ludwig-Maximilians-University, Munich, Nr 42-15 (05-04-2015).

We used a significance level of 5% for all analyses. To account for multiple comparisons p-values were validated by Benjamini-Hochberg Procedure [9]. All statistics have been calculated using SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina). The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

Population

In total, 245 cases were reported to the German pediatric surveillance (ESPED) during the study period. 21 cases were false or double reports, a simultaneous report for AIS and CSVT was given in one case and four questionnaires were not returned. 22 cases were diagnosed using ultrasound and 2 cases were identified by CT. These files were excluded from further analysis in order to include only cases validated by MRI. 51 cases with CSVT and 144 with AIS remained for further analysis. Based on these data, the relative risk of AIS was 2.8 [95% CI 2.1; 3.9] times higher compared to CSVT.

Neuroimaging

Prior to MRI, cerebral ultrasound was performed in 188 (96.4%) cases. In 60% of cases, AIS or CSVT has been recognized on initial ultrasound.

Among 144 AIS cases only one brain area was affected in 36 (25%) patients. The most frequent affected areas were parietal, temporal, frontal and occipital lobe. In 73 cases more than one area was affected. In 35 cases physicians did not specify the affected brain area, but indicated whether the infarction was right, left or bilateral. 75 AIS cases were depicted on the left side while 43 cases were identified on the right side and n = 19 cases were affected on both sides (n = 7, side not specified).

Among 51 CSVT cases, a single sinus was affected in 23 cases (45%). Venous thrombosis was detected in 7 out of 23 cases in the transvers sinus and in 16 of 23 cases in the superior sagittal sinus. In 24 cases (47%) multiple sinuses were affected, predominantly in the combination of superior sagittal and transverse sinus.

Risk factors and case characteristics of AIS and CSVT patients

No differences in anthropometric data and perinatal characteristics were detected (Table 1). Both entities were more common in boys (AIS 96/144, 66.7%; $p < 0.0001$; CSVT 34/51, 66.7%; $p = 0.02$). The ratio of preterm (AIS 13.2%; CSVT 29.2%) infants exceeded the average premature birth rate in Germany (~8%) [10]. However, CSVT was identified more often in premature infants compared to AIS cases ($p = 0.02$) although gestational age was not significantly different between both groups (Table 1).

Table 1. Characteristics of AIS and CSVT patients (n=number of questionnaires with available information)

	AIS		CSVT		p-value
	n		n		
General infant characteristics					
Sex	144		51		
male		96 (66.7)		34 (66.7)	1.00
female		48 (33.3)		17 (33.3)	
Gestational age [weeks^{+days}]	140	39^{+3} (35^{+4}; 40^{+2})	48	39^{+1} (35^{+4}; 40^{+3})	0.21
premature infants (< 37^{+0})	140	19 (13.2)	48	14 (29.2)	**0.02**
gestational age preterm infants [weeks^{+days}]	19	34^{+5} (33^{+3}; 35^{+4})	14	33^{+0} (30^{+6}; 34^{+5})	0.09
Multiples	143		50	3 (6.0)	1.00
Caucasian ethnicity	140	8 (5.6)	51	49 (96.1)	1.00
Stroke, thrombosis, cardiovascular events or other stroke related events in family history	144	135 (96.4)	51	11 (21.6)	0.20
		20 (13.9)			
Anthropometric infantile data					
Head circumference at birth [in cm]	139	34 (33; 35.5)	43	34 (32; 35)	0.17
Length at birth [in cm]	142	51 (48; 53)	46	50 (47; 53)	0.15
Birth weight [in Gramm]	143	3240 (2760; 3690)	48	3200 (2305; 3690)	0.43
SGA (birth weight < 10P)	138	25 (18.1)	47	6 (12.8)	0.40
LGA (birth weight > 90P)	138	15(10.9)	47	5 (10.6)	0.96
Peripartum characteristics					
Delivery mode	142		44		0.56
spontaneous delivery		53 (37.3)		13 (29.6)	
caesarian section		71 (50.0)		26 (59.1)	
vaginal-operative delivery		18 (12.7)		5 (11.4)	
Umbilical artery pH ≤ 7.1	141	19 (13.5)	43	13 (30.2)	**0.01**
5-minute-Apgar score < 7	141	16 (11.4)	43	12 (27.9)	**0.01**
Perinatal asphyxia	144	19 (13.2)	51	13 (25.5)	0.04
Intubation/mask ventilation during initial care	144	30 (20.8)	51	21 (41.2)	**0.004**
Hypothermia treatment	144	6 (4.2)	51	7 (13.7)	**0.02**
Maternal factors					
Maternal age [in years]	138	30 (27; 34)	46	33 (29; 35)	**0.01**
Age ≤ 18 or age ≥ 35	138	32 (23.2)	46	18 (39.1)	**0.04**
Primiparity	144	80 (56.0)	51	28 (54.9)	0.93

