Cerebral sinus venous thrombosis in Swiss children

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LIST OF ABBREVIATIONS

BSID-II	Bayley Scales of Infant Development, second edition
CSVT	Cerebral sinus venous thrombosis
K-ABC	Kaufmann Assessment Battery for Children
SNPSR	Swiss Neuropaediatric Stroke Registry

AIM To describe the characteristics of paediatric cerebral sinus venous thrombosis (CSVT) in Switzerland.
METHOD Data on clinical features, neuroimaging, risk factors, and treatment were collected for all children in Switzerland younger than 16 years of age who had CSVT between January 2000 and December 2008. A follow-up examination and a cognitive assessment were performed (mean follow-up period 26mo). Differences between neonates and children (patients older than 28d) were assessed and predictors of outcome were determined.
RESULTS Twenty-one neonates (14 males, seven females; mean age 9d, SD 8d) and 44 children (30 males, 14 females; mean age 8y 7mo, SD 4y 5mo) were reported. The incidence of paediatric CSVT in Switzerland was 0.558 per 100 000 per year. In neonates, the deep venous system was more often involved and parenchymal injuries were more common. The strongest predictor of poor outcome was neonatal age (odds ratio 17.8, 95% confidence interval 0.847–372.353). Most children showed global cognitive abilities within the normal range, but impairments in single cognitive subdomains were frequent.
INTERPRETATION Paediatric CSVT is rare. Its outcome is poor in neonates. Most children have good neurological outcomes, but some patients have individual neuropsychological impairments.

Cerebral sinus venous thrombosis (CSVT) in children is rare. Based on a Canadian registry, its incidence is 0.67 cases per 100 000 children per year; neonates were the most commonly affected.[1] The risk factors in neonates include maternal conditions, delivery complications, and neonatal comorbidities.[1–4] Older children often use prothrombotic agents such as oral contraceptives or suffer from infections of the head and neck or a chronic systemic illness.[5–8] Prothrombotic states are increased in patients who suffer from CSVT.[1,9] The superficial venous system is most commonly involved.[1,6,10] Parenchymal injuries, such as ischaemic or haemorrhagic infarcts, are often observed in conjunction with CSVT.[1–3,11,12] One-third of term neonates with intraventricular haemorrhage suffer from CSVT.[13]

Two to 10 per cent of the neonates[2,4] and 11 to 17% of the older children died after CSVT[2,6]. A recurrence of the thrombosis occurred in 6%.[10] Thirty-eight per cent of the patients exhibited neurological deficits, such as motor impairment, cognitive problems, or epilepsy.[1] The long-term outcome was especially poor in neonates.[1,2,4] In older children who suffered from CSVT, cognitive assessments with standardized and age-normalized tests showed cognitive performance within the normal range,[14,15] but individual impairments were seen in up to 20% of the patients.[14]

In the present study, we aimed to describe the incidence, clinical manifestation, neuroimaging findings, risk factors, and treatment of children suffering from CSVT in Switzerland. In addition, we systematically assessed outcomes after CSVT and identified predictors of poor outcome.

METHOD

Participants and data collection

The Swiss Neuropaediatric Stroke Registry (SNPSR) is a population-based registry that prospectively collects epidemiological data on childhood stroke (children <16y suffering from arterial ischaemic stroke and CSVT) in Switzerland.[16] The

SNPSR is approved by the local ethics board of the University Hospital of Berne, Switzerland, and by the Swiss Federal Ministry of Health. Every paediatric neurologist in Switzerland is contacted on a monthly basis and asked to report current cases on an obligatory return form. If the neurologist reports a new case, a questionnaire, including data on the presence of risk factors for thromboembolic events, symptoms, clinical findings at manifestation, results of neuroradiological and laboratory investigations, and treatment, is sent to the paediatric neurologist responsible for the child. Six months later, a second questionnaire that included information on the short-term neurological outcome, results of follow-up investigations, and duration of treatment, is sent.

