

A Retrospective Review of Paediatric Cerebral Venous Sinus Thrombosis in a South African Tertiary Hospital

Dissertation submitted for the degree MMed (Paediatrics)

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Declaration

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Dedication

This thesis is dedicated to my loving wife, Coreen and my two beautiful children,
Matthew and Pippa.

Thank you for the unconditional support and inspiration these past four years.

Abbreviations

AGE: Acute gastro-enteritis
ALL: Acute lymphoblastic leukemia
BVR: Basal vein of Rosenthal
CD4: Cluster of differentiation 4
CNS: Central nervous system
CNSA: Coagulase negative Staphylococcus aureus
CSOM: Chronic suppurative otitis media
CT scan: Computed tomography scan
CVST: Cerebral venous sinus thrombosis
ECM: Enterprise content management
GBS: Group B Streptococcus
Hb: Haemoglobin
HIV: Human immunodeficiency virus
ICV: Internal cerebral vein
ISS: Inferior sagittal sinus
LMWH: Low molecular weight heparin
LOC: Level of consciousness
MVC: Mean corpuscular volume
MRI: Magnetic resonance imaging
SSS: Superior sagittal sinus
TB: Tuberculosis
TCH: Tygerberg Children's Hospital
TSV: Thalamo-striate vein
UFH: Unfractionated heparin
UTI: Urinary tract infection
WHO: World Health Organisation

Abstract

Introduction:

Paediatric cerebral venous sinus thrombosis (CVST) is a rare complication associated with many underlying illnesses. It often results in severe neurological complications, which can be severely debilitating.

The aim is to describe the clinical presentation of paediatric patients diagnosed with CVST who presented to Tygerberg Children's Hospital (TCH).

Materials and methods:

This is a retrospective, descriptive case series looking at patients younger than 14 years of age residing in the Western Cape who were referred to TCH and diagnosed with CVST based on neuroimaging over a six-year period.

Results:

Thirty-five patients were included in this study with a male predominance of 57% and a mean age at presentation of 17 months with the majority of patients (80%) presenting during the first year of life. The mean weight-for-age was on the -2 Z-score. Acute gastro-enteritis (AGE) was the most common underlying clinical condition associated with the development of CVST. All of the patients with AGE were hypernatraemic. The majority of our patients (62.9%) had multiple sinus involvement; the transverse sinus was the most common sinus involved. Mortality was 5.7% and morbidity 37.1%. Poor outcome was not associated with convulsions or with decreased level of consciousness at presentation.

Conclusion:

Our study is the first of its kind in South Africa. We demonstrated that hypernatraemia and AGE appear to be significant acute underlying triggers for developing CVST. In this study CVST is more common in younger patients, severe underweight for age and associated with AGE than has previously been reported in studies from high income countries.

Abstrak

Inleiding:

Pediatriese serebrale veneuse sinus trombose (SVST) is 'n raar komplikasie wat kan volg op verskeie onderliggende mediese toestande. Dit kan moontlike debiliterende neurologiese komplikasies tot gevolg hê.

Die doel van hierdie studie is om die kliniese beeld van pasiente te beskryf wat met SVST in Tygerberg Kinderhospitaal presenteer.

Materiale en metodes:

Hierdie is n retrospektiewe, deskriptiewe gevalle reeks van kinders onder 14 jaar wat met SVST gediagnoseer is in 'n 6 jaar periode in Tygerberg Kinderhospitaal in die Wes-Kaap.

Bevindinge:

Vyf-en-dertig pasiënte was in die reeks ingesluit met 'n manlike predominansie van 57%. Die gemiddelde ouderdom van die kinders was 17 maande en 80% van die kinders was jonger as 1 jaar oud. Die gemiddelde gewig-vir-ouderdom was op die -2 Z-telling. Die algemeenste onderliggende siekte-toestand wat met die ontwikkeling van SVST geassosieër was, was akute gastro-enteritis (AGE). Al die pasiënte met AGE het geassosieerde serum hipernatremie gehad. Die transverse sinus was die sinus wat die meeste geaffekteer was en in die meerderheid van die pasiënte (62.9%) was meer as 1 sinus aangetas. Morbiditeit was 37.1% met 'n mortaliteit van 5.7%.

Konvulsies en 'n onderdrukte bewussyn met presentasie was nie geassosieer met 'n slegte uitkoms nie.

Konklusie:

Hierdie studie is die eerste van sy soort in Suid-Afrika. Ons het gewys dat AGE en hipernatremie belangrike onderliggende toestande is in die ontwikkeling van SVST. In hierdie studie is SVST meer algemeen in jonger kinders, dié wat ondergewig vir ouderdom is en die wat geassosieer is met AGE as wat voorheen gepubliseer is in hoër inkomste lande.

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A Retrospective Review of Paediatric Cerebral Venous Sinus Thrombosis in a South African Tertiary Hospital

Chapter 1

Introduction

Paediatric cerebral venous sinus thrombosis (CVST) is a rare complication that occurs in children following several precipitating factors. CVST results in severe neurological complications, which are often severely debilitating. Although this complication has been reported amongst children living in high-income countries there is very little data on the prevalence, causes and outcome of children that develop CVST in resource-constrained countries, especially sub-Saharan Africa. The aim of this thesis is to review the literature and report on CVST in a population of children living in a middle-income African country.

Chapter 2

Literature review

Introduction

Paediatric cerebral venous sinus thrombosis (CVST) is a rare disorder with an estimated incidence of between 0.4 - 0.67 per 100,000 children in developed countries.(1) The severe neurological sequelae and high mortality of this devastating disease emphasize the need for high-quality studies within this field. No data on paediatric CVST are known for South Africa or even continental Africa. Most data are from the high-income countries of America, Europe and Australasia.

Epidemiology

As many as 43% of CVST cases occur in the first month of life (1), with an incidence of 2.6 per 100,000 neonates per year reported in a series investigating a neonatal population.(2) After the neonatal period CVST is almost equally distributed amongst the sexes with a mean age at presentation of 4 - 6 years.(1-7) The incidence of CVST is probably underestimated for several reasons in children with CSVT, particularly neonates. Children often present with subtle neurologic signs making it a challenging diagnosis and the clinical picture overlaps with other causes of neurological disease. The under diagnosis of CVST is further complicated by older neuro-imaging techniques, the variable anatomy of the cerebral sino-venous system and rapid recanalization following the complication.(8)

Pathophysiology

The venous sinus is a cavity formed between the endosteal and meningeal layers of the dura. Channels that allow venous blood to drain from the cranium into the sinuses connect the sinuses. CVST refers to the complete or partial occlusion of the main sinuses. Thrombosis within the sinus system results in outflow obstruction of the venous system resulting in venous congestion and consequently an increase in capillary hydrostatic pressure, driving fluid into the interstitium and producing cerebral oedema. This cerebral oedema increases intracranial pressure, which further impairs the venous drainage. These factors result in intracranial hypertension and/or

venous infarcts. Formation of thrombi in venous channels draining the brain is a consequence of the characteristic risk factors described by Virchow's triad, which includes vessel wall trauma, stasis and a hypercoagulable state.

Aetiology

The origin and pathophysiology of CVST is poorly understood. Published data suggest that CVST is multifactorial in origin with many associated underlying illnesses or chronic conditions.(1,2,4–7,9–11) Aetiological factors can be grouped in three categories: Chronic underlying illnesses, acute associated conditions and pro-thrombotic states. Patients who are diagnosed with CVST seem to have had one or a combination of these risk factors.

Associated acute conditions include common childhood systemic illnesses including infections, dehydration, fever and anaemia. Associated chronic conditions include malignancies, nephrotic syndrome, systemic lupus erythematosus and congenital cardiac diseases.

