A RETROSPECTIVE DESCRIPTIVE STUDY ON PRIMARY HYPEROXALURIA AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL FROM 1984 TO 2017.

M.Med

By submissible format

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Primary hyperoxaluria at Chris Hani Baragwanath Academic Hospital from 1984 to 2017.

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Dedication:

I dedicate this research to my parents, who have instilled in me the value and reward of perseverance and hard work. Today would not have been possible if it were not for them. I also dedicate this to my husband, whose unwavering support and encouragement carried me through this journey to becoming a specialist. This journey would not have been possible without the endless patience, support, guidance and input from my mentors, Professor Petersen and Professor Kala. They have been instrumental in my clinical training and growth as well as in my academic development.

Acknowledgements:

This study would not have been possible had it not been for the endless and effortless guidance, assistance and support from Professor Kala and Professor Petersen. Thank you to the clerks and data capturers of the renal clinic as well as the records team, who assisted with the retrieval of files. Thank you to the National Health Laboratory Service (NHLS) staff, Hellen Nxumalo and Dr T. Pillay, who assisted with access to results as well as the statistician, Lukhanyo Nyathi, Zvifadzo Matsena-Zingoni, Innocent Maposa and Professor Libhaber, available at Philip V. Tobias, University of the Witwatersrand.

Presentations arising from the study:

1. South African Renal Congress 2018 – Poster presentation at Emperors Palace, Johannesburg
2. Paediatric Research Day 2019 – Oral presentation at Marie Curie Lecture theatre, Faculty of Health Science, University of the Witwatersrand, Johannesburg.

Table of Contents

South African Medical Journal (SAMJ) author guidelines

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

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- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
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- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.

- **Objectives:** what the study intends to find out
- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
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- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc

Abstract

Background. Primary hyperoxaluria (PH) is a rare autosomal recessive condition characterized by defects in the metabolism of glyoxylate which leads to increased oxalate production and deposition. It is an important disease to diagnose as it can progress to end stage renal disease (ESRD).

Objective. The objective of this study is to describe the characteristics, diagnosis and management of PH in South Africa and to identify any determinants of ESRD and death.

Method. A retrospective study of all children younger than 16 years of age, diagnosed with PH at the Paediatric Renal Unit, Chris Hani Baragwanath Academic Hospital, from 1984 to 2017.

Results. A total of 24 patients were identified. The median age of presentation was 6.0 years. The common clinical presentations were urolithiasis (90%), ESRD (85%), nephrocalcinosis (75%), urinary tract infections (55%), stunting (40%) and haematuria (30%). Nephrocalcinosis was better detected on abdominal radiograph compared to ultrasonography. Both nephrocalcinosis (p=0.009) and haematuria (p=0.018) were significantly associated with ESRD. Five patients had A112D genetic mutation in the *AGXT* gene and one patient had a heterozygous mutation for two different alleles, c335C>A (p.A112D) and c.473C>T (p.S158L). Of the 17 patients in ESRD, 14 received dialysis. Only four patients were transplanted of which two received combined liver – kidney transplantation. The mortality rate in this study was 58.3%. There were no significant determinants of death identified.

Conclusion. Clinicians should have a high index of suspicion for PH in patients presenting with urolithiasis and ESRD. This study highlights the importance of measuring urine oxalate levels and performing abdominal radiographs in the screening for PH in children presenting with ESRD. Routine urine dipstick analyses done at each clinic visit could assist in early diagnosis and referral to a Paediatric Nephrologist.

Word count: 279

Lists of abbreviations

- AGT (Alanine-glyoxylate aminotransferase)
- Bone marrow aspirate and trephine (BMAT
- CHBAH (Chris Hani Baragwanath Academic Hospital)
- CMJAH (Charlotte Maxeke Johannesburg Academic Hospital)
- CKD (Chronic Kidney Disease)
- CT (Computed Tomography)
- ESRD (End stage renal disease)
- Extracorporeal shock wave lithotripsy (ESWL)
- GO (glycolate oxidase)
- GRHPR (Glyoxylate reductase – hydroxypyruvate reductase)
- GFR (Glomerular filtration rate)
- HD (Haemodialysis)
- IQR (Interquartile range)
- MCV (Mean Corpuscular Volume)
- PH (Primary hyperoxaluria)
- PH1 (Primary hyperoxaluria type 1)
- PH2 (Primary hyperoxaluria type 2)
- PH3 (Primary hyperoxaluria type 3)
- PD (Peritoneal dialysis)
- RRT (Renal Replacement Therapy)
- UTI (Urinary Tract Infection)

Background

Primary hyperoxaluria (PH) is a rare autosomal recessive condition characterized by defects in the metabolism of glyoxylate which leads to an increased oxalate production and deposition.[1] The most common and severe form is type 1 PH (PH1), which is caused by a genetic mutation in the enzyme, alanine-glyoxylate aminotransferase (AGT) found in the liver peroxisomes.[1] There are three clinical subtypes of primary hyperoxaluria currently described in the literature: a) primary hyperoxaluria type 1 (PH1), b) primary hyperoxaluria type 2 (PH2), c) primary hyperoxaluria type 3 (PH3).[1]

In Southern Africa, only homozygous A112D mutations has been documented in two unrelated patients thus far.[2] There is poor correlation between the phenotype and genotype of the mutations; even siblings with the same mutation may have a different clinical presentation, progress and prognosis.[3] The exact prevalence and incidence of PH is unknown.[1]

PH1 rapidly progresses to end stage renal disease (ESRD), which includes the more severe presentation of infantile PH subtype.[4] The age of presentation can range from birth to the sixth decade of life. [1] The most common presentations are urolithiasis with or without nephrocalcinosis, urinary tract infections, haematuria and ESRD. [5-8]

Systemic oxalosis is caused by the deposition of insoluble calcium oxalate crystals in any organ, which usually develops once the glomerular filtration rate (GFR) falls below 40 mL/min/1.73m^2. [3] The diagnostic work-up includes a 24 hour urine or spot urine analysis for oxalate crystals, genetic mutation analysis, imaging and histology. [1,3] Treatment of PH includes high fluid intake of 2-3 L/m^2 of body surface area per day, alkalinisation of the urine and pyridoxine supplementation. [1,3] Combined peritoneal (PD) and haemodialysis (HD) is required for the treatment of PH. [1,3]

The definitive treatment for PH1 is a combined liver and kidney transplant. [1] However there are exciting novel therapies in different stages of clinical trials, such as increased elimination of oxalate through the intestines or through RNA-interference targeting the glycolate oxidase (GO) protein which converts glyoxylate to oxalate. The pre-clinical therapies currently include gene therapies as well as inhibitors of GO. [9]

Although primary hyperoxaluria is a rare genetic disorder, the clinical data on PH has been well documented in developed countries. [5,10,11] There is data emerging from the developing countries with cohorts of 18 patients from Oman, [12] 26 from Egypt, [8] 44 from Tunisia, [7] and 70 from Jordan. [6] However, no studies have yet been published in Sub-Saharan Africa, including South Africa. This study aims to describe the presentation, diagnosis and treatment of PH at Chris Hani Baragwanath Academic Hospital (CHBAH) in South Africa. It also aims to identify any determinants of ESRD and death.

