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REGULAR ARTICLE

Paediatric arterial ischaemic stroke and cerebral sinovenous thrombosis in Denmark 1994–2006: A nationwide population-based study

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Keywords
Arterial ischaemic stroke, Case fatality, Cerebral sinovenous thrombosis, Incidence rate, Neurological sequelae

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ABSTRACT

Aim: To assess the incidence rates (IR), clinical characteristics, risk factors, treatment and outcomes of paediatric arterial ischaemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT).

Methods: Using population-based, nationwide medical registries, we identified all patients aged 0–18 years at the time of hospitalization with first-ever AIS and/or CSVT in Denmark between 1994 and 2006. Medical records were retrieved and reviewed.

Results: We identified 211 patients with AIS and 40 patients with CSVT corresponding to IRs of 1.33 (95% CI 1.16–1.52) and 0.25 (95% CI 0.19–0.34) per 100 000 person-years, respectively. The IRs peaked in infancy (<1 year) for both AIS and CSVT with an additional peak among adolescents (15–18 years) for CSVT. The IR of AIS increased 3.9% per year ($p = 0.036$), whereas no changes were found for CSVT. In total, 48.2% of the patients received antithrombotic treatment; no major complications were observed. All-cause and thrombosis-related 30-day case fatality ratios were 3.6% and 2.4%, respectively; neurological sequelae were found in 56.2% of patients.

Conclusion: The IR of AIS was highest in infants and had increased with 3.9% annually during the observation period. The IR of CSVT had an additional peak in adolescence and remained unchanged over time.

INTRODUCTION

Paediatric cerebral thrombosis, defined as arterial ischaemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT), is a rare but serious event. The improved neuroimaging techniques, greater clinical awareness and intensive treatment of children with previous lethal diseases are likely to have led to an increased detection of cerebral thrombosis. Still, epidemiological data on the incidence rate (IR) of arterial and venous cerebral thrombosis in neonates (<28 days) and children (>28 days to 18 years) are sparse. Previous studies have reported IRs of AIS of 1.8–7.8 per 100 000 person-years (1–5) and of CSVT in the range of 0.25–0.67 per 100 000 person-years (6–8). It is currently unclear whether the IR of paediatric cerebral thrombosis is increasing or stable. The US study found that the IRs of all types of paediatric stroke (including both ischaemic and haemorrhagic stroke) were stable between 1988 and 1999, but the trend specifically for AIS remains unclear (9). In contrast, a dramatic increase in admissions of paediatric venous thromboembolism, including CSVT, was reported in a recent registry-based study, although detailed data on CSVT were not presented in the study (10).

A wide range of possible risk factors have been linked to paediatric AIS and CSVT. Cerebral arteriopathy, cardiac disorders, trauma and infection are often present in children with AIS (3), whereas head and neck infection, malignancy and dehydration appear to play an important role in CSVT (6). Prothrombotic abnormalities have been reported to be present in 20–50% of children with AIS and 33–99% of children with CSVT (11). Despite the increasing understanding of natural history of paediatric cerebral thrombosis, the mortality remains significant (5–12%) and neurological sequelae occur in 61–74% of children with AIS and CSVT (3,12).

In this study, we aimed to determine the IR and mortality of paediatric cerebral thrombosis in Denmark, including

Abbreviations

AIS, arterial ischaemic stroke; APA, antiphospholipid antibodies; ASA, acetyl salicylic acid; CDG, congenital disorder of glycolysation; CGD, chronic granulomatous disease; CI, confidence interval; CT, computed tomography; CSVT, cerebral sinovenous thrombosis; FV Leiden, Factor V Leiden mutation; IQR, interquartile range; IR, incidence rate; LMWH, low molecular weight heparin; MRI, magnetic resonance imaging; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; PT20210A, Prothrombin G20210A mutation; UFH, unfractionated heparin.

changes in IR over time. Secondly, we aimed to evaluate clinical characteristics, prevalence of possible risk factors, treatment and sequelae in patients aged 0–18 years with AIS and CSVT.