Infection appears to be a significant trigger in previously well children without an underlying medical condition. Infections associated with CVST can either be systemic, such as bacterial sepsis, or regional, such as meningitis, mastoiditis and/or otitis media. Other local head and neck disorders can cause thrombosis due to local venous stasis. These include recent head/neck surgery, head trauma and CNS tumours.

CVST has been described as a complication of L-asparaginase use in the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma. L-asparaginase is postulated to create a pro-thrombotic state, alone or in combination with other chemotherapeutic agents.(4,6,12,13)

Anaemia is frequently observed in children with CVST(5,7), though mechanisms for anaemia to contribute to thrombus development are incompletely understood. Iron-deficiency microcytic anaemia appears to be the most common cause of anaemia associated with CVST. Previously healthy children with a stroke were 10 times more likely to have iron-deficiency anaemia than healthy children without stroke.(14)

Prothrombotic states may cause or contribute to the development of CVST in children. Prothrombotic states have been identified in 24- 64% of children with CVST.(1,2,5) The association between prothrombotic risk factors and CVST proves only to be statistically significant if the thrombosis is associated with an underlying medical condition. (2,11) The cause of the hypercoagulable state is difficult to determine as prothrombotic tests are complex and are difficult to interpret as the number and types of tests done over the past 3 decades have varied.

CVST has been described as a complication of dehydration in children. Although CVST secondary to hypernatraemic dehydration in breastfed neonates has been described in the literature (15,16), there is limited clinical data on CVST secondary to hypernatraemic dehydration in the setting of diarrhoeal disease in infants and young children. However, CVST is accepted as a complication of hypernatraemic dehydration due to diarrhoeal diseases by paediatric gastroenterologists and neurologists. (Personal communication: Nel ED, Solomons R)

A review article by Roach et al. stated that hypernatraemia in conjunction with dehydration may cause CVST. (17) He based his observation on two studies published in the 1950's and 1960's by Finberg and Macaulay, however this association has been infrequently reported in the literature.

Clinical Presentation

The clinical manifestations of CVST can be subtle and non-specific. Due to its rarity and the non-specific clinical features at presentation, the diagnosis of CVST is often delayed or may be missed altogether. One study reported an average delay in diagnosis of CVST of up to 4 days(6). Most common clinical features at presentation are seizures, fever, drowsiness/stupor, headaches and generalized weakness. Common neurological abnormalities at presentation are decreased level of consciousness, cranial nerve palsies and hemiparesis. While most of the clinical symptoms can occur at any age, seizures are more common in neonates, whereas focal and diffuse neurologic signs are more common in older infants and children.(1,2,5-7,9,10)

Topographic location of thrombi

The superficial venous system (dural venous sinuses) is more frequently involved than the deep system (composed of traditional veins inside the deep structures of the brain, which join behind the midbrain to form the vein of Galen). The most common sites of CVST are the transverse, superior sagittal, sigmoid, and straight sinuses.(6) The topographic locations involved differ depending on the nature of the underlying intracranial pathology. In one study the transverse sinus was mostly affected following acute bacterial mastoiditis,(18) while in a separate study, lateral sinus thrombosis was associated with mastoiditis and otitis media.(19)

Treatment

The treatment of CVST in children is not well described. The initial management is to treat the underlying cause or associated clinical condition and administer general supportive care. The only randomized placebo-controlled trial of intravenous heparin in adults was stopped early because there was clear evidence of benefit, particularly in terms of mortality. A randomised placebo-controlled trial of subcutaneous low molecular weight heparin (LMWH) in adults showed a trend for better outcome in the treated group.

Anticoagulation therapy has been used inconsistently in children with CVST. The use has been controversial as previously anticoagulation was associated with intracranial haemorrhage. More recently case series have shown that LMWH can be used safely in children, however outcome data is limited to support the efficacy of this treatment.(5) DeVeber(1) initiated a prospective cohort study of anticoagulant therapy in 30 children with CVST from 1992 to 1996, and reported a mortality rate of 3 out of 8 untreated children, compared with 0 of 22 treated children. One series suggested that cognitive outcome may be better in the anticoagulated group.(5) This highlights the importance of further studies investigating treatment options in paediatric patients with CVST.

Recent Canadian guidelines for the treatment of CVST states that children with no associated intra-cranial haemorrhage should be anticoagulated with LMWH or unfractionated heparin (UFH). In the presence of haemorrhage resulting in a local mass effect or intraventricular haemorrhage, it is reasonable to withhold anticoagulation. The presence of less significant intracranial haemorrhage or

parenchymal infarctions are not contraindications to anticoagulation.

The use of anticoagulant agents to prevent CVST has a large evidence base in the adult population, but is very limited in children. There is no evidence for the use of aspirin for CVST prophylaxis in a paediatric population.(20)

Prognosis and outcome

CVST has poor prognosis with morbidity that varies from 17%-62% and mortality between 10%-12%.(1,4-7,9) In an American study, they found that permanent neurological disability was associated with thrombosis of the deep veins with associated infarctions.(3) Coma is the only predictor of death in childhood CVST.(5) One study reports that older age and involvement of the lateral and/or sigmoid sinuses are associated with good cognitive outcome.(5) Common long-term sequelae include motor impairment, cognitive impairment, developmental and/or speech delay, and visual impairment.(1,21,22)

Recurrence of CVST is uncommon. The Canadian study by DeVeber et al in 160 children with CVST identified 12 (<1%) children with recurrent thrombosis.(1) This was supported by an additional study in 266 children with CVST with recurrence of venous thrombosis in 3%.(11)

Chapter 3

Research justification

Previous studies on cerebral venous sinus thrombosis were performed in developed countries of Europe, North America and Australasia. No study on CVST has been performed in Sub-Saharan Africa. The aetiological differences of CVST between developed and resource-constrained countries such as South Africa are not known. It is hypothesized that the aetiology will lean towards CVST being associated with common infectious diseases, such as diarrhoea and meningitis, as these diseases commonly occur in Southern Africa. Although dehydration is mentioned as a cause of CVST in developed countries, the cause of the dehydration and serum osmolality derangements associated with dehydration has not been reported.

Clinicians practicing in low and middle-income countries widely accept that CVST is a complication of hypernatraemic dehydration caused by diarrhoeal diseases but there is a paucity of reports investigating this association.

Secondly, the treatment of paediatric CVST remains controversial. There are currently no well-designed clinical trials in children to support acute or chronic anti-thrombotic therapy with anticoagulants or antiplatelet agents once the diagnosis of CVST is made. Randomized control trials in the paediatric population are required in order for treatment consensus to be reached.

The purpose of this study was to describe the confirmed paediatric cases of CVST in a South African population admitted to a tertiary care hospital and report the potential precipitating factors, clinical presentation, thrombus location and short-term neurological outcome. This will serve as an important pilot study of paediatric cerebral venous sinus thrombosis in Southern Africa. It is hoped that results from this study will lead to improved awareness of the CVST in neonates and children, improve the understanding of the associated risk factors and direct optimal therapy to decrease the mortality and morbidity.

Chapter 4

Aim and objectives

Aims of the study

To describe the clinical picture of paediatric patients diagnosed with CVST who presented to Tygerberg Children's Hospital and investigate the patient profile, associated conditions and treatment received.

Primary Objectives

To describe patients who presented to Tygerberg Children's Hospital diagnosed with CVST with regards to the following:

- Age at presentation.
- The signs and symptoms on admission and any neurologic deficit noted at presentation.
- Any associated acute medical illnesses or underlying chronic medical conditions.
- To assess delay (in days) from presentation to diagnosis.
- Document the thrombotic location on CT scan.
- To document death and/or neurologic deficit at discharge.

Secondary objectives

- To document electrolyte abnormalities at presentation.
- To document haematological abnormalities at presentation.
- To assess anthropometry of the patients at presentation.

Chapter 5

Materials and methods

Study design:

This study is a retrospective, descriptive case series.