Method

The study population was selected from the Paediatric Renal Unit at Chris Hani Baragwanath Academic Hospital, which is a tertiary academic hospital in Gauteng affiliated to the University of the Witwatersrand. This unit serves the population of Soweto but also receives patients referred from other provinces as well as neighbouring countries of South Africa. The unit also has an outpatient follow up service for those that were admitted as in-patients.

This was a retrospective descriptive study spanning 33 years, from 01 January 1984 to 31 December 2017, of all patients younger than 16 years of age and diagnosed with PH. The diagnosis of PH was made if one of the following was fulfilled: high urine oxalate levels (> 0.7mmol/ 1.73m^2) [1] or spot urine analysis in keeping with hyperoxaluria [1] or birefringent oxalate crystals on histology or genetic confirmation.

Demographics, diagnostic tests, management and outcome data were obtained from the records. For the definition of the different variables, please refer to the Supplemented Appendices in the Protocol. The demographics, diagnostic tests, management and outcomes were then further analysed for any association with ESRD and death. This study was approved by the head of the renal unit and permission received to utilize the records.

The categorical data was presented as numbers and percentages and continuous data was presented as medians with inter-quartile ranges. A Pearson's chi-squared test or Fisher's exact test was used to analyse categorical variables for association with ESRD and death. For continuous variables that was not normally distributed, a Mann-Whitney U test was used. The data was analysed at the 95% confidence interval and *p*-value of <0.05 was considered significant. The software used was STATISTICA version 13.3 by TIBCO Software Inc. Ethics approval was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (Clearance Certificate No. M170423) as well as the medical advisory committee at Chris Hani Baragwanath Academic Hospital.

Results

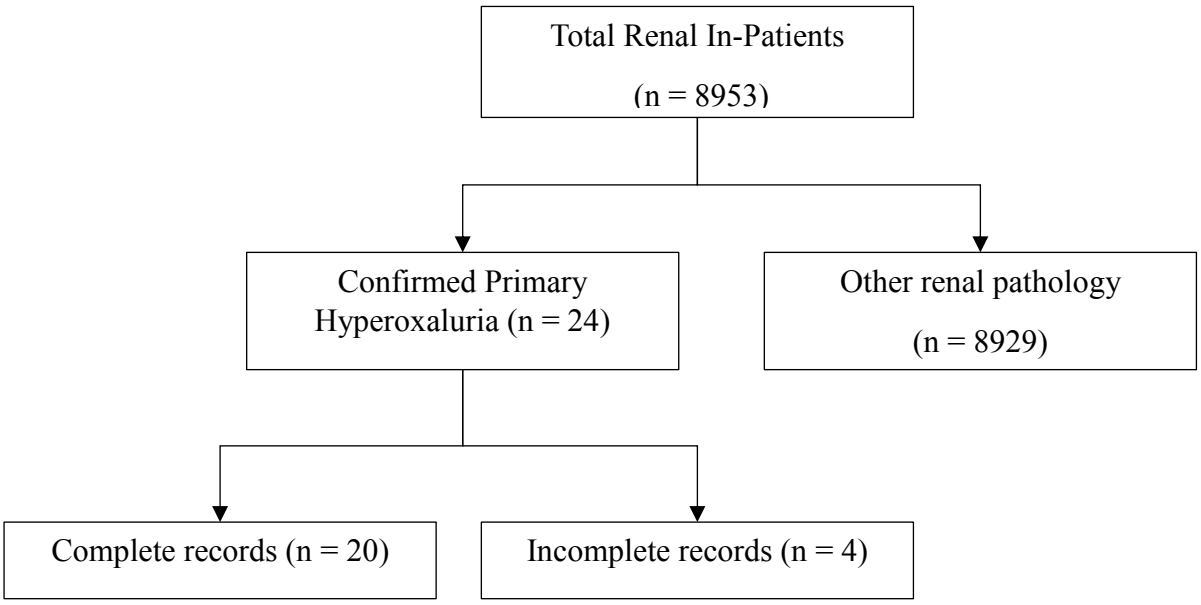

Fig. 1. Flow diagram of the patients included in the study.

A total of 24 patients were identified with PH, of which 20 records were available for complete analysis.

Demographics

Of the 20 patients that were analysed, the median age of onset of symptoms was 67.5 months (IQR: 38.8 - 93.6) while the median age of presentation was 72.0 months (IQR: 44.0-108.0) as shown in Table 1. The median age of confirmatory diagnosis was 68.7 months (IQR: 44.6-

94.7). Nineteen patients (95.0%) were South African and of African descent whilst 1 was from Swaziland but was of British and Caucasian descent. Of the 11 patients from Gauteng, 81.8% were from outside of Soweto. There was no history of consanguinity or a previous family history of kidney disease.

Table 1. Demographics of the patients with PH.

Demographics			
Age		**Median (IQR*)**	**Range**
At first symptom (months)	(n = 20)	67.5 (38.8-93.6)	6.0 – 156.0
At hospital presentation (months)	(n = 23)	72.0 (44.0-108.0)	7.0 – 156.0
At presentation for ESRD† (months)	(n = 17)	64.0 (40.5-91.5)	7.0 – 132.0
Subtypes	(n = 20)	**Number (%)**	
PH‡ Type I (Confirmed with genetics)		6 (30.0)	
PH‡ Type I (No genetics)		12 (60.0)	
Milder clinical types (PH‡ type 2 or 3)		2 (10.0)	
	(n = 20)	**Median (IQR*)**	**Range**
Duration of hospitalisation at presentation (days)		35 (18.3-87.8)	13.0 – 216.0
Duration of follow up per patient (days)		148.5 (21.0 - 430.5)	10.0 – 2957.0
Sex	(n = 24)	**Number (%)**	
Male		14 (58.3)	
Female		10 (41.7)	
South African	(n = 19)	**Number (%)**	
Gauteng		11 (57.9)	
North West		7 (36.8)	
Free State		1 (5.3)	
Outside of South Africa	(n = 1)		
Swaziland		1 (100)	

Gauteng (n = 11)		
Soweto	2 (18.2)	
Outside of Soweto	9 (81.8)	
Stunting (n = 20)		
Moderately stunted (HFA[§] < - 2SD)	2 (10.0)	
Severely stunted (HFA[§] < - 3 SD)	6 (30.0)	
Normal height (HFA[§] - 2SD to + 2SD)	12 (60.0)	

* IQR (Interquartile range), † ESRD (End Stage Renal Disease), ‡ PH (Primary Hyperoxaluria), § HFA (Height for age).