MATERIAL AND METHODS

This population-based study was conducted using data from the entire Danish population (approximately 5.5 million people). The Danish National Health Service provides tax-supported health care to all Danish residents, including free access to general practitioners and hospitals. The Danish Civil Registration System has maintained electronic records of changes in the vital status of all citizens since 1968 (13). Each record carries a unique 10-digit civil registration number that is assigned to every Danish citizen and is used in all Danish registries.

Study population

The study population consisted of all Danish residents aged 0–18 years with a first time hospital discharge diagnoses of cerebral thrombosis from 1 January 1994 through 31 December 2006. The patients were identified in the Danish National Patient Registry, a nationwide administrative database that contains comprehensive information on discharges from all Danish hospitals (14). The methods of validation of patients in our study and collection of data have previously been described in details (15). All patients registered with an ICD-10 diagnosis code for AIS (I63–I64) and CSVT (I676, I636, G08, O87 and O22) were identified. Medical records from all of the patients were retrieved and information on symptoms, imaging, laboratory tests, possible risk factors, treatment and neurological sequelae were obtained. Data on mortality and causes of death were extracted on 1 June 2009 from the Civil Registration System and the National Causes of Death Registry. Patients with AIS were considered confirmed when the clinical presentation was consistent with stroke (i.e. neurological deficits, paresis, seizures and altered mental status) and a computed tomography (CT) scan or magnetic resonance imaging (MRI) showed a focal ischaemic infarct of a location and age consistent with the neurological signs and symptoms. CSVT was considered confirmed if a newly developed neurological dysfunction was described in the medical records and thrombosis of the cerebral veins or venous sinuses was demonstrated by MRI, MRI venography and/or conventional cerebral CT venography. Patients with hypoxic diffuse ischaemia alone and/or primary cerebral haemorrhage not associated with AIS or CSVT were excluded.

Clinical characteristics

The location of the AIS was classified as either anterior circulation including the territories of the internal carotid artery or its branches (middle and anterior cerebral artery) or posterior circulation located in territories of cerebral posterior, basilar, vertebral and/or cerebellar arteries.

Thrombophilia work-up included the tests described in Table 4 performed by the local coagulation laboratories. The diagnosis of thrombophilia was made when a repeated measurement (performed ≥3 months after thrombosis) confirmed the abnormality (except for DNA tests).

Antithrombotic therapy was divided into the groups: unfractionated heparin (UFH), low molecular weight heparin (LMWH), thrombolysis, vitamin K antagonists and acetyl salicylic acid (ASA) or other platelet inhibitors.

Outcomes

All-cause and thrombosis-related deaths were assessed as described in statistical analysis section. Major bleeding during the first 3 months of initial antithrombotic therapy was defined as a haemoglobin drop ≥2 g/dl (=1.25 mmol/L) and/or any intracranial, retroperitoneal or intra-articular haemorrhage and/or need of immediate blood transfusion.

Neurological outcomes were assessed in survivors 12 months (±90 days) after the occurrence of thrombosis. Information was collected from medical records based on at least one examination of a patient by a paediatrician or neurologist. An assessment by a physiotherapist was conducted after neonatal stroke and for primarily older patients. Neuropsychological assessment was conducted if considered required; behaviour disorders were diagnosed by a psychiatric consultant. We assessed neurological outcomes as epilepsy, motoric impairment and/or cognitive problems. Motoric impairment included hemi-, para- or tetraplegy, dyscoordination or dystonia. Cognitive problems were defined as developmental delay, behavioural disorder and/or a statement of special educational needs.

The study was approved by The Danish Data Protection Agency (J.no.: 2007-41-0539) and by The National Board of Health (J.no.: 7-604-04-2/37/EHE).