quantitative variables are expressed as median (IQR). Categorical variables are expressed as n (%). P-values are obtained from chi-square or fisher exact tests for categorical data and from Mann–Whitney U test for continuous variables, significant p-Values after correction for multiple testing with Benjamini-Hochberg Procedure are printed in bold

Clinical signs representing neonatal asphyxia (umbilical artery pH ≤ 7.1, Apgar score < 7 at five minutes or need for intubation/mask ventilation following birth) were more frequent in infants suffering from CSVT compared to AIS cases. In addition, the proportion of infants treated with therapeutic hypothermia was significantly higher in CSVT cases (Table 1).

In our study population mothers of infants with AIS were younger and more likely to be either ≤ 18 years or ≥ 35 years. There were no significant differences in further maternal characteristics (primiparity, rate of abortion), potential risk factors related to pregnancy (chorioamnionitis, gestational diabetes, hypertensive pregnancy disorder or oligohydramnios) or maternal behavior (smoking or alcohol consumption during pregnancy) (Table A1, Additional file).

All associations remained significant after p-value adjustment for multiple comparison with the Benjamini-Hochberg procedure except for perinatal asphyxia (corrected p-value = 0.05) (Benjamini-Hochberg p-values not reported).

Clinical presentation

The most common symptom in both groups was clinical seizure activity (AIS 109/144, 76%; CSVT 35/51, 69%, Table 2). The type of seizure however, differed between CSVT and AIS cases with focal seizures being more prevalent in newborns with AIS (p < 0.0001). This was followed by apneic spells (47/144, 33%) in the AIS group and insufficient drinking/poor suck (16/51, 31%) in infants suffering from CSVT. Lethargy, as a clinical sign of encephalopathy was also more common in cases with CSVT (p < 0.0001).

Table 2. Frequency of symptoms

	AIS (n=144)	CSVT (n=51)	p-value
Seizures	109 (75.7)	35 (68.6)	0.32
focal	66 (60.6)*	7 (20.0)*	**<0.0001**
generalised	11 (10.1)*	18 (51.4)*	
not specified	32 (29.4)*	10 (28.6)*	
Hypoglycaemia	8 (5.6)	6 (11.8)	0.14
Electrolyte imbalances	2 (1.4)	3 (5.9)	0.11
Suspicious limb movement	31 (22.2)	11 (21.6)	0.92
Unspecific symptoms	76 (52.8)	34 (66.7)	0.09
respiratory dysfunction	21 (14.6)	11 (21.6)	0.25
apnoea	47 (32.6)	11 (21.6)	0.14
insufficient drinking/ poor suckling	26 (18.1)	16 (31.4)	0.05
muscular hypotonic	24 (16.7)	15 (29.4)	0.05
symptoms suggesting septicaemia	13 (9.0)	8 (15.7)	0.19
lethargy	6 (4.9)	12 (23.5)	**<0.0001**

results are given as n (%), sum of percentage >100 because of multiple symptoms per patient

p-values are obtained from chi-square or fisher exact tests, significant p-Values after correction for multiple testing with Benjamini-Hochberg Procedure are printed in bold, *percentage related to total number of seizures

Time to onset of symptoms and diagnosis

Information on date of onset of symptoms and date of diagnose were available for n = 37 CSVT and n = 121 AIS cases. Median age at onset of symptoms in infants with AIS was 1 day after birth (IQR 0–2 / range 0–13 days). The median age at onset of symptoms was 2 days in the CSVT group and delayed compared to AIS cases (IQR 0–10 / range 0–17 days; Mann–Whitney U test $p = 0.0002$; log rank test $p < 0.0001$). Accordingly, CSVT cases were diagnosed later in life with a median of 10 days (IQR 4–14 / range 0–22) whereas AIS was identified by cerebral imaging with a median of 3 days of life (IQR 1–5 / range 0–19) (Mann–Whitney U test and log rank test $p < 0.0001$; Fig. 1) irrespectively of frequency and type of symptoms.