For the present study, all CSVT patients registered in the SNPSR between January 2000 and December 2008 were included. The inclusion criteria were symptomatic CSVT confirmed by neuroimaging (computed tomography [CT] and/or magnetic resonance imaging [MRI], MR or CT angiography/venography were not mandatory), and age younger than 16 years. The participants were divided into two age groups: neonates (diagnosis of CSVT within 28d of life) and children (diagnosis of CSVT after 28d of life).

No laboratory investigations were required, but laboratory testing for prothrombotic states were proposed.[16] Normal values for these tests were determined by the local laboratories that performed the investigations. The SNPSR did not provide any recommendations for the treatment of CSVT.

Outcome assessment

The parents of patients who had CSVT dating back at least 18 months were contacted and asked whether they would participate in a follow-up examination, which consisted of a standardized interview, a neurological examination, and a developmental/neuropsychological examination. The assessment was performed in the first language of the child by a paediatric neurologist or a neuropsychologist. Depending on the patient's age, the following test batteries were used: (1) Bayley Scales of Infant Development, second edition (BSID-II); (2) Kaufmann Assessment Battery for Children (K-ABC); (3) Wechsler Intelligence Scale for Children, third edition (WISC-III); and (4) Wechsler Adult Intelligence Scale, third edition (WAIS-III). Outcome was classified as poor if moderate to severe motor disability, mild to severe intellectual disability, developmental delay (IQ or developmental quotient <70), and/or epilepsy were present, or if the patient died. Informed consent was given by the parents of all participating children.

Statistical analysis

The incidence of CSVT was calculated based on the Swiss population according to the publications of the Swiss Federal Statistical Office (http://www.bfs.admin.ch). Differences between neonates and children were assessed by Fisher's exact test. Predictors of poor outcome were illustrated by odds ratios (ORs) and 95% confidence intervals (CIs). The predictor variables included age group, the presence of parenchymal injury in neuroimaging, treatment with anticoagulant drugs, presence of seizures at manifestation, number of involved vessels, distribution of involved vessels, and sex. In an initial screen the predictors were calculated by a univariate analysis. The p values and 95% CIs were adjusted for multiplicity by the Holm–Bonferroni method. As a multivariable model allows parameters to be re-estimated while accounting for potential confounding of explanatory variables, a multivariate logistic regression analysis, including all the predictor variables mentioned, was performed in a second step. The results of the cognitive assessment were illustrated for both age groups by the mean values of each test battery. Statistical comparison with the healthy population was performed for various subtests of the WISC-III by the non-parametric Wilcoxon signed-rank test. This procedure was chosen as normal distribution in the study groups could not be assumed, and no healthy comparison group was examined. To evaluate whether patients showed individual cognitive strengths and weaknesses in the WISC-III assessment ($p<0.05$), the differences between the subtest values and the individual mean values of all subtests were calculated. This procedure was performed according to the WISC-III test manual. SPSS for Windows (version 15.0; SPSS Inc., Chicago, IL, USA) was used to analyse data.

What this paper adds

- Epidemiological information on paediatric cerebral sinus venous thrombosis (CSVT).
- The outcome of CSVT is poorer in neonates than older children and in patients with parenchymal brain injuries, and might be influenced by the use of anticoagulant medication.
- Although the general outcome of CSVT in older children is good, impairments in cognitive function are common.

RESULTS

Sixty-five children with CSVT were registered in the database (21 neonates [32%]: 14 males, seven females; 44 children [68%]: 30 males, 14 females). In the neonates, the mean age at diagnosis was 9 days (SD 8d, range 0d–27d), mean gestational age was 37 weeks (SD 4wks, range 25–41wks), and the mean birthweight was 2720g (SD 889g, range 770–3960g). Four neonates were born preterm. One neonate had Down syndrome. Another neonate was suspected as having a genetic syndrome; he presented with dysmorphic features, congenital heart disease, and hypoplasia of the vermis cerebelli.

The mean age of the children at the time of diagnosis was 8 years 7 months (SD 4y 5mo; range 9mo to 15y 7mo).