Statistical analysis

The following age groups were analysed: infants (<1 year), children (1–14 years), adolescents (15–18 years). Among infants, neonates (<28 days) were also analysed separately. We defined neonatal thrombosis as thrombosis manifested and diagnosed in patients up to 28 days after birth. Preterm born children (≤37 completed gestational weeks) aged 28 days-1 year at the time of thrombosis were attributed to the age group 'infants' (n = 1).

The incidence rates were presented per 100 000 person-years with 95% confidence intervals (CI) based on the Poisson regression. To calculate IR, we used the number of thromboses as the numerator and the sum of person-time at risk as denominator. Information on the number of persons at risk, stratified by age, gender and year was obtained from Statistics Denmark (16). For neonates, the IRs were calculated per 100 000 live births and for neonatal risk time, separately. Neonatal risk time was defined as the first 28 days of life. Using Poisson regression, we fitted yearly counts of incidence rates of AIS and CSVT to examine possible time trends. Two models were applied, one with a non-linear trend considering time as a categorical variable and one with a linear trend; hence, the slope was interpreted as yearly percentage change on the original scale. Likelihood ratio test was performed to test whether the

trend was sufficiently described as linear. Whenever the linear trend was accepted, the presence of effect modification by age and gender was evaluated including interaction terms into the model. The slope of the trend assessed the development of thrombosis incidences during the study period.

The end of follow-up for all patients was 1 June 2009. All-cause and thrombosis-related 30-day case fatality ratios were calculated as the number of all deaths or number of deaths directly related to thrombosis divided by the number of patients at risk. The IRs of fatal AIS and CSVT (number of deaths directly related to AIS or CSVT within 30 days after diagnosis divided by the sum of person-time at risk) were presented per 100 000 person-years.

Mean and median values were presented with 95% CI and interquartile range (IQR), respectively. Mann–Whitney and Kruskal–Wallis test were used to compare medians and percentages. p-Values <0.05 were considered statistically significant. We used STATA version 10 (Stata Corporation, College Station, TX, USA) for all statistical analyses.

RESULTS

IR

Our study included a total of 15 846 627 person-years of observation (8 121 116 men and 7 725 511 women) during which 251 cases of a first-ever paediatric cerebral thrombosis were confirmed corresponding to an IR of 1.58 (CI 1.40–1.79) per 100 000 person-years.

Table 1 shows the distribution and the corresponding IRs according to age and sex. The highest IRs of AIS and CSVT were found among infants with an additional peak in adolescence for CSVT. Risk time of neonatal thrombosis only includes the first 28 days of life; consequently, the substantial number of cases among neonates was reflected by particular high IRs in this age group: 79.5 (95% CI 59.40–104.27) and 10.7 (95% CI 4.30–22.05) per 100 000 person-years for AIS and CSVT, respectively. No statistical significant differences in age-specific IRs of AIS ($p = 0.14$) and CSVT ($p = 0.39$) were found when comparing boys with girls.

An annual increase of 3.9% in IR of AIS was seen during the study period ($p = 0.036$), while no significant changes were seen in the IR of CSVT ($p = 0.27$) (Fig. 1). The changes of IR during the study period did not differ according to age and sex (data not shown).

Clinical characteristics

Symptoms at presentation are summarized in Table 2. Seizures were the most frequent debut of AIS in infancy, whereas hemiparesis was observed in 64.7% of patients with AIS ≥1 year. Seizures were also the main debut in CSVT among infants, while the main part of CSVT patients ≥1 year had unspecific complaints (Table 2).