Discussion

In this population-based surveillance study, we analyzed the relative risk for AIS and CSVT in a defined population including term and preterm infants. Although AIS is the most common type of perinatal stroke as in our study, the relative risk was lower than previously reported [2, 11–15]. This could be due to ascertainment by one data source only, without correction for underreporting. Completeness of case ascertainment by ESPED is between 30–60% depending on the type of disease [16]. The validity of the relative risk estimate, however, is not concerning because of likely equal underreporting in both conditions.

With 29%, we identified a high number of CSVT cases in preterm infants compared to the literature. Incidence in this population is not well defined because in most studies preterm infants have been not included due to gestational age-related differences in brain and clotting system development. However, premature infants are at higher risk for dehydration, sepsis, perinatal complications and displacement of occipital bones due to birth trauma or non-invasive ventilation all known risk factors for CSVT which could impact mechanisms leading to CSVT [17]. In addition, serial cranial ultrasound in preterm infants can depict thrombosis at an early stage increasing the number of chance findings and asymptomatic cases.

Furthermore, we explored the prevalence of comorbidities, risk factors and symptoms in affected newborn infants. The pattern of most risk factors and comorbidities in CSVT and AIS in our population was in accordance with published literature [13, 18–20]. Direct comparison, however yielded several differences, which are unlikely to be explained by multiple testing. The higher prevalence of perinatal asphyxia in CSVT and the later onset of symptoms may indicate a more important role of perinatal asphyxia in the causal pathway of CSVT than for AIS. CSVT is frequently associated with unspecific symptoms and acute underlying diseases, making the diagnosis and to pursue cerebral imaging more challenging and maybe delaying time to confirmation [21]. In particular, severe asphyxia requiring hypothermia treatment, previously reported as a risk factor for CSVT [22], is clearly more common in CSVT than in AIS cases. Risk for CSVT has been attributed to a prolonged supine position in hypothermia treatment affecting cerebral venous blood flow [23]. Additionally, birth trauma may lead to impairment of venous drainage in the central nervous system [23]. Nevertheless, a clinical picture with generalized seizure activity, encephalopathy and lethargy like in our CSVT population could mimic hypoxisch-ischemic encephalopathy and may trigger whole body cooling ultimately increasing the number of hypothermia treated CSVT cases.

Our findings regarding onset of symptoms are in accordance with the literature with clinical presentation of AIS within the first 12–72 h after birth in 70–90% [3] but there is scarce data on the onset of symptoms in CSVT. However, some evidence supports our finding that newborns with CSVT often present later with unspecific signs within the first week of life [24]. In a recent paper we discussed risk factors for AIS and identified an important role for prenatal risk factors [25]. Perinatal asphyxia in AIS might as well be a consequence of AIS.

Seizures and/or apnea occur in about 75% of cases with CSVT and are the presenting symptoms in the literature [26, 27]. The pattern of symptoms in CSVT observed in our study was similar to that description with seizures, lethargy, poor feeding, apnea or suspicious limb movement as most common symptoms. A study by Berfelo distinguished between generalized and focal seizures and found generalized seizures to be more common in infants suffering from CSVT as in our data [12]. In contrast, AIS is an acute arterial event with interruption of blood flow followed by impaired tissue oxygenation and ischemic brain damage presenting mostly with focal seizure activity. In our data, lethargy was more common in CSVT than in AIS cases maybe reflecting a more random distribution of brain injury related to limited venous drainage and multiple areas affected by venous congestion and parenchymal hemorrhages. Thrombosis of cerebral sinuses may even occur without visible parenchymal lesion or with cerebral lesions secondary to venous congestion or infarction. Slower formation and progression of brain lesions in CSVT compared to AIS may be a further explanation for later, subsequent symptoms and diagnosis [28].

In a study from the Canadian stroke registry, the superior sagittal sinus was reported to be most frequently affected, followed by the lateral sinus and the straight sinus [29]. Kersbergen et al.[30] showed that in the majority of CSVT case several sinuses were affected. Our data support these findings independent of gestational age.