Study site:

Tygerberg Children's Hospital (TCH) in Cape Town is a large tertiary center that accepts referrals from clinics, day hospitals, and district hospitals as well as regional hospitals from within the Western Cape Province of South Africa. Tygerberg Children's Hospital services a population of approximately 2,5 million people and admits approximately 17000 neonates and children per annum.

Population:

Children younger than 14 years of age (including neonates) admitted to the TCH paediatric wards served as the population from which the study population was collected.

Study Sample:

Children younger than 14 years of age (including neonates) admitted to Tygerberg Children's Hospital paediatric wards from January 2009 to December 2014 who were diagnosed with CVST were included in the study.

Inclusion criteria:

- Confirmed Diagnosis of CVST based on neuroimaging (Brain computed tomography (CT scan) imaging)
- Admission to TCH between 1 January 2009 and 31 December 2014
- Age between 1 day and 14 completed years

Exclusion criteria:

- Incomplete patient documentation
- Inconclusive neuro-radiological diagnosis of CVST after independent review by a radiologist

Patient Tracing:

Study patients were identified from discharge summaries obtained from the different paediatric wards in TCH. Patients who were diagnosed as suffering from CVST were crosschecked against the neuro-radiology database, and only those children and neonates with a confirmed neuro-radiological diagnosis of CVST were included.

Chapter 6

Data Management

Data collection:

- The patient's clinical data was collected retrospectively from their clinical patient file, either from the hard copy patient files or from the electronic patient files on the Enterprise Content Management (ECM) system. The ECM system did not contain all patient files due to its recent inception in Tygerberg Hospital.
- Patient radiological data, MRI and CT Scan images, was collected from Tygerberg Hospital's iSite enterprise.
- Patient blood results were collected from the National Health Laboratory Service electronic database. Laboratory parameters that were investigated included serum sodium, urea, creatinine, haemoglobin and the mean corpuscular volume levels. The normal values as used by the clinical service were used.
- After data capturing was completed, the data was categorized, processed and analyzed.
- All data was stored in Microsoft Excel on a password-protected computer. This password was only known to the primary investigator.

Data Capturing:

The following data was captured on a data capture sheet for each individual patient:

- Demographic information:
 - Age and weight on admission.
 - Gender
 - The weight on presentation for each patient was standardized on the weight-for-age Z score chart.
- Associated underlying illnesses:

- These were conditions diagnosed alongside the CVST during the same admission.
- If an infective illness was identified: Micro-organism microscopy and culture was performed.

- Chronic illnesses:
 - These are underlying chronic medical conditions that the patient was known with.

- Signs and symptoms at presentation:
 - These were the presenting signs and symptoms in the paediatric emergency ward.

- Neurological signs at presentation:
 - Neurological fallout present at presentation to the paediatric emergency ward, including:
 1. Loss of consciousness (Glasgow Coma Scale)
 2. Focal motor deficit

- Seizures:
 - Seizures present at the time of diagnosis of CVST.
 - Character of seizure – generalized or focal.

- Time delay of diagnosis (Time from admission to imaging).

- Serum electrolyte abnormalities:
 - Serum sodium on admission (within 24 hours).
 - Serum urea and creatinine on admission (within 24 hours).

- Haemoglobin and mean corpuscular volume level at diagnosis.

- Neurological deficit on discharge from Tygerberg Children's Hospital

- Neuro Imaging:

- The diagnosis of CVST was confirmed by independent review by two radiologists. Disagreement in interpretation was resolved by consensus.
- Radiological data that was captured:
 1. Imaging technique used
 2. Location of thrombosis
 3. Size of thrombosis
 4. Presence of associated venous infarct or bleed
 5. Presence of associated hydrocephalus

Definitions:

- Cerebral venous sinus thrombosis: The presence of acute blood clot formation in the dural venous sinuses, diagnosed by neuro-imaging.
- Hypernatraemia: Serum sodium level >145mmol/L
- Anaemia: A haemoglobin level of less than 14g/dL in the first month of life, less than 10g/dl between 1 and 12 months and <11g/dl in older children, were regarded as anaemic.(23)

Chapter 7

Statistical Analysis

Statistica® version 12 (Statsoft) was used to analyse the data.

Descriptive Statistics:

Variables recorded during the study was summarized using standard descriptive statistical methods:

- Continuous variables that follow a normal distribution were described by a mean and standard deviation.
- Continuous variables that do not follow a normal distribution were described by the median and inter-quartile range.
- Proportions were described by the proportion estimate and the 95% confidence interval.

Inferential Statistics:

- Differences between groups (e.g. presence or absence of neurological complications, venous infarct, associated diseases) were analyzed by analysis of variance (ANOVA) or the non-parametric equivalent (where data could be categorised).
- Associations between variables were analyzed by regression (linear, logistical, simple or multiple) analysis. (e.g. association between highest serum sodium concentration and presence of neurological outcome)

Chapter 8

Ethical considerations

Confidentiality:

Patient demographic data was kept strictly confidential at all times by only using study numbers in the data management and analysis stages of this study. The information for this study was collected in such a way as to protect patient confidentiality at all times. The data capture sheet and electronic database only contained a study code. The identifying information that is linked to the study code was kept in a separate, password-protected database. Access to this database was restricted to the primary investigator. All data will be kept for a maximum of 5 years in a safe, password-restricted database in the Department of Paediatrics and Child Health.

Consent:

A waiver of individual informed consent was granted by the Human Research Ethics Committee, as this was a retrospective study with minimal risks to the study participants. Permission was requested and granted to conduct this retrospective study from the Medical Superintendent of Tygerberg Hospital as the custodian of the data.

Ethical approval:

The Committee of Human Research of the Faculty of Health Sciences, University of Stellenbosch, approved the protocol for the proposed study. Ethical approval (S14/09/194) was obtained before data collection was started. (Appendix C)

Chapter 9

Results

Fifty-seven patients were identified with CVST from their electronic discharge summaries. Ten patients were excluded from the study, as their neuroimaging was unavailable. A further 12 were excluded after their neuroimaging was found to be not compatible with the criteria of CVST. Thirty-five patients were enrolled in this study.

Demographic information:

Twenty (57%) of the patients who presented with CVST were males and 15 (43%) were female. The mean age of the study patients at presentation was 17 months (range 2 weeks to 12 yrs). Five patients (14.3%) presented in the first month of life; 23 patients (65.7%) presented between the 1st and the 12th month of life; 3 patients (8.6%) were between 1 to 5 years old while 4 patients (11,4%) were older than 5 years. The mean weight-for-age of our patients was exactly -2.0 Z score (SD 2.03).

Symptoms and signs on presentation:

Symptoms on presentation were non-specific in nature. Twenty-two patients (62.8%) presented with vomiting, 23 (65.7%) presented with diarrhoea, 12 (34,3%) presented with fever, 10 (28.6%) presented with poor feeding and 3 (8.6%) presented with shortness of breath. Convulsions were present in 71.4% (25 patients) of which 17 (68%) presented with generalized and 8 presented with focal convulsions. On assessment, 77.1% (27 patients) had a normal level of consciousness on presentation, while 8 (22.9%) had a decreased level of consciousness. (see Table 1)

Eleven patients (31.4%) had neurological fallout on presentation. One patient had a hemiparesis, 2 patients had increased tone in their upper limbs, 1 patient had an opsithotonic posture and 1 patient had a decorticate posture. Six patients had globally increased tone on presentation.

Table 1.