The most common symptoms at presentation in the neonates were seizures (n=12) irritability and/or apathy (n=7) apnoea and/or respiratory distress (n=5) poor feeding (n=5) and tone abnormalities (n=5). In the children, the most common symptoms were headaches (n=29) decreased level of consciousness (n=13) nausea and/or vomiting (n=14) visual impairment (n=9) seizures (n=9) hemiplegia (n=4) and ataxia (n=3). The overall incidence of paediatric CSVT in Switzerland was 0.558 per 100 000 per year in inhabitants aged under 16 years, and the incidence of neonatal CSVT was 0.034 per 1000 live births per year.

The risk factors for neonates and children are summarized in Table I. In the neonates, prenatal risk factors were present

Table I: Risk factors and laboratory investigations for prothrombotic states in children and neonates

Risk factors in neonates (n=21), n					
Maternal conditions		Birth complications		Neonatal comorbidities	
Any	11	Any	12	Any	13
Multiple pregnancy	1	Meconium aspiration	3	Jaundice	9
Smoking	4	Asphyxia	3	Sepsis	7
Diabetes	2	Preterm birth	4	Meningitis	1
Preeclampisa/hypertension	3	Caesarean section	12	Pneumonia	1
Streptococci B	1	Vacuum/forceps	4	RDS	9
Thrombosis	1			Mechanical ventilation	8
Premature contractions	2			Kidney disease	2
Feto-fetal transfusion	1			Genetic disorder	2
				Inotropics	4
				Heart disease	2

Risk factors in children (n=44), n					
Acute disorders		Chronic disorders		Thrombophilic agents	
Any	27	Any	15	Any	4
ENT Infection	23	Leukaemia	5	PEG-asparaginase	4
Middle ear infection	19	Lymphoma	1		
Mastoiditis	16	Histiocytosis	1		
Sinusitis	3	Infl. bowel disease	2		
Meningitis	5	Behcet's disease	3		
TBI	2	Nephrotic syndrome	1		
		Diabetes mellitus	1		

Prothrombotic states in children and neonates				
	Neonates		Children	
	Observed/examined		Observed/examined	
Any[a]	6/14		17/40	
Protein S deficiency	1/11		4/29	
Protein C deficiency	2/12		1/29	
Antithrombin III deficiency	1/12		1/29	
Elevated Lp(a)	2/3		4/18	
ACLA	1/5		0/28	
Factor V	het: 1/7	hom: 1/7	het: 2/28	hom: 0/28
Prothrombin G2021	het: 1/5	hom: 1/5	het: 2/26	hom: 0/26
MTHFR C677	het: 2/2 (100)	hom: 0/2	het: 10/17	hom: 0/17
Elevated homocysteine	1/3		1/28	

[a]Heterozygous MTHFR C667 mutation not considered as prothrombotic risk factor. RDS, respiratory distress syndrome; Infl., inflammatory; TBI, traumatic brain injury; PTS, prothrombotic state; Lp(a), lipoprotein (a); ACLA, anti-cardiolipid antigen; MTHFR, methylenetetrahydrofolate reductase deficiency; het, heterozygous; hom, homozygous.

in 11, perinatal risk factors were present in 12, and neonatal comorbidities were present in 13. In the children, the most common risk factors were infections of the head and neck, and chronic medical conditions. Four patients were treated with polyethylene glycol (PEG)-asparaginase. The use of oral contraceptives was not documented. Laboratory investigations for prothrombotic risk factors were available for 14 neonates and 40 children. One or more prothrombotic risk factors were found in 6 of the 14 neonates and in 17 of the 40 children.

For the diagnostic evaluation, MRI was performed in 20 neonates and 32 children. Magnetic resonance venography was performed in 7 neonates and 17 children. Four neonates and 31 children underwent CT. All 21 neonates had a power Doppler ultrasound, which detected 48% of the instances of CSVT. The localization of the CSVT differed between neonates and children (Table II). In the neonates, the deep venous system (straight sinus, vein of Galen, internal veins, jugular veins) was more commonly affected (neonates: n=15 children: n=15 p=0.005). Multiple sinus involvement was more common in the neonates (neonates: n=16; children: n=20 p=0.018). In the children, the lateral sinuses were predominantly involved (neonates: n=9 children: n=34 p=0.007). Parenchymal lesions were more common in the neonates (neonates: n=18 children: n=8 p<0.001). The parenchymal injuries in the neonates were haemorrhagic infarctions of the cerebral white matter (n=10) intraventricular haemorrhage (n=8) haemorrhagic lesions of the basal ganglia/the thalamus (n=7) arterial ischaemic stroke (n=2) and subarachnoid haemorrhage (n=1). One child had cerebellar hypoplasia in the context of an underlying dysmorphic syndrome. The parenchymal injuries in the children were haemorrhagic lesions of