The strength of this dataset is the contemporaneous and uniform assessment of risk factors and symptoms in newborns with AIS or CSVT in a population-based study allowing for valid comparison. A limitation to our data is the absence of a standardized imaging procedure for diagnosis in all cases. Confinement to MRI confirmed cases with description of the radiographical findings may limit this source of bias.

Conclusion

These data show that the relative risk for AIS is higher than for CSVT in neonates. A higher proportion of infants with perinatal asphyxia and a later onset of symptoms may hint to a more important role of postnatal risk factors for CSVT than for AIS. A better understanding of the clinical picture, the causality and frequency of risk factors could help to create a more standardized approach to investigations in the NICU and to select patient for future neuroprotection studies.

Abbreviations

ESPED "Erhebungseinheit seltene pädiatische Erkrankungen in Deutschland" – acronym for the German Pediatric Surveillance Unit

IQR Interquartile range

LGA large for gestational age

MRI magnetic resonance imaging

CSVT Cerebral sinovenous thrombosis

AIS Arterial ischemic stroke

SGA small for gestational age

Declarations

Ethics approval and consent to participate

Due to anonymous reporting in ESPED the need for parental consent was waived. Ethical approval was obtained by the ethics committee of the Medical Faculty of the Ludwig-Maximilians-University, Munich, Nr 42-15 (05-04-2015).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and design. ALS and RK performed material preparation, data collection and final analysis. The first draft of the manuscript was written by MD, MK, ALS and RK. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Not applicable

References

1. Raju TNK, Nelson KB, Ferriero D, Lynch JK. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics. 2007;120:609–16. doi:10.1542/peds.2007-0336.
2. Ferriero DM, Fullerton HJ, Bernard TJ, Billinghurst L, Daniels SR, DeBaun MR, et al. Management of stroke in neonates and children: A scientific statement from the American Heart Association/American stroke association. Stroke. 2019:e00–46. doi:10.1161/STR.0000000000000183.
3. Dunbar M, Kirton A. Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury. The Lancet Child Adolescent Health. 2018;2:666–76. doi:10.1016/S2352-4642(18)30173-1.
4. Klemme M, Gerstl L, Weinberger R, Olivieri M, Flemmer A, Kries R von, et al. Neonatal arteriell ischämischer Schlaganfall – eine Krankenhaus basierte Deutschlandweite Beobachtungsstudie. Klin Padiatr. 2017;229:142–6. doi:10.1055/s-0043-104699.
5. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. Pediatrics. 1981;68:36–44.
6. Toh VC. Early predictors of adverse outcome in term infants with post-asphyxial hypoxic ischaemic encephalopathy. Acta Paediatr. 2000;89:343–7.
7. Giraud A, Guiraut C, Chevin M, Chabrier S, Sébire G. Role of Perinatal Inflammation in Neonatal Arterial Ischemic Stroke. Front Neurol. 2017;8:612. doi:10.3389/fneur.2017.00612.