As seen in Table 2, the most common clinical presentation of the 20 patients was urolithiasis (90.0%) and ESRD (85.0%). The median GFR was 6.1 ml/min/1.73m^2 (IQR: 4.2 – 9.0) and two patients had normal renal functions as seen in Table 3. Figure 2, depicts nephrocalcinosis and urolithiasis detected by plain abdominal radiograph.

Table 2. Clinical presentation of the patients with primary hyperoxaluria.

Clinical presentation (n = 20)	**Number (%)**
Urolithiasis	18 (90.0)
ESRD[*]	17 (85.0)
Nephrocalcinosis (by radiographs)	15 (75.0)
UTI[†]	11 (55.0)
Stunted	8 (40.0)
Haematuria	6 (30.0)

* ESRD (End Stage Renal Disease), † UTI (Urinary Tract Infection).

Table 3. Renal function and stage of chronic kidney disease of the study population at presentation.

Renal function (n = 20)	**Number (%)**
Stage 5 CKD[*] (GFR[†] less 15 mL/min/1.73m^2)	17 (85.0)
Stage 4 CKD[*] (GFR[†] 15-29 mL/min/1.73m^2)	1 (5.0)
Normal	2 (10.0)

* CKD (Chronic Kidney Disease), † GFR (Glomerular filtration rate).

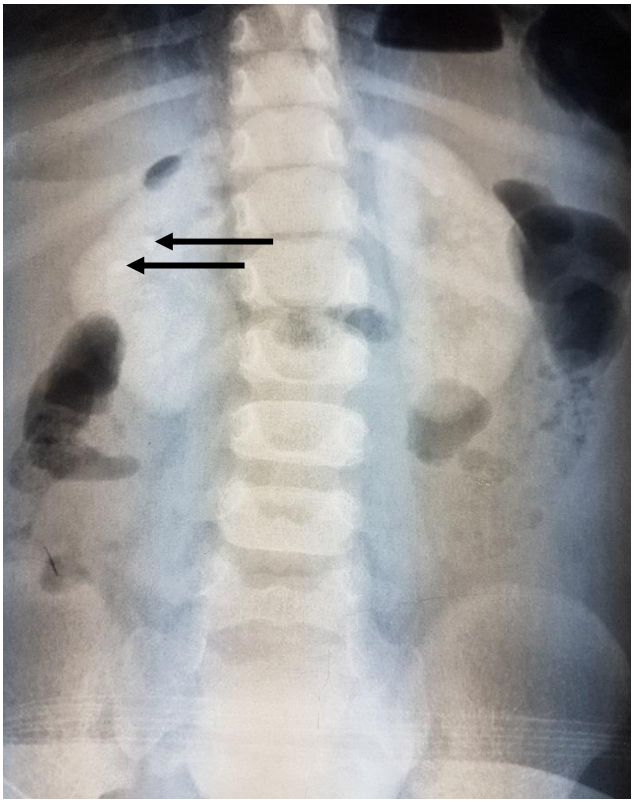

Fig. 2. Abdominal x-ray of a patient with primary hyperoxaluria showing nephrocalcinosis, as delineated by the radio-opacities outlining both kidneys, and urolithiasis as indicated by the arrows.

Anaemia was present in 18 patients, according to age appropriate reference range (see attached appendix 1), of which 17 had ESRD and one patient had CKD stage 4. Of those, 14 had normocytic anaemia, and four had microcytic anaemia. The two patients that had normal renal functions did not have anaemia. As seen in Table 4, the iron studies for 12 of the patients were normal but all had raised ferritin levels. The reticulocyte production index (RPI) was done in seven patients and all showed inadequate bone marrow response with levels less than 1%.

Table 4. Anaemia in patients with primary hyperoxaluria at presentation.

Anaemia		**Median (IQR*)**	**Range**
Haemoglobin (g/dL)	(n = 20)	7.3 (5.1 – 9.7)	3.4 – 13.5
MCV† (fL)	(n = 20)	74.6 (69.0 – 83.9)	55 – 87.6
Reticulocyte production Index (%)	(n = 7)	0.2 (0.1 – 0.6)	0.1 – 0.6
Iron (μmol/L)	(n = 12)	14.6 (12.1 – 28.9)	11.1 – 37.0
Transferrin (g/L)	(n = 12)	1.7 (1.6 – 1.8)	1.2 – 3.3
% Saturation (%)	(n = 12)	34.0 (28.0 – 78.0)	26.0 – 463.0
Ferritin (μg/L)	(n = 12)	434.5 (313.5 – 676.3)	169.0 – 1342.0

* IQR (Interquartile range), † MCV (Mean Corpuscular Volume). Expected normal values for the following parameters: Iron (9.0 – 21.5); Transferrin (1.74 - 3.99); % Saturation (15 – 50); Ferritin (4-67). Age appropriate reference range for haemoglobin is attached in appendix 1 (under Table 4.a).

Most of the patients had more than one test performed for the diagnosis of PH as seen in table 5. The median 24 hour urine oxalate excretion was 1.4 mmol/1.73m2/day (IQR: 0.8 – 2.0) and 323.6 μmol/mmol (IQR: 232.5 – 594.1) for spot urine oxalate to creatinine ratio. Bone marrow aspirate and trephine (BMAT) was performed on 16 patients of which five (31.3%) confirmed oxalate crystals under polarized light. Renal biopsy was done on 11 of the patients, including one post mortem biopsy, and all confirmed oxalate crystals under polarized light. Of the 11 renal biopsy patients, eight records were available, and three of the eight patients had documented mild, transient, macroscopic haematuria post renal biopsy.

Table 5. Diagnostic procedures done for primary hyperoxaluria.

Diagnostic procedure		**Done n (%)**	**Positive n (%)**
24 urine oxalate	(n = 20)	8 (40.0)	7 (87.5)
Spot urine oxalate	(n = 20)	13 (65.0)	10 (76.9)
Fundoscopy	(n = 20)	10 (50.0)	0
Genetics	(n = 20)	6 (30.0)	6 (100.0)
Ultrasound	(n = 20)	17 (85.0)	5 (29.4)
Abdominal radiograph	(n = 20)	20 (100)	14 (70.0)
CT* abdomen	(n = 20)	2 (10.0)	2 (100.0)
Stone analysis	(n = 20)	2 (10.0)	2 (100.0)
Serum oxalate	(n = 20)	0	0
Liver biopsy	(n = 20)	0	0
Bone biopsy	(n = 20)	1 (5.0)	1 (100.0)
Renal biopsy	(n = 23)	11 (47.8)	11 (100.0)
BMAT†	(n = 21)	16 (76.2)	5 (31.3)

*CT (Computed Tomography), † Bone marrow aspirate and trephine (BMAT).