Table 1 Incidence rates (IRs) in cerebral thrombosis stratified by age and sex

		Male		Female		All
Thrombosis	Age	n	IR (95% CI)	n	IR (95% CI)	IR (95% CI)
AIS						
Neonatal*	<28 days	31	7.05 (4.96–10.0)	21	5.04 (3.28–7.72)	6.07 (4.63–7.97)
Childhood	<1 year†	42	9.48 (7.01–12.83)	33	7.84 (5.57–11.03)	8.68 (6.92–10.89)
	1–4 years	36	2.00 (1.4–2.78)	17	0.99 (0.62–1.60)	1.51 (1.16–1.98)
	5–9 years	15	0.68 (0.41–1.12)	14	0.66 (0.39–1.12)	0.67 (0.47–0.96)
	10–14 years	8	0.39 (0.19–0.77)	14	0.71 (0.42–1.20)	0.55 (0.36–0.83)
Adolescence	15–18 years	17	1.07 (0.66–1.72)	15	0.99 (0.60–1.64)	1.03 (0.73–1.46)
All	0–18 years	118	1.45 (1.21–1.74)	93	1.20 (0.98–1.48)	1.33 (1.16–1.52)
CSVT						
Neonatal*	<28 days	4	0.91 (0.34–2.43)	3	0.72 (0.23–2.23)	0.82 (0.39–1.71)
Childhood	<1 year†	5	1.13 (0.47–2.71)	5	1.19 (0.49–2.85)	1.16 (0.62–2.15)
	1–4 years	1	0.06 (0.01–0.40)	2	0.12 (0.03–0.47)	0.09 (0.03–0.27)
	5–9 years	2	0.09 (0.02–0.36)	1	0.05 (0.01–0.34)	0.07 (0.02–0.22)
	10–14 years	3	0.15 (0.05–0.45)	1	0.05 (0.01–0.36)	0.10 (0.04–0.26)
Adolescence	15–18 years	6	0.38 (0.17–0.84)	14	0.92 (0.55–1.56)	0.64 (0.42–1.00)
All	0–18 years	17	0.21 (0.13–0.34)	23	0.30 (0.20–0.45)	0.25 (0.19–0.34)
CNS total						
Neonatal*	<28 days	35	7.96 (5.72–11.09)	24	5.76 (3.86–8.59)	6.89 (5.34–8.89)
Childhood	<1 year†	47	10.61 (7.97–14.12)	38	9.03 (6.60–12.41)	9.84 (7.95–12.17)
	1–4 years	37	2.06 (1.50–2.84)	19	1.11 (0.71–1.74)	1.60 (1.23–2.08)
	5–9 years	17	0.77 (0.48–1.23)	15	0.71 (0.43–1.18)	0.74 (0.52–1.05)
	10–14 years	11	0.53 (0.29–0.96)	15	0.76 (0.46–1.26)	0.64 (0.44–0.95)
Adolescence	15–18 years	23	1.45 (0.96–2.19)	29	1.91 (1.33–2.75)	1.67 (1.27–2.20)
All	0–18 years	135	1.66 (1.40–1.97)	116	1.50 (1.25–1.80)	1.58 (1.40–1.79)

*Based on 856 624 live births (439 575 males and 417 049 females).

†Including neonates.

CI = confidence interval; AIS = arterial ischaemic stroke; CSVT = cerebral sinovenous thrombosis.

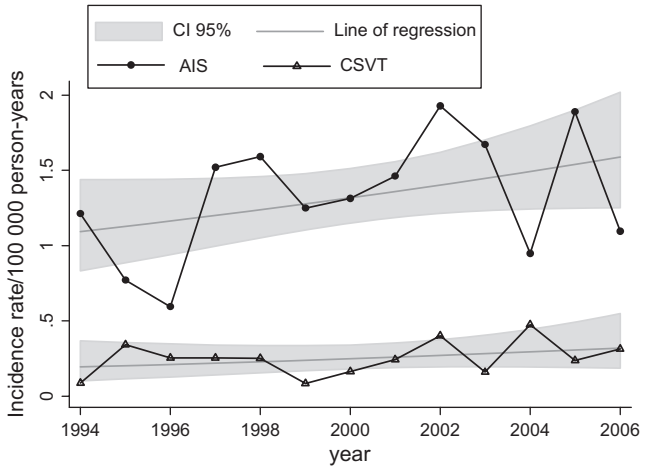

Figure 1 Changes of IRs of AIS and CSVT during the study time. AIS = arterial ischaemic stroke; CI = confidence interval; CSVT = cerebral sinovenous thrombosis; IR = incidence rate.