Table II: Distribution of the thromboses (Fisher's exact test)

	Neonates (*n*=21), *n*	Children (*n*=44), *n*	*p*
Superficial venous system			
Superior sagittal sinus	17	20	0.006
Inferior sagittal sinus	1	0	0.323
Lateral sinus	9	34	0.007
Deep venous system			
Straight sinus	13	7	<0.001
Vein of Galen	6	2	0.011
Internal veins	8	1	<0.001
Jugular veins	0	10	0.014
Cavernous sinus	0	1	0.068
Distribution			
Multiple vessels involved	16	20	0.018
Deep venous system involved	15	15	0.005

the cerebral white matter (*n*=5) haemorrhagic lesions of the basal ganglia/the thalamus (*n*=2) intraventricular haemorrhage (*n*=1) and chronic subarachnoid bleeding/hygroma (*n*=1).

Seven neonates and 38 children received an anticoagulant medication. The therapeutic treatment consisted of standard heparin (20–30U/kg/h) in 2 neonates and in 24 children. Low-molecular-mass heparin was used in 5 neonates and in 12 children (enoxaparine 1.5mg/kg/dose or nadroparine 85 anti-FXa U/kg/dose twice daily). Prophylactic treatment consisted of low-molecular-mass heparin in 7 neonates and in 26 children (enoxaparine 0.75mg/kg/dose twice daily or nadroparine 60 anti-FXa U/kg/dose once daily) as well as oral anticoagulation (phenprocoumone, acenocoumarolum, and danaparoid sodium) in 11 children. The duration was based on clinical outcome and follow-up investigations, and ranged from 1 week to 9 months. One patient with chronic inflammatory bowel disease suffered from significant gastrointestinal bleeding during oral anticoagulation. Otherwise, no serious side effects were reported. In two children no anticoagulant treatment was initiated, but prophylactic treatment with aspirin was started. Follow-up imaging studies were available for 41 patients. Eighteen patients showed complete recanalization, 19 showed partial recanalization, and 4 showed no recanalization.

Two patients died. One neonate who had dysmorphic features and presented with respiratory distress and seizures died a few months after presentation. His MRI revealed multiple CSVTs of the deep and superficial venous system and hypoplasia of the vermis cerebelli. The details of his death are unknown but are probably not related to CSVT. One male infant died during the acute event. He was born preterm and had had intraventricular haemorrhage with parenchymal involvement in the perinatal period; he had epilepsy and presented with sudden loss of consciousness at the age of 3 years 8 months. The MRI showed multiple CSVTs, with involvement of the deep and superficial venous system. In the laboratory investigations, a very low level of protein S was found, and congenital protein S deficiency was suspected.

Fifty-two patients with a follow-up duration of more than 18 months were considered for follow-up assessment. Five patients or parents refused participation and 10 patients could not be contacted. A standardized follow-up assessment was performed in 13 neonates (three were born preterm, one was born at <32wks gestational age; the neonate who had Down syndrome was not included) and in 24 children with a mean follow-up duration of 26 months. In summary, the outcome was considerably worse in the neonates. Five of the 13 neonates were diagnosed with epilepsy whereas epilepsy was not reported in any of the children. For the neurological examination, moderate or marked motor impairment was found in 7 neonates (spastic hemiplegia in four and spastic tetraplegia in three). One child had mild spastic hemiplegia, which was not functionally limiting. Two children developed idiopathic intracranial hypertension.