8. Statistisches Bundesam Destatis, editor. GENESIS-Online: Statistik der Geburten Lebendgeborene: Deutschland, Jahre, Geschlecht. 2018. https://www-genesis.destatis.de/genesis/online;jsessionid=FFFD2C900F1350C21C97FB22F20A8991.tomcat_GO_1_3?operation=previous&levelindex=2&levelid=1534941870245&step=2. Accessed 24 Nov 2018.
9. Benjamini Y, Hochberg Y. Controlling The False Discovery Rate - A Practical And Powerful Approach To Multiple Testing. J Royal Statist Soc Series B. 1995;57:289–300. doi:10.2307/2346101.
10. Institut für Qualität und Transparenz im Gesundheitswesen. Geburtshilfe. 2018. https://iqtig.org/qs-verfahren/gebh/. Accessed 22 Aug 2018.
11. Grunt S, Mazenauer L, Buerki SE, Boltshauser E, Mori AC, Datta AN, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. Pediatrics. 2015;135:e1220-8. doi:10.1542/peds.2014-1520.
12. Berfelo FJ, Kersbergen KJ, van Ommen CHH, Govaert P, van Straaten HLMI, Poll-The B-T, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. Stroke. 2010;41:1382–8. doi:10.1161/STROKEAHA.110.583542.
13. Yang JYK, Chan AKC, Callen DJA, Paes BA. Neonatal cerebral sinovenous thrombosis: sifting the evidence for a diagnostic plan and treatment strategy. Pediatrics. 2010;126:e693–700. doi:10.1542/peds.2010-1035.
14. Deveber GA, Kirton A, Booth FA, Yager JY, Wirrell EC, Wood E, et al. Epidemiology and Outcomes of Arterial Ischemic Stroke in Children: The Canadian Pediatric Ischemic Stroke Registry. Pediatr Neurol. 2017;69:58–70. doi:10.1016/j.pediatrneurol.2017.01.016.
15. Nelson KB, Lynch JK. Stroke in newborn infants. Lancet Neurol. 2004;3:150–8. doi:10.1016/S1474-4422(04)00679-9.
16. Ebrahimi-Fakhari D, Zemlin M, Sauer H, Poryo M, Graf N, Meyer S. Erhebungseinheit für seltene pädiatrische Erkrankungen in Deutschland (ESPED) – 25 Jahre pädiatrische Epidemiologie: Eine Bestandsaufnahme. Klin Padiatr. 2018;230:215–24. doi:10.1055/a-0586-4365.
17. Raets MMA, Sol JJ, Govaert P, Lequin MH, Reiss IKM, Kroon AA, et al. Serial cranial US for detection of cerebral sinovenous thrombosis in preterm infants. Radiology. 2013;269:879–86. doi:10.1148/radiol.13130401.
18. Li C, Miao JK, Xu Y, Hua YY, Ma Q, Zhou LL, et al. Prenatal, perinatal and neonatal risk factors for perinatal arterial ischaemic stroke: a systematic review and meta-analysis. Eur J Neurol. 2017;24:1006–15. doi:10.1111/ene.13337.
19. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA. 2005;293:723–9. doi:10.1001/jama.293.6.723.
20. Harteman JC, Groenendaal F, Kwee A, Welsing PMJ, Benders MJNL, Vries LS de. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. Arch Dis Child Fetal Neonatal Ed. 2012;97:F411-6. doi:10.1136/archdischild-2011-300973.
21. Bousser M-G, Ferro JM. Cerebral venous thrombosis: an update. Lancet Neurol. 2007;6:162–70. doi:10.1016/S1474-4422(07)70029-7.

22. Radicioni M, Bini V, Chiarini P, Fantauzzi A, Leone F, Scattoni R, Camerini PG. Cerebral Sinovenous Thrombosis in the Asphyxiated Cooled Infants: A Prospective Observational Study. Pediatr Neurol. 2017;66:63–8. doi:10.1016/j.pediatrneurol.2016.09.006.
23. Tan M, Deveber G, Shroff M, Moharir M, Pontigon A-M, Widjaja E, Kirton A. Sagittal sinus compression is associated with neonatal cerebral sinovenous thrombosis. Pediatrics. 2011;128:e429-35. doi:10.1542/peds.2010-3896.
24. Fluss J, Dinomais M, Chabrier S. Perinatal stroke syndromes: Similarities and diversities in aetiology, outcome and management. Eur J Paediatr Neurol. 2019. doi:10.1016/j.ejpn.2019.02.013.
25. Sorg A-L, Kries R von, Klemme M, Gerstl L, Weinberger R, Beyerlein A, et al. Risk factors for perinatal arterial ischaemic stroke: a large case-control study. Dev Med Child Neurol. 2019. doi:10.1111/dmcn.14347.
26. Ramenghi LA, Govaert P, Fumagalli M, Bassi L, Mosca F. Neonatal cerebral sinovenous thrombosis. Semin Fetal Neonatal Med. 2009;14:278–83. doi:10.1016/j.siny.2009.07.010.
27. Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. Arch Neurol. 2006;63:405–9. doi:10.1001/archneur.63.3.405.
28. Kersbergen KJ, Groenendaal F, Benders MJNL, van Straaten HLM, Niwa T, Nievelstein RAJ, Vries LS de. The spectrum of associated brain lesions in cerebral sinovenous thrombosis: relation to gestational age and outcome. Arch Dis Child Fetal Neonatal Ed. 2011;96:F404-9. doi:10.1136/adc.2010.201129.
29. Deveber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, et al. Cerebral sinovenous thrombosis in children. N Engl J Med. 2001;345:417–23. doi:10.1056/NEJM200108093450604.
30. Kersbergen KJ, Vries LS de, van Straaten HLMI, Benders MJNL, Nievelstein RAJ, Groenendaal F. Anticoagulation therapy and imaging in neonates with a unilateral thalamic hemorrhage due to cerebral sinovenous thrombosis. Stroke. 2009;40:2754–60. doi:10.1161/STROKEAHA.109.554790.