Echocardiography was done on 15 patients, eight (53.3%) of which had normal findings and seven (46.7%) had abnormal findings: three patients (20.0%) had left ventricular hypertrophy, three patients (20.0%) had small pericardial effusions (Range: 4-8mm), one patient (6.7%) had diastolic dysfunction and one patient (6.7%) had a patent ductus arteriosus (PDA). Echo-bright myocardium was observed in one patient (6.7%) but no speckling was observed. There were seven echocardiograms (ECG) available for analysis, four were normal

but three patients had prolonged QTc intervals. Of the three patients, two patients had documented hypocalcaemia.

Genetic studies were done on six patients and all had confirmed type 1 PH. Five of the patients were homozygous for A112D mutation and the other had a heterozygous mutation for two different alleles, c335C>A (p.A112D) and c.473C>T (p.S158L).

On initial clinical presentation, 15 (75.0%) patients had nephrocalcinosis on abdominal radiograph. Of the remaining two patients with ESRD, one only had urolithiasis evident on abdominal radiograph whilst the other's radiograph was not available. This is in contrast to the 17 ultrasounds that were preformed, where only five (29.4%) ultrasounds confirmed the presence of medullary or cortical nephrocalcinosis. Of the remaining 12 ultrasounds, five reported hyperechoic kidneys and the remaining seven sonars did not identify nephrocalcinosis. All five of the patients that had nephrocalcinosis had ESRD. Nephrocalcinosis was significantly associated with ESRD (p=0.009).

Management

Routine management included alkalinisation of urine, high fluid intake and pyridoxine. The median dose of pyridoxine was 6 mg/kg/dose (IQR: 5-10). A gastrostomy tube was inserted for a seven month old infant to ensure adequate fluid and protein intake. Three patients had endoscopic lithotripsy by the urologist prior to referral to the renal unit.

Table 6 shows the management and outcomes of the patients. A total of 14 patients received dialysis and four patients died prior to the initiation of dialysis. Of the 11 patients that were referred for transplantation, four had been transplanted, of which two received combined liver – kidney transplantation, while two were waiting to be listed. Of the 11 that were referred, four patients demised prior to transplantation and one was lost to follow up. The mortality rate in this study was 58.3%.

Table 6. Management and outcome of patients with primary hyperoxaluria.

Management		**Number (%)**
Endoscopic lithotripsy	(n = 20)	3 (15.0)
RRT*	(n = 20)	14 (70.0)
Referred for transplantation	(n = 22)	11 (45.8)
Transplanted		4 (16.7)
Outcomes	(n = 24)	**Number (%)**
Alive and still attending clinic		5 (20.8)
Lost to follow up		4 (16.7)

Unknown	1 (4.2)
Death	14 (58.3)

*RRT (Renal Replacement Therapy)

In terms of identifying the determinants of ESRD and death, there were significant associations between the following factors with ESRD: nephrocalcinosis (p=0.009), haematuria (p=0.018) and anaemia (p=0.016). There were no significant associations identified between the other factors and ESRD. No significant determinants of death were identified as seen in Table 7.

Table 7. The determinants of ESRD and death.

Determinants	**ESRD**		***p*-value**	**Death**		***p*-value**
Age at presentation (months), median (IQR) (n = 21)	72 (44 - 102)		p = 0.062	72 (44 - 102)		p = 0.512
Determinants (n = 20)	**ESRD Present**	**No ESRD**	***p*-value**	**No Death**	**Death**	***p*-value**
Nephrocalcinosis	15	0	p= 0.009	7	8	p = 0.319
No nephrocalcinosis	2	3		4	1	
Urolithiasis	15	3	p= 1.00	10	8	p = 1.000
No urolithiasis	2	0		1	1	
Urinary Tract infection	10	1	p= 0.566	7	4	p = 0.653
No urinary tract infection	7	2		4	5	
Haematuria	3	3	p = 0.018	5	1	p = 0.157
No haematuria	14	0		6	8	
Anaemia	17	1	p = 0.016	9	9	p = 0.479
No anaemia	0	2		2	0	
RRT	13	1	p = 0.202	9	5	p = 0.336
No RRT	4	2		2	4	

* ESRD (End Stage Renal Disease), † IQR (Interquartile Range), ‡ RRT (Renal Replacement Therapy)

Discussion

This is one of the first studies done on PH in South Africa, which highlighted the important differences in the presentation of patients in this cohort compared to other countries such as North Africa and Middle East, especially regarding age of presentation. There was no history of consanguinity in this study compared to the North African [7] and Middle Eastern cohorts. [8,6,12] The high prevalence of PH seen in the North African and Middle Eastern countries was

due to the high rates of consanguinity. [1] In this study, the median age of the onset of first symptoms was 67.5 months (5.6 years), which is comparable to the Dutch cohort (median age of 6.0 years). [11] The median age of presentation was 72 months (6 years) which is much older compared to the Egyptian cohort of 3 years of age. [8] The difference in age of presentation was a result of the higher proportion of infantile PH (35.3% - 6 of 17 patients) in the Egyptian cohort [8] compared to this study cohort of 4.2% (1 of the 24 patients).

Regarding ESRD, the median age of onset in the study was 5.3 years (64 months). This is in contrast to that of the Omani cohort, which was 4 years of age. [12] The younger median age of ESRD is also due to a larger proportion of infantile PH (39%) in the Omani cohort. [12] In this cohort, the median age of ESRD was less than the age of presentation because of the two outliers with normal renal functions, which were removed. There was also no association between ESRD and death.

The most common clinical presentation in this study was urolithiasis, ESRD and nephrocalcinosis, which was similar to the other international cohorts. [5,8,11,12] In this cohort, nephrocalcinosis was identified on plain abdominal radiographs, as seen in figure 2, and reported in other studies.[13,14]

Nephrocalcinosis is typically detected on ultrasound, and it has been shown in a few studies that cortical nephrocalcinosis is associated with rapid progression to ESRD. [7,8,10,11,15] In this cohort, there was a statistically significant association between nephrocalcinosis and ESRD (p=0.009). Of the five patients that had sonographic evidence of nephrocalcinosis, only two patients had documented cortical nephrocalcinosis.

A total of 17 ultrasounds were done, of which five patients had documented medullary or cortical nephrocalcinosis, all of whom had ESRD, and five had hyperechoic kidneys. Hyperechoic renal parenchyma on ultrasound could represent nephrocalcinosis, but the imaging modality on its own has a low diagnostic yield and a high inter-observer variability. [16] In this study, abdominal radiographs contributed better to the diagnosis of nephrocalcinosis compared to the ultrasounds. This highlights the importance of plain abdominal radiographs as well as the utilization of more than one imaging modality to increase the yield of nephrocalcinosis diagnosis in PH.