Signs and symptoms	Number (n=35)	Percentage (%)
Fever	12	34.3%
Vomiting	22	62.8%
Diarrhoea	23	65.7%
Poor feeding	10	28.6%
Shortness of breath	3	8.6%
Convulsions	25	71.4%
- Generalized	17	48.6%
- Focal	8	22.8%
Depressed LOC	27	77.1%
Neurological deficit	11	31.4%

Signs and symptoms on presentation of patients diagnosed with CVST

CVST: cerebral venous sinus thrombosis; LOC: level of consciousness

Associated conditions:

The following chronic medical conditions were present: 4 patients (11.4%) were born prematurely and 5 (14.3%) were HIV positive. The blood CD4 counts and viral load counts were not ascertained. One patient (2.9%) had Tolosa-Hunt syndrome, 1 patient had a cow's milk protein allergy and 1 patient had asthma. (see Table 2)

The following acute medical conditions were present on admission. Twenty-four patients (68.6%) had associated acute gastro-enteritis, 9 patients (25.7%) had associated meningitis, 6 patients (17.1%) had pneumonia, 6 patients had associated sepsis, 4 patients (11.4%) had a brain abscess, 2 patients had protein-energy-malnutrition in the form of kwashiorkor, 2 patients (5.7%) had a urinary tract infection, 2 patients had presumed (unproven but suspected) disseminated tuberculosis, 2 patients had chronic suppurative otitis media and 1 patient (2.9%) had encephalitis. Two patients (5.7%) had no associated acute conditions. None of these patients had a prothrombotic screen.

Eight patients (22.9%) had 3 or more acute associated conditions, 11 patients (31.4%) had 2 acute associated conditions and 14 patients (40%) had 1 associated acute condition.

Table 2.

Acute associated conditions	Number (n=35)	Percentage (%)
Gastro-enteritis	24	68.6%
Meningitis	9	25.7%
Pneumonia	6	17.1%
Septicaemia	6	17.1%
Kwashiorkor	2	5.7%
UTI	2	5.7%
Disseminated TB	2	5.7%
CSOM	2	5.7%
Brain abscess	4	11.4%
Encephalitis	1	2.9%
Mastoiditis	1	2.9%
Chronic underlying conditions		
Prematurity	4	11.4%
HIV	5	14.3%
Asthma	1	2.9%
Tolosa-Hunt syndrome	1	2.9%
Cow's milk protein allergy	1	2.9%
Number of associations		
≥3 associations	8	22.9%
2 associated conditions	11	31.4%
1 associated condition	14	40%
0 associated conditions	2	5.7%

Acute and chronic underlying conditions associated with CVST.

UTI: urinary tract infection; TB: tuberculosis; CSOM: chronic suppurative otitis media; HIV: human immunodeficiency virus

Delay in diagnosis:

The time from initial presentation to Tygerberg Children's Hospital to the time of imaging was recorded. Neuroimaging was performed a median of 2 days after presentation.

Radiological features:

All 35 patients had contrasted CT scan neuroimaging to confirm the diagnosis. Thirty-four patients (97.1%) had superficial cerebral sinus involvement and 10 (28.6%) had deep cerebral sinus involvement. Twenty-five patients (71.4%) had superficial involvement alone, 1 patient (2.9%) had deep involvement alone and 9 patients (25.7%) had combined superficial and deep venous sinus involvement. Thirteen patients (37.1%) had a single sinus involved and 22 patients (62.9%) had multiple sinus involvement.

A total number of 109 sinuses were involved in our series of 35 patients. The most frequent sinus involved was the left transverse sinus. Nineteen patients (54.3%) had left transverse sinus involvement followed by 14 patients (40.0%) with superior sagittal sinus involvement, 13 patients (37.1%) with right transverse sinus involvement and 12 patients (34.3%) with straight sinus involvement. Of the 13 patients with a single sinus involvement, 6 patients had superior sagittal sinus involvement which was the most frequent single sinus involved, followed by the straight sinus (3), left transverse sinus (2), right transverse sinus (1) and right sigmoid sinus (1).

Associated brain parenchymal involvement was assessed. Four patients (11.4%) had radiological features of haemorrhage, 3 patients (8.6%) had hydrocephalus and 20 patients (57.1%) had features of oedema.

Table 3.

Venous system involved	Number (n=35)	Percentage (%)
Superficial system -total	34	97.1%
Deep system - total	10	28.6%
Superficial system - alone	25	71.4%
Deep system – alone	1	2.9%
Combined	9	25.7%
Single sinus involvement	13	37.1%
Multiple sinus involvement	22	62.9%
Brain parenchymal involvement		
Parenchymal oedema	20	57.1%
Haemorrhage	4	11.4%
Hydrocephalus	3	8.6%

Radiological features: Breakdown of the involvement of the superficial and deep cerebral venous sinus systems and brain parenchymal involvement.

Table 4.

Sinus Thrombosed	Number (n=109)	% of total sinuses	% of total patients
Superficial system			
SSS	14	12.8%	40.0%
ISS	4	3.7%	11.4%
Left transverse sinus	19	17.4%	54.5%
Right transverse sinus	13	11.9%	37.1%
Left sigmoid sinus	2	1.8%	5.7%
Right sigmoid sinus	1	0.9%	2.9%
Straight sinus	12	11.0%	34.3%

Cortical veins	6	5.5%	17.1%
Deep system			
Right ICV	9	8.3%	25.7%
Left ICV	9	8.3%	25.7
Vein of Galen	7	6.4%	20.0%
Right BVR	4	3.7%	11.4%
Left BVR	3	2.8%	8.6%
Right TSV	3	2.8%	8.6%
Left TSV	3	2.8%	8.6%

Radiological features: Breakdown of specific sinus involvement.

SSS: superior sagittal sinus; ISS: inferior sagittal sinus; ICV: internal cerebral vein;
BVR: basal vein of Rosenthal; TSV: thalamostriate vein

Laboratory findings:

The average serum sodium level of the patients on presentation was 152.1mmol/L. Seventeen patients (48,6%) were hypernatraemic. Fifteen patients (42.9%) had normal sodium levels (135-145mmol/L), 2 patients (5.7%) had a sodium level below 135mmol/L and in 1 patient the serum sodium was not available. The highest recorded serum sodium was 199mmol/L. Of the 24 patients who had associated acute gastro-enteritis, 17 (70.8%) had hypernatraemia. All cases of serum hypernatraemia were associated with acute gastro-enteritis. Patients with hypernatraemia were more likely to have thrombosis of the deep venous sinus system ($p < 0.006$) and an age of less than 6 months ($p < 0.05$)

Renal function in our patients was difficult to assess without information about urine output and glomerular filtration rate, but the average creatinine level of our patients was 79.8umol/l and 18 patients (51.4%) had an urea:creatinine ratio >10 that might indicate acute kidney injury with intravascular volume depletion.

At presentation the mean haemoglobin level of our patients on presentation was 9.7g/dL \pm 2.4 g/dL. Twenty-five patients (71.4%) were anaemic when corrected for

age. Four out of the 5 patients who presented in the first month of life were anaemic while 17 (74%) infants between 1-12 months and 4 (57%) children older than 1 year were anaemic. The average mean corpuscular volume of our patients was $87.7\text{fL} \pm 12.4\text{fL}$. Five patients (14.3%) had a microcytic anaemia on presentation.

Of the 35 patients in our study, 11 (31.4%) had organisms isolated in various specimen samples. Seven patients (20.0%) had positive blood cultures of which 3 were positive for *Group B Streptococcus* (all 3 patients were neonates between 2 and 3 weeks old), 2 were positive for *Coagulase negative Staphylococcus*, 1 was positive for both *Enterococcus faecalis* and *Morganella moranii* and 1 was positive for *Candida albicans*.

Two patients (5.7%) had positive isolates in their stool, 1 patient had a positive *Rotavirus* PCR and 1 patient had a positive stool culture for *Campylobacter jejuni*. One patient (2.9%) had a positive CSF culture for *Streptococcus pneumoniae*.