Figures

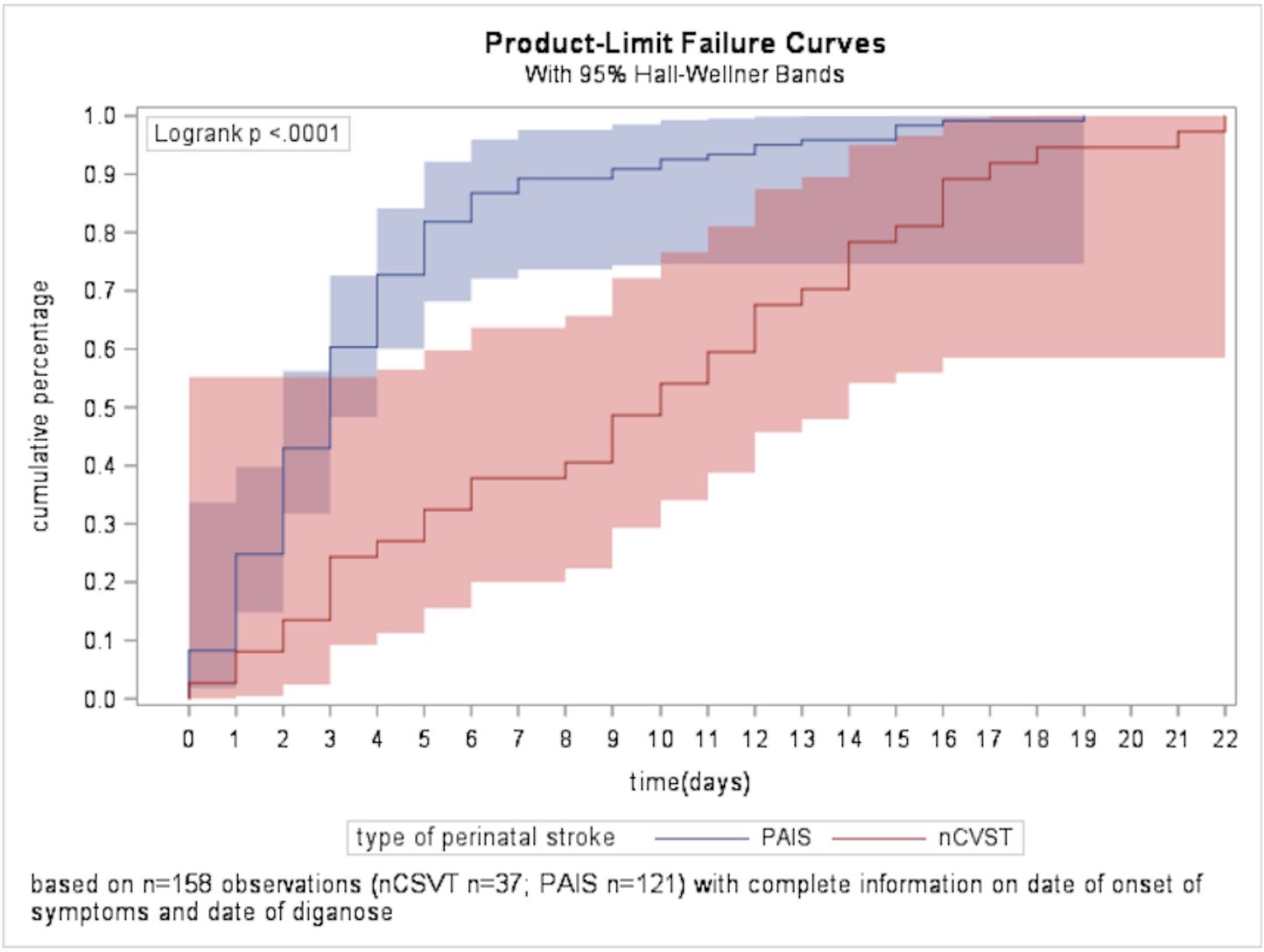

Figure 1

Cumulative percentage with age at time of diagnosis

Supplementary Files

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- ncVSTvsPAIS2904MDMKASsuppl.Table1.docx