In this cohort, more spot urine oxalate creatinine samples were sent compared to 24 hour urine samples, but the percentage of positive results in the 24 hour urine collections (87.5%) was higher compared to the spot urine samples (76.9%). A 24 hour urine collection is preferred over spot urine sample, but it is technically more challenging and it requires accurate timing and collection of all urine passed in that time period. [17] An inaccurately timed collection of spot urine can also result in a falsely elevated oxalate: creatinine ratio, especially if taken post-prandial with exogenous dietary sources of oxalate. [17]

In adult studies, the sensitivity and specificity for 24 hour urine calcium oxalate varied from 42% to 79% and differed between males and females. [18] Further studies need to be done in children in order to shed more light on the sensitivity and specificity of urine for the diagnosis of PH. The decline in GFR would result in reduction in urine oxalate excretion and increased systemic oxalosis. [17] In this cohort, 13 patients had confirmatory urine oxalate levels, despite 11 of them having a GFR of less than 30 mL/min/1.73m^2. This highlights the importance of urine oxalate in the diagnosis of PH. As seen in Table 7, haematuria was

shown to be significantly associated with ESRD (p=0.018), thus highlighting the importance of routine urine dipsticks.

Liver biopsy was previously considered to be the gold standard diagnosis of PH through direct measurement of the AGT and glyoxylate reductase-hydroxypyruvate reductase (GRHPR) levels of enzyme activity. [3] However genetic testing is now the investigation of choice for definitive diagnosis. [1] Liver biopsy is only considered in cases where there is a strong clinical suspicion but all genetic testing for the different subtypes of PH are negative. [1] In this study, no liver biopsy was performed and this could be explained by the confirmation of the diagnosis through other tissue samples such as renal biopsy. Minor complications, such as transient haematuria, were noted in the patients who had the renal biopsy.

Genetic testing was performed on six of the patients and five patients had homozygous A112D mutation (type 1 PH). This mutation was previously identified in two unrelated patients, one from Botswana and one South African. [2] A112D is most likely a common mutation in the Southern African population as previously suggested. [2] One patient was heterozygous for two different alleles, c335C>A (p.A112D) and c.473C>T (p.S158L). The remaining 11 patients that did not have genetic analysis, and who had presented with ESRD and oxalosis, were most likely type 1 PH.

Given the small sample size there was no significant association noted between the genetic mutations with ESRD (p=1.0). Interestringly, of all the patients with confirmed type 1 PH based on genetics, four had ESRD whilst the one had normal renal functions. The patient with the normal renal function likely had slow progression of the disease despite having type 1 PH. This highlights that simply having the genotype does not necessarily translate into full phenotypic expression and further studies would need to be done to identify phenotypic correlation to homozygous A112D mutation.

Screening for systemic oxalosis in this cohort was important given that 85.0% of the patients had ESRD. Of the 47.8% that had renal biopsies, all confirmed oxalosis and of the 76.2% that had BMAT, only 31.3% confirmed oxalate birefringent crystal deposition when viewed under polarized light. This together with a few other case reports highlights the value of BMAT in the diagnosis of PH and systemic oxalosis. [19-21] There was no significant association between systemic oxalosis with ESRD or death.

Anaemia was a significant finding seen in all the patients with ESRD (p=0.016). Of those that had anaemia, seven patients had RPI results showing inadequate bone marrow response (<1%). The anaemia was either due to the chronic renal failure [22] or a direct result of oxalate deposition in the bone marrow, or both. [21] The high ferritin levels documented in the 12 patients suggest the inflammatory effects of oxalosis.

In addition in our cohort, cardiac abnormalities were noted in 46.7% of the study population. The abnormalities noted were left ventricular hypertrophy and diastolic dysfunction. These findings could be related to the hypertension seen in chronic kidney disease but it could also be attributed to oxalate deposition as observed in other studies. [23]

The increased cardiac echogenicity has also been described in patients with PH as a result of deposition of oxalate crystals, [24,25] which was observed in one study patient with an echo-bright myocardium. From our cohort, one patient had a prolonged QT interval with normal

calcium levels and this could possibly be a result of oxalate deposition as arrhythmias have been described in PH patients. [23] Patent ductus arteriosus (PDA) was also identified in one of the study patients, which was also described in a case report of a 19 year old from Turkey. [26] There was no significant association between the cardiac manifestations and ESRD or death. This study does highlight the importance of non-invasive screening for cardiac involvement in all patients with PH. Prospective studies would be valuable in characterizing the cardiac manifestations of PH.

All the patients with ESRD and the Stage 4 CKD were dialysed except for four patients, of which two patients died before they could be dialysed and the other two patients were not dialysed due to social constraints. Poor socio-economic circumstances in South Africa is a limiting factor in the care of renal patients. The renal department refers patients with social constraints to the department of social services. The social grants provided by the government amounts to 52.6% of the total monthly income of some South African families. [27]

There were 11 patients that were referred for transplantation at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a quaternary hospital in Gauteng. In a study done by Strobele et al, up until 2013 a total of 43 paediatric liver transplants had been done, of which eight were combined liver-kidney transplants. [28] Out of the four of the 11 patients that were transplanted, two received a combined liver and kidney transplantation. At the time of the study, there were two patients waiting to be listed. The remaining four patients died prior to transplantation and one patient was lost to follow up. In type 1 PH combined liver and kidney transplantation is recommended. [1]

It is important to consider that there is a shortage of deceased donor organs in South Africa but for patients listed for transplant living related donors is also considered. [28] Certain socio-economic factors will also preclude the patients from transplantation such as poor sanitation or poor access to adequate medical follow up. [29] In this cohort, a large proportion of the study population were referred from the North West (36.8%) and those that were from Gauteng, 81.8% were from outside of Soweto, the drainage area for CHBAH. This highlights the high social strain and disruption to families as they need to relocate in order to access dialysis and further treatment. Transportation costs incurred by patients account for 27.1% of the average family income. [27]

It is possible that the mortality rate in this study was higher than 58.3%, as three of the four patients that defaulted follow up had GFR of less than 15 mL/min/1.73m^2. This mortality was higher compared to the Egyptian cohort of 42.3%, of which 65.4% of the patients had ESRD. [8] The higher mortality rate in this study, was likely due to late presentation as well as the higher portion of ESRD (85.0%) in this cohort and one patient was diagnosed at post mortem.

Limitations

This retrospective study was limited by the small sample size, the lack of availability and completeness of the records. Logistic models for analysis of the determinants of ESRD and death could not be done due to the small sample size. There is a referral bias given that only patients that were referred to the renal unit were included. The milder and more severe types of PH may be missed, as the former may be asymptomatic and the latter die before referral or presentation.

Conclusion

Clinicians should have a high index of suspicion for PH in patients presenting with urolithiasis and ESRD. This study highlights the importance of urine oxalate levels and abdominal radiographs in screening for PH in children presenting in ESRD. Routine urine dipsticks done at each clinic visit could assist in early diagnosis, and early referral to a Paediatric Nephrologist.