Table 5

Laboratory findings	Number (n=35)	Percentage (%)
Serum Sodium (mmol/l)		
- >145	17	48.6%
- 135-145	15	42.9%
- <135	2	5.8%
- unknown	1	2.9%
Haemoglobin (g/dL)		
-Age <1 month, Hb <14	4	11.4%
-Age 1-12 months, Hb<10	17	48.6%
-Age >12 months, Hb<11	4	11.4%
Organisms isolated		
Blood	7	20%
-GBS	3	8.6%
-CNSA	2	5.8%
-Enterococcus faecalis	1	2.9%

-Morganella morganii	1	2.9%
-Candida albicans	1	2.9%
Stool	2	5.8%
-Rotavirus	1	2.9%
-Campylobacter jejuni	1	2.9%
Cerebrospinal fluid	1	2.9%
-Streptococcus pneumoniae	1	2.9%

Laboratory findings of patients with CVST

Hb: haemoglobin; GBS: group B streptococcus; CNSA: coagulase negative staphylococcus aureus

Neurological outcome at discharge:

Two patients (5,7%) demised and 13 patients (37.1%) had neurological deficits at discharge. These neurological deficits included increased tone globally without obvious weakness, decreased tone globally, cortical blindness, spastic quadriplegia, cranial nerve palsies and a patient with a persistent vegetative state. Long term neurological assessment was not documented.

Eleven of the thirteen patients who had neurological deficits at discharge presented with convulsions. Only 4 of these thirteen patients had neurological fallout on presentation. Six of the 13 patients had a normal level of consciousness and 7 had a depressed level of consciousness at presentation. Of the 25 patients that presented with convulsions, 13 (52%) had no neurological deficits at discharge and 11 (44%) had neurological deficits at discharge. Seizures were not a statistically significant predictor of poor neurological outcome. ($p=0.25$)

Of the 8 patients who presented with a depressed level of consciousness, 7 (87.5%) had neurological deficits at discharge. Six of the 27 patients (22.2%) who presented with a normal level of consciousness had neurological deficits at discharge. Of the 2 patients who demised, both presented with a normal level of consciousness and had no neurological fallout on presentation. One of the two patients had generalized convulsions on presentation. A poor neurological outcome was not associated with

convulsions ($p=0.25$) or a decreased level of consciousness at presentation ($p=0.89$). Age of <6 months and the involvement of the deep venous system was also not associated with poor neurological outcome ($p>0.5$).

Chapter 10

Discussion

This is a case series of 35 children who developed a cerebral venous sinus thrombosis (CVST) as proven by contrasted brain CT imaging in a tertiary care hospital in a resource-constrained country. The development of CVST was strongly associated with hypernatraemic dehydration following acute gastroenteritis, an association not well-documented in the literature. Neurological deficit (37.1%) at discharge was common although the mortality was only 5.7%.

The mean age of the patients in our study was 16.9 months. This is younger than reported in previous studies where the mean age varied between 4 and 5.6 years.(4,9) This difference might be due to the burden of infectious disease and particularly of gastro-enteritis in children younger than 2 years in the Western Cape Province of South Africa. In our study, the patients less than a year old made up 80% of the case series. This trend is also seen in the Canadian series and a large series from the USA.(1,7)

Our study further differs in that we have much fewer neonates (13.9%) than reported in previous studies (19%-69%).(1,2,4,7,11) The difference might be explained by a sampling bias as only neonates admitted to the general paediatric wards were included. We report a higher proportion of male children (57%) who develop CVST but this is concordant to other studies.(2,4-6,9,24)

The mean weight on admission (mean weight for age Z-score = -2) of our study patients reflects that our patients are severely underweight for age according to the WHO classification. This might be an over-estimate of the degree of malnutrition as more than half of the children included in this series presented with acute gastro-enteritis (AGE). These children's weight could have been underestimated due to dehydration. Two patients had documented kwashiorkor. No previous study on CVST has reported on the association of malnutrition, acute gastroenteritis and CVST. The pathogenesis of CVST might differ in this vulnerable group of patients.

Acute gastro-enteritis was the single most important acute associated illness found in our study (68.6%). This indicates the high prevalence of AGE in our setting. What could also be a contributing factor is that the Rotavirus vaccine was introduced in South Africa only in 2009 and the national roll-out thereof was only introduced in April 2010.(25) Patients in this study would have only benefitted from the 2 doses towards the end of 2010.

In stark contrast to this study where AGE was the commonest precipitating factor in the development of CVST, other studies have not found this strong association. Heller et al. mentioned gastroenteritis as an acute associated illness (4/149) (2.6%)(2) and Sebire et al. found 12% of the patients in his series had acute diarrhoea.(5) These studies reported on high-income countries where AGE causing severe dehydration is less common which could explain the differences between the studies. All the other studies mention dehydration as an associated condition and potential risk factor but the cause of the dehydration is not stated. The incidence of dehydration in these studies is between 0.05% - 21%.(5-7)

The second most common acute associated condition in our study was meningitis (25,7%), which is classified as a local infection. In previous studies meningitis had an incidence of between 3%-13(2,4,6,7) Only Barnes et al.(9) found a higher incidence (44%), but their figure included cases of brain abscesses. Our findings of meningitis are much higher than previous studies. This might again be due to the great burden of poor social circumstances and high incidence of infectious diseases we see in our resource-constrained setting.

Mastoiditis has an incidence of between 23%-47%.(4-7,9,11) Only Heller et al. had a lower incidence of 9%.(2) In our study only 1 patient was found to have mastoiditis. This might be due to referral bias. Paediatric patients who need specialist ENT services gets referred directly to the ENT department and are not admitted to the paediatric wards. As mentioned before only Barnes et al found brain abscesses as an acute associated finding. In our study 4 patients (11.4%) had brain abscesses. Two abscesses were associated with presumed bacterial meningitis, 1 abscess was associated with disseminated tuberculosis and 1 abscess was associated with a post-operative complication for oesophageal dilatation after caustic ingestion. This again

reflects the burden of infectious diseases such as meningitis and tuberculosis in the population this hospital serves.

Our study found that chronic underlying conditions were not a significant risk factor for the development of CVST. In our study, 14.3% of the CVST cases were HIV-infected. This is the first report on the association of HIV-infection with CVST but this association is probably complex as all 5 of the HIV-infected children also suffered from AGE. Due to the study design this multivariate association could not be explored.

It is widely reported in the literature that children that develop CVST have underlying predisposing diseases. In our study only 5.7% (n=2) of the patients did not have an associated disease. Although our figure agrees with the 3% reported by DeVeber it differs significantly from the normally reported 10-30%.(2,6,7,11) This finding is not easy to explain but considering that AGE was the commonest associated disease with CVST it might indicate that delayed access to health care and/or severe dehydrating AGE are important factors in the development of CVST. Similarly, it has been reported that multiple predisposing factors are present in children who develop CVST.(7) In our study we report that 54.3% of those who developed CVST had 2 or more predisposing factors. We demonstrate in our cohort, that malnutrition, AGE and multiple predisposing factors uniquely elevate the risk of developing CVST in a resource-constrained setting. None of our patients had prothrombotic screens done. It is unsure whether patients in our population would benefit from this screen seeing that only 2 patients had no underlying cause found. This is a rather expensive screen and prospective studies with prothrombotic screens are recommended in our setting to validate these high costs.

Level of consciousness, seizures and abnormal neurological signs are consistently described as clinical features associated with CVST. Twenty-five patients (71.4%) in our study had seizures at presentation. This number is higher than expected when compared to previous studies. Previous studies reported associated seizures between 25%-58%.(1-4,9,22,24) This discordancy might be due to the high number of patients with hypernatraemia (48.6%) in our study. Hypernatraemia alone predisposes patients to seizures and the rapid correction thereof further predisposes the patient to seizures.

The high number of patients with meningitis and brain abscesses can further be a cause for the high number of patients who presented with seizures. Level of consciousness and neurological fallout in our study matched the previous studies.