A developmental/neuropsychological test battery was performed in 32 patients (11 neonates, 21 children; BSID-II in 10, K-ABC in 6, WISC-III in 14, and WAIS-III in 2). The results are shown in Table III. In summary, intellectual disability or developmental delay (IQ or developmental quotient <70) was observed in 8 neonates, but no child exhibited intellectual disability. In the neonates, the mean BSID-II mental index and motor index scores were 1.6 standard deviations below the typical population. In one neonate, no BSID-II was performed, but a K-ABC at 8 years showed intellectual disability (IQ 47). In the children, the mean values for the total scores were within the normal range for all test batteries. There were no significant differences compared with the healthy population in any of the subtests of the WISC-III (data for subtests not shown). More children than expected showed individual cognitive weakness on the WISC-III in one or more subtests. Individual cognitive weakness in one subtest was found in four children. Eight children had individual weaknesses in two subtests, one child had individual weaknesses in three subtests, and one child had individual weaknesses in four subtests.

The results for the predictors of poor outcome are listed in Table IV. The univariate analysis showed a significant association between poor outcome and neonatal age (OR 43.21, 95% CI 1.89–986.80, p=0.007), the presence of parenchymal injuries (OR 20.01, 95% CI 0.82–487.87, p=0.040), and the absence of anticoagulant treatment (OR 12.57, 95% CI 1.16–135.95, p=0.030). In the multivariate analysis neonatal age (OR 17.78, 95% CI 0.85–373.35) and the absence of anticoagulant treatment (OR 7.54, 95% CI 0.58–97.08) remained the strongest predictors of poor outcome. The analysis was performed separately for patients without neurological comorbidities and chronic disease; the results were similar.

DISCUSSION

The aim of the present study was to describe the incidence, manifestation, neuroimaging findings, and risk factors for CSVT in Swiss children younger than 16 years. Furthermore, we aimed to evaluate differences between neonates and older children, to assess the outcome after CSVT, and to identify predictors of outcome. All cases were prospectively collected by the SNSR, a nationwide collaborative project including all Swiss neuropaediatricians. The yearly incidence of CSVT was

Table III: Cognitive performance at follow-up examination in neonates and children

	Mean	Range	95% CI	*n*	Mean (norm)	SD (norm)	*p*
Neonates							
BSID-II MDI	74	50–116	56–91	10	100	15	NA
BSID-II PDI	75	50–117	57–93	10	100	15	
K-ABC total IQ	47	NA		1	100	15	
K-ABC SED	69			1	100	15	
K-ABC SGD	47			1	100	15	
K-ABC NV	44			1	100	15	
Children							
K-ABC MPS	96	88–111	83–109	5	100	15	NA
K-ABC SED	80	59–90	65–95	5	100	15	
K-ABC SGD	107	93–126	90–125	5	100	15	
K-ABC NV	106	94–123	84–129	4	100	15	
WISC-III total IQ	104	77–140	95–116	14	100	15	0.414
WISC-III verbal	107	74–140	95–121	14	100	15	0.221
WISC-III Performance	103	69–131	95–114	13	100	15	0.441
WAIS-III total IQ	99	84–114	NA	2	100	15	NA
WAIS-III verbal	94	76–112		2	100	15	
WAIS-III performance	106	98–114		2	100	15	

BSID-II, Bayley Scales of Infant Development, second edition (MDI, Mental Developmental Index; PDI, Performance Developmental Index); K-ABC, Kaufmann Assessment Battery for Children (MPS, Mental Processing Scale; SED, Sequential Processing Scale; SGD, Simultaneous Processing Scale; NV, Non-verbal Scale); WISC-III, Wechsler Intelligence Scale for Children, 3rd edition; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition.

Table IV: Univariate analysis (with and without adjustment for multiplicity) and multivariate analysis for the predictors of poor outcome for all patients who underwent follow-up examination

	Univariate analysis					Multivariate analysis	
		Not adjusted for multiplicity		Adjusted for multiplicity			
	OR	95% CI	*p*	95% CI	*p*	OR	95% CI
Multiple sinuses involved	7.32	0.82–65.45	0.750	0.45–119.70	1.000	0.27	0.00–16.80
Absence of ACT	12.57	2.14–73.62	0.005	1.16–135.95	0.030	7.54	0.58–97.08
Seizures at manifestation	2.55	0.54–12.07	0.240	0.35–18.50	0.960	1.02	0.06–17.02
Male sex	2.35	0.25–22.31	0.460	0.13–41.49	1.000	6.58	0.05–902.20
Deep venous system involved	6.55	1.17–36.59	0.032	0.73–58.79	0.128	3.00	0.19–47.74
Neonatal age	43.21	4.42–422.20	0.001	1.89–986.80	0.007	17.78	0.85–373.35
Parenchymal injury	20.01	1.77–226.44	0.008	0.82–487.87	0.040	4.16	0.15–115.64

OR, odds ratio; CI, confidence interval; ACT, anticoagulant therapy.