Acknowledgements. The authors wish to acknowledge the clerks, renal clinic data capturers and to the paediatricians involved in the care of the above patients as well as the statisticians at Philip Tobias, University of Witwatersrand.

Author contributions. CLC: conception of research question, data collection, data analysis, manuscript preparation and revision; KLP and UKK: conception of research question, data analysis, revision and approval of final manuscript.

Funding. None

Conflicts of interest. None

Word count: 4289

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Appendix 1:

Table 4.a. Age appropriate reference range for anaemia in children.

Age	Haemoglobin (g/dL) at -2 Standard Deviation (SD)
Birth (term infants)	13.5
1 month	10.7
2 months	9.4
3-6 months	9.5
6 months – 2 years	10.5
2 – 6 years	11.5
6 – 12 years	11.5
12 – 18 years	
Males	13
Females	12

Protocol for MMED research report

***Title*:**

Primary Hyperoxaluria at Chris Hani Baragwanath Academic Hospital from 1984 to 2017.

Dr Chih-Luo Chang

0500348K

***Supervisors*:**

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Lists of abbreviations

1. AGT (Alanine-glyoxylate aminotransferase)
2. ESRD (End stage renal disease)
3. GRHPR (Glyoxylate reductase – hydroxypyruvate reductase)
4. GFR (Glomerular filtration rate)
5. HOGA (4-hydroxy-2-oxoglutarate aldolase)
6. PH (Primary hyperoxaluria)
7. PH1 (Primary hyperoxaluria type 1)
8. PH2 (Primary hyperoxaluria type 2)
9. PH3 (Primary hyperoxaluria type 3)
10. Extracorporeal shock wave lithotripsy (ESWL)

Introduction

Primary hyperoxaluria (PH) is a rare autosomal recessive condition which results in defects in the metabolism of glyoxylate which results in increased oxalate production[1]. There are four clinical subtypes of primary hyperoxaluria currently described in the literature: a) primary hyperoxaluria type 1 (PH1), b) primary hyperoxaluria type 2 (PH2), c) primary hyperoxaluria type 3 (PH3) and d) non-1 and non-2 primary hyperoxaluria [1]. The exact prevalence and incidence of this disease is unknown but the most common clinical subtype is PH1[1]. Type 1 also has the worst prognosis as there is a rapid progression to end stage renal disease (ESRD) but it also includes the more severe presentation, the infantile PH [1] .

Clinical presentation

Clinical data on PH1 has been well documented in developed countries [2-4]. Data is also slowly emerging from the developing countries, such as in North Africa [5-7] and Middle East [8, 9]. Currently no known data exists on PH in South Africa. In a large cohort conducted in the Netherlands, of the 57 patients 16% had infantile PH [2] compared to the 38% of infantile PH in Tunisia [8]. The incidence of PH in North Africa and Middle East is also much higher compared to the international incidence and this is due to increased consanguineous marriages within those population [1]. The age of presentation can range from birth to late adulthood [1]. The median age of onset of symptoms was seven months in the Omani cohort [8], three years in an Egyptian cohort [5], six years in Dutch cohort [2]; where as in Japan the median age of diagnosis was 13 years [4].

The most commonly reported symptoms at presentation in all the reviewed cohorts were as follows: urolithiasis with or without nephrocalcinosis, urinary tract infections, haematuria and end stage renal disease (ESRD) [3, 6, 7, 9]. In the paediatric population, the reported incidence of chronic renal disease due to PH, is 1-2.7% in Europe and 0.5% in America [10]. However

this is much higher in Kuwait and Tunisia, with a reported incidence of 10% and 13% respectively, which again reflects the high prevalence of consanguinity [11].

Complication

Systemic oxalosis usually develop once the patients develop stage 3 chronic kidney disease [1]. The most common sites of oxalate deposition are the kidneys, walls of the vessels, the bones, the heart and the central nervous system [1, 12]. Patients can present with signs ranging from livido reticularis to fractures, to polyradiculoneuropathies as well as involvement of the retina and bone marrow [13]. Cardiac manifestations can vary from cardiomyopathy to heart block or conduction defects [12].

Diagnosis

In all the studies reviewed, part of the diagnostic work up included a 24 hour urine or spot urine analysis for oxalate crystals [2-9]. In patients with a normal GFR, a 24 hour urinary oxalate that is persistently above 0.5 /1.73m^2 is highly suggestive of hyperoxaluria [2]. However if the GFR is reduced the urine oxalate may be falsely low [12]. In the spot urine samples, the urinary oxalate: creatinine ratio can be calculated and compared to age – appropriate reference ranges for PH [1]. In the presence of urolithiasis, stone analysis for dumbbell-shaped monohydrate calcium oxalate (whewellite) crystals can be used to diagnose PH [5, 6].

Genetics

The genetic defects in PH type 1 is due to a mutation in the gene coding for the enzyme, alanine-glyoxylate aminotransferase (AGT) found in the liver peroxisomes [1]. In type 2 there is a deficiency and an ineffective glyoxylate reductase-hydroxypyruvate reductase enzyme (GRHPR) located in the cytosol [1]. Type 3 is characterized by defects in the 4-hydroxy-2-oxoglutarate aldolase (HOGA) enzyme in the mitochondria [1]. Genetic mutation analysis was utilised in the Dutch, Egyptian, Tunisian and Omani cohorts [2, 5, 8, 9]. In Southern African

only homozygous A112D mutation has been documented in two unrelated patients [14]. Currently in South Africa, genetic studies can be done by the NHLS, which includes full gene sequencing and the A112D mutation testing [15].

Imaging

Imaging can further aid in diagnosis, long bone x-rays with features of radio dense metaphyseal bands with diffuse demineralisation and a course trabecular pattern is suggestive of oxalate osteopathy [16]. Abdominal x-ray may also reveal nephrocalcinosis [12]. Ultrasonography identifies the presence and extent of urolithiasis and nephrocalcinosis [12]. Reports from Africa as well as the Netherlands, have shown a correlation between presence of cortical nephrocalcinosis and progression to ESRD [2, 5, 6].

Management

Treatment of primary hyperoxaluria is complex and requires the input of multiple disciplines [1]. The treatment modalities are the same in both the developed and developing countries, including high fluid intake of 3-4 L/m^2 of body surface area per day, alkalinisation of the urine and pyridoxine supplementation [2-9]. Alkalinisation of urine can be achieved either with potassium citrate or sodium citrate in patients with renal failure [12]. Dialysis is initiated before patients develop ESRD in order to prevent systemic oxalosis establishment or progression [12]. Modes commonly implemented in the developed world are combined peritoneal (PD) and haemodialysis (HD) [12]. Peritoneal dialysis on its own does not sufficiently remove the oxalate [13]. Patients in the Omani study, received either haemodialysis or peritoneal dialysis but never combined; which partially contributed to the poorer outcome as removal of oxalate was insufficient [8]. Currently no available data exist in South Africa, hence in our study it will be pertinent to establish which modes of dialysis were utilised.