Hypernatraemia was a significant abnormal laboratory finding in our study. High serum osmolality has not been described in the literature as a risk factor for CVST. In our study 17 patients (48.6%) had a serum sodium level of >145mmol/l which was associated with AGE in all the cases. Dehydration has previously been described as causative of CSVT in resource-constrained countries, but the cause thereof and osmolality was not reported. CVST secondary to hypernatraemic dehydration caused by diarrhoeal diseases is widely accepted by clinicians through clinical experience in South Africa. In a review article by Roach et al. he stated that hypernatraemia in conjunction with dehydration may cause CVST.(17) He based this on two studies published in the 1950's and 1960's by Finberg and Macaulay, however it has been reported infrequently in the literature. Vieira et al. reported a single patient with hypernatraemic dehydration in his study.(6)

Anaemia has been described in the literature as a possible risk factor for CVST. In our study 25 patients (71.4%) was classified as being anaemic for age. This is higher than the 10% reported by Wasay et al, and 52% reported by Sebire et al. This might be due to the poor food security and lack of quality animal protein in our population's diet. We have failed to show a low MCV count in our patients as previously described as a risk factor for stroke.(14)

Our study is the first study to document organisms isolated from the study patients. This is significant because it reinforces the burden of infectious diseases in a resource-constrained country like South Africa. Of the 35 patients in our study, 31.4% had organisms identified in various sample types.

The superior sagittal, transverse and straight sinuses were more frequently involved in our patient population, which is similar to other studies in the literature.(5,14,18,26) We report that multiple sinus thrombosis was common and occurred in almost two-thirds of our patients, which was similar to the reported literature (11%-70%). The superficial venous system alone was affected more often (97.1%), correlating with the

literature.(1,22,24) A unique statistically-significant finding in our study was thrombosis of the deep venous sinus system associated with hypernatraemia following AGE. Hydrocephalus as an associated involvement occurred in 8.6% of our patients, which has not previously been described. Only 4 patients (11.4%) had associated haemorrhage, which is lower than mentioned in the literature. Morbidity, as well as mortality in our study correlates with the literature.(2,5,6,11)

The major limitation of this study is the retrospective nature. There is possible sampling bias, as not all the patients suffering from CVST were included, especially neonates. Only neonates admitted to the paediatric wards were included. The sample size of the study is relatively small, limiting the ability of the study to determine associations that may differ when comparing resource-constrained to adequately resourced countries.

Another limitation of this study is that the diagnosis of CVST would more likely occur in children with specific signs and symptoms such as focal convulsions, depressed LOC and neurological deficit. Asymptomatic cases would remain unidentified.

Although this study has considerable internal validity the external validity and applicability to paediatrics in Southern Africa needs to be determined.

Conclusion:

CVST is a relatively uncommon disorder in neonates and children, which is often not clinically suspected but has the potential to result in severe neurological disability especially in children living in resource-constrained settings. Our study is the first of its kind in South Africa and for that matter in any other resource-constrained country. In this study we demonstrated that hypernatraemia and AGE appear to be a significant acute underlying risk factor for developing CVST. Further, we found that CVST is more common in younger children, in those with severe underweight-for-age and when associated with AGE, than has previously been reported in studies from adequately resourced countries. Further studies in resource-constrained countries are required to confirm these important associations to develop interventions to prevent CVST occurring in these vulnerable children.

Chapter 11

Recommendations

Prospective studies in the South African context should be conducted on paediatric CVST. These studies should include response to treatment and serum thrombotic workup as part of the protocol as the role of inherited or acquired underlying thrombotic predisposition in our population is not known.

Awareness of the occurrence of CVST in the Southern African context needs to be increased to ensure that complications are not underdiagnosed and mismanaged. For improved outcome, better vigilance of CVST should be exercised in children who present with hypernatraemic dehydration with seizures and/or neurological deficits, so that neuroimaging can be timeously obtained to guide the initiation of anticoagulation therapy.

As the clinical features of CVST can be subtle, patients with hypernatraemia should be closely followed up after discharge and assessed for neuro-developmental, neurological or cognitive deficits to ensure appropriate treatment.

A prospective study should be carried out in a neonatal population to determine the risk factors for the development of CVST and determine the extent of neurological damage in this group.

As AGE is the commonest cause of CVST in a resource-constrained country a study to investigate the impact of rotavirus immunization on the prevalence of CVST should be carried out.

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Appendix A

Protocol

A Retrospective Review of Paediatric Cerebral Venous Sinus Thrombosis in a South African Tertiary Hospital

Introduction

Paediatric cerebral venous sinus thrombosis (CVST) is a rare disorder with an estimated incidence of 0.67 per 100,000 children in developed countries.(1) It is a devastating disease with potentially severe neurological sequelae and a high mortality rate, highlighting the need for high-quality studies within this field. No data on paediatric CVST are known for South Africa or even the continent of Africa. Most data are from developed countries of America, Europe and Australasia.

Epidemiology

As many as 43% of CVST cases occur in the first month of life(1), with an incidence of 2.6 per 100,000 children per year in one series in the neonatal period(2). CVST after the neonatal period has an almost equal sex ratio with a slight increase in males over females and a mean age of presentation of between 4 – 6 years. (1–7)

Pathophysiology

Cerebral venous sinus thrombosis is thrombosis of intracranial venous sinuses and/or cerebral veins. Thrombosis within the venous system results in outflow obstruction, venous congestion, and a consequent increase in capillary hydrostatic pressure, driving fluid into the interstitium and producing oedema. This also leads to impaired venous drainage and consequently to intracranial hypertension and/or venous infarcts.

Aetiology

The origin and pathophysiology of CVST is poorly understood. Published data suggest that CVST is multifactorial in origin with many associated underlying illnesses or chronic conditions.(1,2,4,6,7,9–11,22)

Associated underlying illnesses include common childhood systemic illnesses such as infections, dehydration, fever and anaemia. Associated chronic conditions include malignancies, nephrotic syndrome, systemic lupus erythematosus and congenital cardiac diseases.

Infection appears to be a significant trigger in previously well children without underlying medical conditions. Infections associated with CVST can either be systemic, such as bacterial sepsis, or regional, such as meningitis, mastoiditis and otitis media. Other local head and neck disorders can cause thrombosis due to local venous stasis. These include recent head/neck surgery, head trauma and CNS tumours.

CVST has been described as a complication of L-asparaginase use in the treatment of acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma. L-asparaginase is thought to create a pro-thrombotic state, alone or in combination with other chemotherapeutic agents.(4,6,12,13)

Anaemia is frequently observed in children with CSVT(7,22), though mechanisms for its contribution to thrombus development are incompletely understood. Iron deficiency microcytic anaemia are most commonly described in CVST. It is found that previously healthy children with stroke were 10 times more likely to have iron deficiency anaemia than healthy children without stroke.(14)

Prothrombotic states may cause or contribute to CVST in children. The association between prothrombotic risk factors and CVST proves only to be statistically significant if the thrombosis is in combination with an underlying condition. (2,11)

CVST has been described as a complication (underlying/associated illness) of dehydration in children. Although CVST secondary to hypernatraemic dehydration in breastfed neonates has been described in the literature(15,16), there is limited clinical

data on CSVT secondary to hypernatraemic dehydration due to diarrhoeal disease in infants and young children. However, (Personal communication: Nel ED, Solomons R), CSVT is however widely accepted as a complication of hypernatraemic dehydration due to diarrhoeal diseases by paediatric gastroenterologists and neurologists.