Table 2 Clinical characteristics in patients with AIS and CSVT

Symptoms	Infants (<1 year), %	Children (1–14 years), %	Adolescents (15–18 years), %
AIS	n = 75	n = 104	n = 32
Seizures	85.3	19.2	21.9
Hemiparesis	17.3	71.2	43.8
N. facialis paresis	2.7	35.6	12.5
Altered mental status	5.3	17.3	34.4
Visual disturbances	0	9.6	15.6
Speech problems/aphasia	0	21.2	25.0
Miscellaneous*	6.7	28.9	46.9
CSVT	n = 10	n = 10	n = 20
Seizures	80.0	20.0	35.0
Altered mental status	40.0	40.0	25.0
Visual disturbances	0	30.0	45.0
Miscellaneous†	0	70.0	75.0

*Headache, syncope, abnormal muscle tonus, nausea/vomiting.
†Headache, neck pain, nausea/vomiting.
AIS = arterial ischaemic stroke; CSVT = cerebral sinovenous thrombosis.

Arterial ischaemic stroke was primarily confirmed using MRI (n = 145) and to a smaller extent CT scan (n = 65). The ischaemic infarcts were left hemisphere (48.6%), right (36.1%) or bilateral (15.4%). Anterior circulation was involved in the majority of the cases (82.9%), particularly among infants (98.6%). In patients with CSVT (n = 40), 33 cases were confirmed by MRI, seven by CT scan. The deep venous sinuses (straight sinus, vein of Galen, internal, jugular veins) were involved in 25 patients. Multiple sinuses involvement was seen in 65% of patients. A haemorrhage at the initial imaging was seen in 9.5% and 22.5% of patients with AIS and CSVT.

Table 3 Possible risk factors in patients with AIS and CSVT aged ≥28 days to 18 years

Trigger	AIS, n = 159 %	CSVT, n = 33 n
Cardiac disease	15.2	3.0
Infection	14.6	36.4*
Surgery	12.2	6.1
Trauma	5.8†	0
Contraceptive‡	36.8	85.7
Cancer	0.6	6.1
Steroids	1.3	12.1
Dehydration§	4.4	3.0
Other conditions	22.8¶	9.1**

*Meningitis (n = 3), brain abscess (n = 2), infection in respiratory sinuses, mastoid cavity, or salivary glands (n = 7).
†Dissection of cerebral arteries (n = 3).
‡Among women aged ≥13 years.
§Within 3 days from the start of symptoms.
¶Varicella infection within 1 year (n = 18), Moyamoya (n = 3), Marfan syndrome (n = 1), cutis marmorata-telengiectasia syndrome (n = 1), Sturge-Weber syndrome (n = 1), MELAS syndrome (n = 1), Klippel–Trenaunay Weber syndrome (n = 1), Sallas disease (n = 1), CDG (n = 1), unspecified immune disease(n = 1), CGD (n = 1), celiac disease (n = 1), colitis ulcerosa (n = 1), an infant aged of 54 days with a history of maternal drug abuse (n = 1), a. basilaris aneurysme (n = 1), subarachnoidal bleeding (n = 1), terminal renal failure (n = 1).
**polycytemia vera (n = 1), thyreotoxicosis (n = 1), sequelae of masteidoctomy (n = 1).
AIS = arterial ischaemic stroke; CDG = congenital disorder of glycolysation; CGD = chronic granulomatous disease; CSVT = cerebral sinovenous thrombosis; MELAS = mitochondrial myopathy = encephalopathy, lactic acidosis and stroke-like episodes.