0.558 per 100 000 inhabitants under 16 years old. This is somewhat lower than the findings from the Canadian registry, which included patients younger than 18 years.[1]

Compared with the Canadian study, we report fewer neonates.[1] In Switzerland, transcranial Doppler ultrasonography is the standard neuroradiological investigation in neonates. CT or MRI is often not routinely performed in sick neonates. Compared with CT/MRI, ultrasonography detected only 48% of the instances of CSVT. Although ultrasonography is a powerful tool for diagnosing neonatal CSVT in the superior sagittal sinus,[17] instances with involvement of the deep venous system might have been missed. We assume that CSVT is underdiagnosed, especially in neonates, and therefore plan to develop evidence-based guidelines for the diagnostic evaluation of CSVT. In contrast to the Canadian study[1], we found significant differences between neonates and children in the location of the CSVT. The deep venous system, particularly the straight sinus, was more commonly involved in neonates than previously reported.[1,4,5,11] We do not have a satisfactory explanation for this finding. The risk factors for CSVT in neonates and children were similar to previous findings.[1–8]

Previous studies have assessed the outcome after CSVT with varying time intervals and included children with a very short follow-up. In the present study, only patients with a follow-up duration of 18 months or more were included for the outcome assessment. The outcome was considerably worse in neonates. Moreover, neonatal age at presentation was the strongest predictor of poor outcome. In contrast, children who experienced a CSVT after the neonatal period showed intellectual abilities within the normal range, but a considerable number of the children showed a heterogeneous cognitive profile with partial disturbances of cognitive performance. This might indicate that, despite normal general

intellectual functioning, children suffering from CSVT may have attention and perception problems that only become evident under increasing academic demands.

The choice of medication and the length of treatment vary between centres; this was also the case in the present study. Guidelines for the treatment of CSVT have been published only recently.[18,19] In the children who were registered in the SNPSR, anticoagulation therapy was given to 33% of the neonates and 86% of the children. It was not the primary aim to evaluate the efficacy and safety of anticoagulation therapy, although for the study population anticoagulation therapy was associated with a better outcome and few side effects. Randomized controlled studies are needed to analyse the value of anticoagulation therapy in the treatment of paediatric CSVT.

Limitations

The diagnostic evaluation for the diagnosis of CSVT was not standardized in the present study. Diagnostic procedures differed between the centres, which may have led to an underestimation of the incidence of paediatric CSVT. One of the largest tertiary paediatric hospitals in Switzerland reported 38% of instances, mainly in children suffering from mastoiditis. CSVT was mostly diagnosed by CT with a contrast medium, which is routinely performed to evaluate mastoiditis at this centre but not at other participating centres. We assume that other centres might have missed CSVT in children with mastoiditis. We therefore recommend routine CT with a contrast medium in all children who have mastoiditis. The laboratory investigations were mandatory, differed between patients, and were not performed by the same laboratory. However, the frequency of prothrombotic states may represent an under- or overestimation. Because no case–control design was used in the present study, the association of risk factors and CSVT is only presumptive. The results for the treatment of CSVT must be interpreted with extreme caution. No standardized treatment protocol was used, and the side effects were not noted in a standardized manner. For the neuropsychological outcome, comparison with a typically developing population was limited because no comparison group of healthy children was examined.

CONCLUSION

CSVT is rare in the paediatric population. However, its incidence may be underestimated. Clinical features and risk factors differ between neonates and children. The outcome after CSVT is considerably worse in neonates. Despite the relatively good neurological outcome and intellectual functioning in children, some patients may suffer from individual neuropsychological impairments.

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