Clinical Presentation

The clinical manifestations of CVST can be subtle and are nonspecific. Due to its rarity and the nonspecific clinical features at presentation the diagnosis of CVST is often delayed and may be missed altogether. One study reported an average delay in diagnosis of CVST of up to 4 days.(6) Most common clinical features at presentation are seizures, fever, drowsiness/stupor, headaches and generalized weakness. Common neurological abnormalities at presentation are decreased level of consciousness, cranial nerve palsies and hemiparesis. While most of the clinical symptoms can occur at any age, seizures are more common in neonates, and focal and diffuse neurologic signs are more common in older infants and children.(1,2,5–7,9,10)

Topographic location of thrombi

The superficial venous system (dural venous sinuses) is more frequently involved than the deep system (composed of traditional veins inside the deep structures of the brain, which join behind the midbrain to form the vein of Galen), and the most common sites of CSVT are the transverse, superior sagittal, sigmoid, and straight sinuses.(6)

These topographic locations differ however with presence of underlying intracranial pathology. In one study the transverse sinus was mostly affected secondary to the high incidence of mastoiditis.(18)

Treatment

The treatment of CVST in children is not well described. The primary treatment is to treat the underlying cause or associated clinical condition and general supportive care. Anticoagulation therapy has been used in children with CVST. Case series reports

have shown that LMWH (low molecular weight heparin) can be used safely in children, however data is limited to support the efficacy of this treatment. (22) In a study on treatment practices in neonatal CSVT it was found that antithrombotic treatment practices demonstrate considerable variability and uncertainty about the indications for antithrombotic therapy. This highlights the importance of further studies around treatment options of paediatric CVST. (27)

Prognosis and outcome

CVST has a variable prognosis with three major studies in Europe(5), North America(1) and Australia(9) estimating its morbidity between 38% - 60% and mortality between 10% -12%. In an American study they found that permanent neurological disability was associated with thrombosis of the deep veins with associated infarctions.(3) Coma is the only predictor of death in childhood CVST.(5) One study reports that older age and involvement of the lateral and/or sigmoid sinuses are associated with good cognitive outcome.(5) Common long-term sequelae include motor impairment, cognitive impairment, developmental and/or speech delay, and visual impairment. (1,5,21)

Recurrence of CSVT is uncommon. The Canadian study by DeVeber et al in 160 children with CSVT identified 12 children with recurrent thrombosis.(1)

The study by Kenet et al. in 266 children with CSVT found that venous thrombosis recurred in 3%.(11)

Unanswered questions

Previous studies that have been done on cerebral venous sinus thrombosis were done in developed countries of Europe, North America and Australasia. No study on CVST has been done in developing Sub-Saharan Africa, or more specifically, South Africa. The aetiological differences of CSVT between developed and developing countries such as South Africa are not known. It is expected that the aetiology will lean more towards complications of infections such as diarrhoea and meningitis because of the high incidence of these diseases in South Africa.

Dehydration is mentioned as a cause of CSVT in developed countries but the cause of dehydration and osmolality is not mentioned or known.

CSVT secondary to hypernatraemic dehydration caused by diarrhoeal diseases is widely accepted by clinicians through clinical experience, however this is not proven.

Treatment of Paediatric CVST is still very controversial. There are currently no well-designed clinical trials in children to support acute or chronic antithrombotic therapy with anticoagulants or antiplatelet agents once the diagnosis of CSVT is made.

Randomized control trials in the paediatric population are needed in order for treatment consensus to be reached.

The aim of this study is to evaluate and study the confirmed cases of CVST in a South African population to see the differences in this disease between developed and developing countries. This will serve as an important pilot study for cerebral venous sinus thrombosis as it will be the first of its kind in South Africa. By studying this disease in a South African setting we can come to a better understanding of the risk factors and associated factors of CSVT. It will be of great benefit in early recognition and swift treatment in order to decrease expected morbidity and mortality of the disease.

STUDY AIMS

To describe the patients diagnosed with CVST who presented to Tygerberg Children's Hospital with regards to patient profile, clinical presentation, aetiology and outcomes and to see how this data differs from data from developed countries.

OBJECTIVES

To describe patients who presented to Tygerberg Children's Hospital diagnosed with CVST with regards to the following parameters:

1. Age at presentation and sex.
2. To describe the signs and symptoms on admission and to describe any neurologic deficit noted at presentation.
3. Any associated acute medical illnesses or underlying chronic medical conditions.
4. To document any electrolyte abnormality at presentation. (refer to data capture sheet)
5. To document haematological abnormalities at presentation. (Haemoglobin, Platelet level)
6. To assess anthropometry of the patients at presentation.
7. To assess time delay (in days) from presentation to diagnosis.
8. Document the thrombotic location on CT scan or MRI scan.
9. To document neurologic deficit at discharge.

METHODOLOGY

Study Type

Retrospective, descriptive clinical study.

Study population

Children between the ages of 1 day to 12 years admitted to Tygerberg Children's Hospital from January 2009 to February 2014 who were diagnosed with cerebral venous sinus thrombosis.

Inclusion Criteria

- Admission dates: 1 January 2009 to 28 February 2014
- Ages: 1 day to 12 completed years
- Diagnosis of Venous Sinus Thrombosis on CT Scan/MRI

Exclusion Criteria

- Radiological images not available.
- Clinical notes not available

Intervention

No intervention

DATA MANAGEMENT

Patient tracing

Patients eligible for this study will be identified from electronic discharge summaries obtained in the general and specialist paediatric wards in Tygerberg Children's Hospital.

Database and data collection

- Patient clinical data will be collected retrospectively from their patient files: either from the hard copy patient files or from the electronic patient files on the Enterprise Content Management (ECM) system. The ECM system might not contain all patient files due to its recent inception in Tygerberg Hospital.

- Patient radiological data, MRI and CT Scan data, will be collected from Tygerberg's iSite enterprise.
- Patient blood results will be collected from the National Health Laboratory Service application.
- After data capturing is completed, the data will be categorized, processed and analyzed in order for the dissertation to be written.
- All data will be stored in Microsoft Excel on a password protected computer. This password will only be known to the primary investigator.

Data Capturing

The patient data will be captured on a research data form, which will not contain any identifiable personal information, only the study number of the patient. (See addendum A). The following information will be captured:

- Demographic information:
 - Age and weight on admission.
 - Gender
- Associated underlying illnesses:
 - These are conditions diagnosed alongside the CVST on the same admission.
 - If an infective illness is identified: Micro-organism isolated/cultured
- Chronic illnesses:
 - These are underlying chronic medical conditions that the patient is known with.
- Signs and symptoms at presentation:
 - These are signs and symptoms that the child presented with in the emergency centre
 - If dehydration was present – percentage of dehydration

- Neurological signs at presentation:
 - Neurological fallout present at presentation to the emergency centre.
 1. Loss of consciousness (Glasgow-coma scale)
 2. Focal motor deficit

- Seizures:
 - Seizures present around time of diagnosis of CVST during admission
 - Character of seizure – generalized or focal in nature
 - Duration of seizure
 - Seizure response to anticonvulsant

- Time delay of diagnosis (Time from admission to imaging)

- Electrolyte abnormalities:
 - Serum sodium on admission (within 24 hours)
 - Serum urea and creatinine on admission (within 24 hours)
 - If there was a derangement in the above – time (in hours) to correction

- Haemoglobin, platelet and mean corpuscular volume level at diagnosis:
 - To establish whether haematological abnormalities were present at presentation.

- Neurological deficit on discharge from Tygerberg children's Hospital

- Neuro Imaging:
 - Radiological data, MRI and CT Scan data, will be collected from Tygerberg's iSite enterprise.
 - Radiological images will be reviewed by Dr R Solomons, Specialist Paediatric Neurologist and sub-investigator of this study, to confirm the diagnosis of CSVT and will be independently reviewed by a paediatric radiologist. Disagreements in interpretation will be resolved by consensus and reported as such.

- Radiological data that will be captured are:
 1. Imaging technique used
 2. Location of thrombosis
 3. Size of thrombosis
 4. Presence of associated venous infarct or bleed
 5. Presence of associated hydrocephalus

Sample Size

The estimated sample size according to existing departmental statistics is 40 patients.

STATISTICAL ANALYSIS

Statistica® version 12 (Statsoft) will be used to analyse the data.