Possible risk factors

An underlying acute or chronic illness and/or external trigger to thrombosis were present in 53.4% (134/251) of all patients with cerebral thrombosis. The distribution of possible risk factors among patients with AIS and CSVT aged ≥28 days is presented in Table 3. Among neonates with AIS (n = 52), no patients had cardiac disease, only one was born preterm, two had Apgar score <7 at 5 min and five were treated for sepsis. Among patients with neonatal CSVT (n = 7), one patient had Apgar score <7 at 5 min and four were treated for sepsis.

Thrombophilia work-up was conducted in 61.7% of patients (Table 4), more frequent in patients with CSVT than in patients with AIS. Thrombophilia was diagnosed in 21 of 150 patients investigated, corresponding to 31.3% of the tested CSVT and 9.3% of the tested patients with AIS. Looking at all age groups and diagnoses, thrombophilia was rather frequent in adolescents having CSVT (47.1%), whereas it was only present in 6–14% in all other groups. Factor V (FV) Leiden was the most frequent finding in patients with AIS and CSVT(Table 4).

Antithrombotic treatment

Antithrombotic treatment was initiated in 118 patients (48.2%) with cerebral thrombosis (available n = 245).

Table 4 Thrombophilia in patients with AIS and CSVT

	AIS		CSVT	
Thrombophilia	n/n^{available}	%	n/n^{available}	%
Tested				
Total	118/204	57.8	32/39	82.1
<1 year	28/75	37.3	8/10	80.0
1–14 years	73/100	73.0	7/9	77.8
15–18 years	17/29	58.6	17/20	85.0
	n/n^{tested}	%	n/n^{tested}	%
Documented				
Total	11/118	9.3	10/32	31.3
<1 year	4/28	14.3	1/8	12.5
1–14 years	6/73	8.2	1/7	14.3
15–18 years	1/17	5.9	8/17	47.1
Prothrombotic factors				
Protein C deficiency	0/103	–	0/24	–
Protein S deficiency	0/101	–	0/23	–
AT III deficiency	0/93	–	0/23	–
FV Leiden	8*/86	9.3	4/22	18.2
PT20210A	0/43	–	2/18	11.1
Lupus anticoagulant	1/65	1.5	0/14	–
Anticardiolipin IgG	0/72	–	1/21	4.8
β glycoprotein IgM	0/23	–	0/5	–
β glycoprotein IgG	0/46	–	1/7	14.3
Total APA	1/97†	1.0	2/23†	8.7
Hyperhomocysteinaemia‡	2/76	2.6	2/16	12.5
Elevated F VIII	0/36	–	0/3	–
Lipoprotein(a)	0/4	–	0/2	–
Combined defects	0/118	–	0/32	–

*Homozygote (n = 1).

†Minimum one of APA tested.

‡Defined as se-homocystein ≥12 μmol/L.

AIS = arterial ischaemic stroke; APA = antiphospholipid antibodies; CSVT = cerebral sinovenous thrombosis; FV Leiden = Factor V Leiden mutation; PT20210A = Prothrombin G20210A mutation.

Neonates received almost entirely supportive care alone (56 of 59 cases or 94.9%). In AIS, antithrombotic treatment (any type) was given to 8.0% of infants, 56.4% of children and 75.9% of adolescents. The majority of patients with AIS (89.4%) received ASA with a median duration of 183 (IQR 53–561) days, (n = 29). LMWH was used in 11 patients with AIS for median 8 (IQR 6–18) days. Only one patient was treated with t-PA. In CSVT, any type antithrombotic was given to 4 infants (n = 10), 9 children (n = 20) and all adolescents (n = 20). LMWH treatment (n = 18) was continued for median 31.5 (IQR 7–91) days, and warfarin was prescribed for 62.5% of patients with CSVT for median 181 (IQR 92–265) days (n = 19). Two patients received t-PA.

Outcomes

In total, 21 of 251 patients were dead after the end of follow-up. Median follow-up time was 8.0 (IQR 5.4–11.2) years. Nine patients died within 30 days from diagnosis, corresponding to an all-cause 30-day case fatality ratio of 3.6% (CI 1.7–6.7). Six deaths were directly attributable to thrombosis, equivalent to a thrombosis-related 30-day case fatality ratio of 2.4% (CI 0.9–5.1) All six patients had AIS and died acutely because of cerebral oedema and incarceration; thus, the IR of fatal AIS was estimated to 0.04 (CI 0.01–0.08) per 100 000 person-years. No patients died directly of CSVT, but one infant died of complications of meningitis.

Minor bleeding during antithrombotic therapy was relatively rare: Only 4 of 80 patients during ASA treatment, 2 of 33 patients during warfarin therapy (one got warfarin + ASA) and one patient experienced bleeding during thrombolytic therapy. No major or fatal bleeds were observed.

Data on neurological outcomes among survivors of CNS thrombosis are presented in Table 5. Neonates with AIS had sequelae in 16 of 49 cases (37.2% (CI 20.0–47.5)), comprising epilepsy (n = 5), motoric impairment (n = 12) and developmental delay (n = 4).

Twenty-four children with CSVT (n = 40) were re-examined by MRI, four by CT scan. Resolution was reported in 20 (83.3%) patients (complete recanalization, n = 11) after median 77 (IQR 24–178) days. Sequelae in patients with CSVT differed from AIS: more frequently, cognitive or other problems as headache or visual problems were diagnosed (Table 5). Normal outcomes after neonatal CSVT were seen in 3 of 4 patients.

DISCUSSION

We estimated the IRs, changes in the IR over time and mortality of the first-ever cerebral thrombosis among persons aged 0–18 year in the Danish population. The highest IR of cerebral thrombosis was in infancy with a second peak in the IR of CSVT in adolescence. We found a slight increase in the IR of AIS during study time, while the IR of CSVT was unchanged. The clinical presentation varied in the different age groups, and the constellation of possible risk factors depended on age group and type of event. Bleeding was rare during different treatment modalities. The case fatality was far from negligible, and morbidity was significant.

Strengths and limitations of the present study

The strengths of this study included the access to population-based data sources, covering the entire Danish population with negligible referral and diagnostic biases (14), and validation of all events by review of medical records by a paediatrician familiar with paediatric thrombosis (RT) (15). Obviously, the number of diagnoses not registered in the nationwide database is unknown, but it appears unlikely that such severe disorder as cerebral thrombosis should not be registered if recognized by the health care system.

The limitations included the lack of standardized prospectively collected data on clinical characteristics, possible risk factors, treatment and morbidity during follow-up. Instead, we had to rely on data extracted from medical records. Further, we could not draw any conclusions about the role of the possible risk factors as we did not have a control group for comparison. Finally, the number of cases was moderate to small in some of the subgroups and

Table 5 Neurological sequelae in patients with cerebral thrombosis after 12 months (±90 days) follow-up

			Sequelae		Epilepsy	Motoric disability	Cognitive problems	Other‡
Patients with cerebral thrombosis	N*	N†	n	%, (CI, 95%)	n	n	n	n
AIS	199	176	101	57.4 (49.7–64.8)	17	70	27	9
<1 year	73	69	30	43.5 (31.6–56.0)	11	20	7	0
1–14 years	99	92	60	65.2 (54.6–74.9)	3	48	15	8
15–18 years	27	15	11	73.3 (44.9–92.2)	3	2	5	1
CSVT	39	27	13	48.1 (28.7–68.1)	2	2	7	6
<1 year	9	6	2	33.3 (43.3–77.8)	0	0	2	1
1–14 years	10	8	4	50.0 (15.7–84.3)	1	1	1	4
15–18 years	20	13	7	53.9 (25.1–80.8)	1	1	4	4
Total	238	203	114	56.2 (49.0–63.1)	19	72	34	15

*Number of survivors.

†Number of patients with available data.