Descriptive Statistics

Variables recorded the study will be summarized using standard descriptive statistical methods:

1. Continuous variables that follow a normal distribution will be described by a mean and standard deviation.
2. Continuous variables that do not follow a normal distribution will be described by the median and inter-quartile range.
3. Proportions will be described by the proportion estimate and the 95% confidence interval.

Inferential Statistics

1. Differences between groups (e.g. presence or absence of neurological complications, venous infarct, associated diseases) will be analysed by analysis of variance or the non-parametric equivalent (where data can be categorised).
2. Associations between variables will be analysed by regression (linear, logistical, simple or multiple) analysis (e.g. association between highest serum sodium concentration and presence of neurological

outcome, association between size or location of the infarct and neurological outcome, association between age and infarct size, neurological outcome)

3. Odds ratios will be calculated for univariate categorical data analysis

ETHICAL CONSIDERATIONS

Confidentiality

Patient demographic data will be kept strictly confidential at all times by only using study numbers in the data management and analysis stages of this study.

The information for this study will be collected in such a way as to protect patient confidentiality at all times. The data capture sheet and electronic database will only contain a study code. The identifying information that is linked to the study code will be kept in a separate, password protected database. Access to this database will be restricted to the primary investigator.

All data will be kept for a maximum of 5 years in a safe, password restricted database in the department of pediatrics and child health

Consent

We request a waiver of individual informed consent as this is a retrospective study with minimal risks to the study participants.

We have requested permission to conduct this retrospective study from the Medical Superintendent of Tygerberg Hospital as the custodian of the data.

Benefit to the Individual Participant

This study will not have any benefit to the specific participants due to the retrospective nature thereof.

However if it is found that a participant with significant complications has been lost to follow up or has not received optimal treatment (e.g. occupational therapy for neurological deficit) they will be contacted and referred to the appropriate service.

Benefit to the community

There are many unanswered questions surrounding CVST in the paediatric population in not only the world, but in South Africa. The aetiology and prognosis of paediatric CVST in South Africa are not known. This study will be the first study in South Africa to assess paediatric CVST and will serve as the basis for further studies to identify the risk factors associated with and prevention of CVST in order for early identification of the disease can be made and rehabilitation can be facilitated as soon as possible.

Ethical approval

The protocol for the proposed study will be submitted for approval to the Committee of Human Research of the Faculty of Health Sciences, University of Stellenbosch. Formal ethical approval will be obtained before any data collection will commence.

BUDGET

- The total cost of the study, which is projected to be at a minimum, will be covered by the investigators.

Projected budget:

Item	Amount	Cost per unit	Total
Pages and printing	1000	32c	R320
Publication			R5000
Total			R5320

STRENGTHS AND LIMITATIONS

- Because of the retrospective nature of the study and the unknown incidence of the proposed study topic in the South African population it is uncertain how big the study population will be. Due to the lack of a formal stroke registry and rarity of the condition it is expected that the study population will be small.
- It is unsure how much of the data intended for collection have been recorded in the clinical notes and therefore how much will be available for capturing.
- The greatest strength of this study is that this topic have not been reviewed in South Africa or Sub-Saharan Africa. This study can serve as a pilot study for future prospective studies.

REPORTING OF RESULTS

This study will be published in a peer review journal and presented at National conferences

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Appendix B

Data Capture sheet

Study Number:	
Age:	
Gender:	
Weight and Z Score:	
<u>Associated chronic illness:</u>	
<u>Associated medical illness:</u> If Infection: Organism isolated?	
<u>Symptoms on presentation:</u>	
<u>Neurological signs or symptoms on</u>	

<p><u>presentation:</u></p> <p>Focal signs</p> <p>Level of consciousness</p>	
<p><u>Seizures present:</u></p> <p>Focal/Generalized</p> <p>Seizure duration</p> <p>Response to anticonvulsant</p>	
<p><u>Electrolytes:</u></p> <p>Sodium on admission</p> <p>Time for sodium to normalize</p> <p>Urea on admission</p> <p>Creatinine on admission</p>	
<p><u>Haematology:</u></p> <p>Haemoglobin on admission</p> <p>MCV level on admission</p>	
<p><u>Imaging:</u></p> <p>Technique</p> <p>Location of CSVT (Sinus involved)</p> <p>Size of thrombosis</p> <p>Associated infarct</p> <p>Associated haemorrhage</p> <p>Associated hydrocephalus</p>	

Time from admission to diagnosis(days):	
Neurological deficit on discharge:	

Appendix C

Confirmation letter: Ethical Approval



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jou kennisvenoot • your knowledge partner

Approved with Stipulations

New Application

21-Oct-2014
Liebenberg, Hendrik Schalk HS

Ethics Reference #: S14/09/194

Title: A retrospective review of paediatric cerebral venous thrombosis in a South African tertiary hospital.

Dear Dr Hendrik Schalk Liebenberg,

The **New Application** received on **25-Sep-2014**, was reviewed by Health Research Ethics Committee 2 via Committee Review procedures on **15-Oct-2014**.

Please note the following information about

your approved research protocol: Protocol

Approval Period: **15-Oct-2014 -15-Oct-2015**

Present Committee Members:

Blaauw, Renee R
Botha, Philip PR
Etoe, Sheila SL
Khondowe, Oswald O
Holgate, Sandi SL
Davids, Mertrude MA
Fernandez, Pedro P
Ginindza-Ncube, Nondumiso NBQ
Van der Merwe, Anita AS
De Roubaix, John JAM
Willett, Derrick DWE

Edwards, C E

The Stipulations of your ethics approval are as follows:

1. Waiver of informed consent granted.

Please remember to use your **protocol number (S14/09/194)** on any documents or correspondence with the HREC concerning your research protocol. Please note that the HREC has the prerogative and authority to ask further questions, seek additional information, require further modifications, or monitor the conduct of your research and the consent process.

After Ethical Review:

Please note a template of the progress report is obtainable on www.sun.ac.za/rds and should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly for an external audit. Translation of the consent document to the language applicable to the study participants should be submitted.

Federal Wide Assurance Number: 00001372

Institutional Review Board (IRB) Number: IRB0005239

The Health Research Ethics Committee complies with the SA National Health Act No.61 2003 as it pertains to health research and the United States Code of Federal Regulations Title 45 Part 46. This committee abides by the ethical norms and principles for research, established by the Declaration of Helsinki, the South African Medical Research Council Guidelines as well as the Guidelines for Ethical Research: Principles Structures and Processes 2004 (Department of Health).

Provincial and City of Cape Town Approval

Please note that for research at a primary or secondary healthcare facility permission must still be obtained from the relevant authorities (Western Cape Department of Health and/or City Health) to conduct the research as stated in the protocol. Contact persons are Ms Claudette Abrahams at Western Cape Department of Health (healthres@pgwc.gov.za Tel: +27 21 483 9907) and Dr Helene Visser at City Health (Helene.Visser@capetown.gov.za Tel: +27 21 400 3981). Research that will be conducted at any tertiary academic institution requires approval from the relevant hospital manager. Ethics approval is required BEFORE approval can be obtained from these health authorities.

We wish you the best as you conduct your research.

For standard HREC forms and documents please visit: www.sun.ac.za/rds

If you have any questions or need further assistance, please contact the HREC office at 0219389207.

Included Documents:

20140923 HREC Checklist
Investigator declaration_Liebenberg
20140923 Synopsis
20140923 HREC Application form
20140923 Letter to Dr Marinus
20140923 CV_Solomoms
20140923 CV-Liebenberg
20140923 Investigator declaration_Pitcher
20140923 CV_Pitcher
20140923 CV_Nel
20140923 Investigator declaration_Nel
Investigator declaration_Solomons
20140923 Protocol

Sincerely, Mertrude Davids
HREC Coordinator
Health Research Ethics Committee