‡Visual disturbances, severe headache, benign intracranial hypertension, speech problems.

AIS = arterial ischaemic stroke; CSVT = cerebral sinovenous thrombosis.

consequently, caution is needed when interpreting some of the presented findings because of statistical imprecision.

Comparison with other studies

The IRs of AIS and CSVT are somewhat lower in our study than the majority of previously reported studies (1–8), although they are in agreement with IRs in Northern European populations (5,7). This difference could reflect that some misclassified cases may have been included in some of the existing studies. In our study, the discharge diagnoses of AIS and CSVT were validated and the positive predictive values were found to be 58.1% and 66.7%, respectively (15). The lower IR in our study might also be partially explained by the homogeneous ethnicity (Caucasian) of the Danish population with e.g. no cases of sickle-cell-disease-related AIS, an entity comprising 7–39% of patients with AIS in studies with diverse ethnicity (17–19).

Previous studies have also observed a higher incidence of stroke among boys (17,18). We found a higher percentage of men among patients with AIS, but not significantly higher IRs in the different age groups, although we cannot exclude the possibility that the sample size in our study may have been too small to identify more subtle gender disparities. In accordance with previous studies, we observed the peak of AIS and CSVT incidence rates in infancy (1,4,6,8). Neonates had a particular high IR of cerebral thrombosis, which may be explained by the constellation of an immature haemostatic system and the existence of a wide range of peri- and postnatal risk factors. An additional increase in IR in adolescence was noted in CSVT, which was in contrast to the Canadian study of 160 paediatric patients (6). Interestingly, in our study, the main part of adolescent girls with CSVT received oral contraceptives versus 26.7% of girls of similar age in the entire Danish population (20) and 18.8% in the Canadian study (6).

To the best of our knowledge, no studies have investigated changes in IR over time for paediatric AIS and CSVT separately. Kleindorfer et al. found a stable level of IR of overall stroke, though, without separately analysing the trend of AIS (9). We observed a slight increase in the IR of AIS and no changes of CSVT over time. The reasons behind our findings are unknown, but better diagnostic equipment and greater clinical awareness, especially among patients at high risk, might have contributed to the increase in the IR of AIS.

The distribution of risk factors in our study was in accordance with other published studies (1–8). MRI angiography was used in patients with likely vasculopathic aetiology; however, it is possible that some patients were missed. In our study, the number of patients consistent with a presumed perinatal stroke (21) was small (n = 5) and were included in the group of 'infants'.

Recently, a meta-analysis revealed thrombophilia as a risk factor for paediatric cerebral thrombosis, without differences in association between AIS and CSVT (22). Prothrombotic defects in our study were more common in patients with CSVT comparing to AIS, but without reaching statistical significance. Frequent findings were FV Leiden and PT20210A, which are rather prevalent in the Danish population (6.6% and 2.1%, respectively), also, our findings were not statistically different from the background population, probably because of a low number (23,24). In our study, the management of patients was in accordance with the existing recommendations (25–27), although we observed various modalities of the antithrombotic treatment without major complications. The significant morbidity in our population was in agreement with previous studies (28); however, results can be difficult to interpret in patients with other underlying conditions also affecting the neurophysiological development. During the last years, more data on paediatric cerebral thrombosis have been generated from international registries (12,29), but because of the low IR, clinical trials designed to improve therapy are difficult to perform. The development of standardized guidelines for the investigation and management is still a challenge and currently international and national guidelines are mainly consensus based (25–27). The Nordic Society of Paediatric Haematology and Oncology (30) has initiated a collaborative work on this issue, resulting in more data optimizing of diagnosis, therapy and outcomes in children with thrombosis.

In conclusion, the present study adds new evidence about IR and the trend of IR during 13 years besides data on risk factors, treatment and sequelae of paediatric cerebral thrombosis in the Danish population. Still, international data are needed to elucidate many unsolved issues in paediatric thrombosis.

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