The definitive treatment for type 1 primary hyperoxaluria is a combined liver and kidney transplant [1]. This ensures enzyme replacement as well as recovery of renal functions [1]. In the Egyptian study three of 26 study patients and two of the 18 study patients in Oman, underwent combined liver and kidney transplantation [5, 8]. These results from developing countries are encouraging. Currently no data is available in South Africa. The transplants are primarily done at Charlotte Maxeke Johannesburg Academic Hospital and Red Cross Children's Hospital, Cape Town.

Although primary hyperoxaluria is a rare genetic disorder; there are numerous reports on it in the developed countries [2-4] and a few are emerging from the developing countries, such as in North Africa [5, 6] and the Middle East [8, 9]. However, no studies have yet been published in Sub-Saharan Africa, including South Africa. This study aims to describe the presentation, diagnosis and treatment of primary hyperoxaluria at Chris Hani Baragwanath Academic Hospital in South Africa.

Study Objectives

Primary objective is to describe the following in patients with primary hyperoxaluria:

- Clinical presentation and diagnosis
- Complications
- Management
- Outcome

Secondary objectives:

Compare the determinants of ESRD and Death

- Clinical presentation and diagnosis
- Complications developed
- Management

Methods

Study population

The study population will be selected from the paediatric renal clinic at Chris Hani Baragwanath Academic Hospital, which is a tertiary academic hospital in Gauteng with an affiliation to the University of Witwatersrand. This clinic serves the population of Soweto and also receives patients referred from other provinces as well as neighbouring countries of South Africa.

The estimated sample size is about 30 patients diagnosed with primary hyperoxaluria from the Paediatric Renal Clinic will be included from January 1984 to December 2017. The data will be collected using Redcap.

It is estimated that 1500 files will be screened by looking at the diagnoses written on the renal folders. The folders with the following will be scrutinised:

1. Haematuria
2. Urolithiasis
3. Nephrocalcinosis
4. ESRD
5. CKD
6. Hyperoxaluria
7. Oxalosis

The files fulfilling the following inclusion criteria will then be included in the study:

1. All patients less than 16 years of age
2. Persistently high urine oxalate (> 0.5mmol/ 1.73m^2) or spot urine analysis in keeping with hyperoxaluria [2-8].
3. Birefringent crystals on bone marrow trephine[3].

4. Birefringent crystals on kidney biopsy [3, 5, 6].
5. Birefringent crystals in any other tissues or on histology [3-6, 9].
6. ESRD / dialysis patient with oxalate crystals on any histology.

Exclusion criteria would be those who present with urolithiasis or ESRD but with no evidence of oxalate crystals or high urinary oxalate. Only the first presentation and last clinic visit will be used to collect the data utilizing the data capture sheet as attached in Appendix 1.

Study design

This is a retrospective descriptive study as the data will be collected from files from 01 January 1984 to 31 December 2017 of all patients with primary hyperoxaluria.

Data analysis

The data will be manually captured from reviewing the existing records in the individual files. Each file will then be assigned a number on REDCap, and only the investigator will have access to the file number correlating to the REDCap number. Furthermore, date of birth will not be included in the data sheet, hence the identity of the individuals will be kept confidential. REDCap version 7.5.2, the standard release by Vanderbilt and hosted by the University of Witwatersrand [17], will be utilised as it will create a virtual database and electronic database for capturing of information on this rare disease.

In terms of the descriptive data such as the demographics, clinical presentation, diagnosis and methods of diagnosis as well as treatment, it will be represented in terms of frequency, means and medians. The data will be assessed for normality and the difference in groups in continuous variables will be analysed using a student *t*-test. If the continuous variables are not normally distributed then Mann-Whitney U test will be used. For the categorical variables the statistical test utilised will be Pearson's chi-squared test. To assess the determinants of ESRD and death a logistic regression will be used. All the data will be analysed at the 95%

confidence interval and *p*-value of <0.05 is considered significant. The software which will be utilised will be STATISTICA version 13.2 by TIBCO Software Inc.

Ethics

Ethics approval has been obtained from the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate no. M170423). Permission from the medical advisory committee at Chris Hani Baragwanath Academic Hospital has also been received.

Limitations

This is a retrospective study on existing records hence there may be inadequate documentation as well as missing information of the research data in the records. The other limitation is the small sample size, thus any statistically significant findings may either underestimate or miss significant findings. Since this study is over a period of 30 years, improvements in the diagnosis and management may be reflected in this historic co-hort. The overall mortality may not represent current mortality. In addition genetic data may only be available in a few patients; hence this may make any comparison difficult especially to international data. Another limitation may also be files been missed if they do not fulfil the screening criteria hence potentially missing patients with primary hyperoxaluria.

Timing

	1/5/2016- 1/5/2017	2 /5/2017- 31/8/ 2017	1/9/2017- 31/1/2017	1/2/2017- 31/3/2018	1/4/2018- 30/4/2019
Literature review					
Preparing Protocol					
Protocol Assessment					
Ethics application					

Collecting data					
Data Analysis					
Writing up					

Budget

The entire study will be privately funded, including materials utilised such as photocopying.

It estimated to be around R1540.

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Appendix 1 - Data Capture Sheet

Age

Age: _____

Age of onset: _____

Age at Diagnosis: _____

Age at Death: _____

Demographics:

Place of birth: _____

Place of residence: _____

Ethnicity: _____

Sex: _____

Family History of PH: Y ☐ N ☐

Consanguinity: Y ☐ N ☐

Clinical presentation at onset

Please tick

• Haematuria ☐ ____

• Abdominal Pain ☐ ____

• Flank Pain ☐ ____

• Failure to thrive ☐ ____

• Nephrocalcinosis ☐ ____

• ESRD ☐ ____ • Urolithiasis ☐

• Urinary Tract Infection ☐

Anthropometry at presentation

Date of measurements: _____

Weight: ____ (Kg) Height: _____ (cm)

Wt/Ht: _____(Z-score)

Weight for Age (WFA): _____(Z-score)

Height for Age (HFA):_____ (Z-score)

Weight for height for Age:_____ (Z-score)

Diagnosis

Age at Diagnosis: _____

Diagnostic procedure:

• Urine Oxalate (24hr) ☐ • Genetics ☐

• Serum Oxalate ☐ • Liver biopsy ☐

•Kidney Biopsy ☐ • Bone Marrow ☐

• Fundoscopy ☐ • Ultrasound ☐

• X-ray ☐

• Other methods of diagnosis

Please specify: _____

Urine

• Microscopy: ☐ Erythrocytes

☐ Crystals

• If RBC: ☐ Glomerular

☐ Non-Glomerular

• 24 hour urine oxalate: _____

• Urine oxalate: creatinine ratio: _____

Serum:

• Genetic mutations: ☐ Y ☐ N

PH Type • Type 1 ☐ • Type 2 ☐

• Type 3 ☐ • Non type 1 and 2 ☐

• Infantile PH ☐

Management

*Prescribed the following***:**

• Alkalinisation of Urine: Y ☐ N ☐

• High fluid intake: Y ☐ N ☐

• Pyridoxine therapy: Y ☐ N ☐

• Gastronomy tube inserted: Y ☐ N ☐

Urolithiasis:

• Endoscopic Lithotripsy: Y ☐ N ☐

• ESWL Y ☐ N ☐

• Renal replacement therapy:

➢ Peritoneal Dialysis (PD): Y ☐ N ☐

Duration of PD: _____

➢ Haemodialysis (HD): Y ☐ N ☐

Duration of HD: _____

Complications

Systemic Oxalosis: Y ☐ N ☐

If **YES**, Which systems were involved:

Please tick

• Skin: Levido reticularis ☐

• Joints: Arthritis ☐

• Bone Marrow:

Erythropoeitin resistant anaemia ☐

• Eye: Retinal oxalate deposition ☐

• Cardiac:

Arrhythmia ☐

Heart block ☐

Conduction defects ☐

• CNS:

Myopathies ☐

Polyradiculoneuropathies ☐

• Other ☐ _____

• Dialysis related Y ☐ N ☐

• **If yes, please specify: _____**

_____

• Recurrent Urolithiasis Y ☐ N ☐

• **If yes, please specify: _____**

_____

• Age at onset of Systemic Oxalosis: ____

➢ Serum oxalate: _____

• Age at onset of ESRD: _____

Staging of CKD:

• Stage I ☐ Age at onset:_____

• **S**tage II ☐ Age at onset:_____

• Stage III ☐ Age at onset:_____

• Stage IV ☐ Age at onset:_____

• Stage V ☐ Age at onset:_____

• Creatinine clearance: _____

(ml/min/1.73m^2)

Outcome

• Referral for transplant: Y ☐ N ☐

Referred at GFR of: _____

Referred at CKD stage:_____

• Alive Y ☐ N ☐

• Still attending the clinic: Y ☐ N ☐

• Lost to follow up: Y ☐ N ☐

• Death: Y ☐ N ☐

• Death from time of diagnosis: _____

Appendix 2 - Definitions

Creatinine is calculated through enzymatic method performed on Roche Cobas 8000. The enzymes involved in the calculation are: creatinase, creatininase and sarcosine oxidase. The other agents involved are: formaldehyde and hydrogen peroxide. The end product is a chromogen which is directly proportional to the concentration of creatinine. The method of measuring is based on the modified Jaffé reaction.

However, there are various factors that may interfere with the accuracy of creatinine measurement, such as bilirubin levels, haemolysis, ketones and drugs, such as cephalosporin. Cephalosporin can cause false positive values of the serum creatinine. This information is as per package insert for Roche Cobas 8000.

The references ranges for normal 24 hour urine oxalate is: <0.7 mmol/1.73m^2. The urine oxalate: creatinine ratio is as follows [(1)]:

Age (years)	Reference range (µmol/mmol)
< 1	15 - 260
1 – 5	11 – 120
5 – 12	60 – 150
> 12	2 – 80

The GFR that will be used in the study will be calculated using the modified Schwartz formula [18]: GFR (mL/min/1.73m^2) = (k x height (cm)) / Creatinine (mg/dL).

k – is constant based on age

Age	k constants
Term (Neonate)	0.45
Children	0.55
Adolescent girls	0.55
Adolescent boys	0.7

To assess stages of chronic kidney disease the following staging will be utilized [19]:

Stage	**GFR (mL/min/1.73m^2)**
1	≥ 90
2	60-89
3	30-59
4	15-29
5 (ESRD)	<15 (or Dialysis)

Anaemia in the study will be defined as haemoglobin less than two standard deviation below the mean for age as seen the table below [20].

Age	Haemoglobin (g/dL) at -2 Standard Deviation (SD)
Birth (term infants)	13.5
1 month	10.7
2 months	9.4
3-6 months	9.5
6 months – 2 years	10.5
2 – 6 years	11.5
6 – 12 years	11.5
12 – 18 years	
Males	13
Females	12

Weight and height will be recorded from the files and it will be charted using WHO Z-score application charts (Growth Charts):

- Weight (weight for age (WFA)):
    - Underweight for age: -1 to -2 SD
    - Moderately underweight for age: -2 to -3 SD
    - Severely underweight for age is < -3 SD
- Height (height for age (HFA)):
    - Stunted for age: - 1 to -2 SD
    - Moderately stunted for age: -2 to -3 SD

    - Severely stunted for age is < -3 SD

- Weight for height (WFH):
    - Moderate acute malnutrition: WFH -2 to -3 SD
    - Severe acute malnutrition: WFH < -3 SD

Appendix 1 - Turn it in

a0022668:Turnitin_May_2020.docx

ORIGINALITY REPORT

10%	6%	6%	3%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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27	Elizabeth C. Lorenz, Clement J. Michet, Dawn S. Milliner, John C. Lieske. "Update on Oxalate Crystal Disease", Current Rheumatology Reports, 2013 Publication	<1%

Appendix 2 - Ethics clearance

R14/49 «Tit init name»

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170423

NAME: (Principal Investigator)	Dr Chih-Luo Chang
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital Paediatric Renal Department
PROJECT TITLE:	Descriptive Study of Primary Hyperoxaluria at Chris Hani Baragwanath Academic Hospital in South Africa from January 1984 to December 2016
DATE CONSIDERED:	05/05/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof U. Kala and Dr K. Peterson
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/05/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary 3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review in April and will therefore be due in the month of April each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 22/6/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE
WITWATERSRAND,
JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
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Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

11 June 2018
Person No: 0500348K
TAA

Dr C Chang
P O Box 410003
Craighall
2024
South Africa

Dear Dr Chang

Master of Medicine: Change of title of research

I am pleased to inform you that the following change in the title of your Research Report for the degree of **Master of Medicine** has been approved:

From:	**Primary hyperoxaluria at Chris Hani Baragwanath Academic Hospital from 1984 to 2016**
To:	**Primary hyperoxaluria at Chris Hani Baragwanath Academic Hospital from 1984 to 2017**

Yours sincerely

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

Appendix 3 - Hospital Ethics Clearance

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 23rd January 2018

TITLE OF PROJECT:

A descriptive study of Primary Hyperoxaluria at Chris Hani Baragwanath Academic Hospital in South Africa from January 1984 to December 2017.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr Chang

Department: Paediatrics

Supervisor : K Petersen

Permission Head Department (where research conducted): Yes

Date of start of proposed study: April 2017
Date of completion of data collection: Dec 2019

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 23/01/2018

Approved/Not Approved
Hospital Management
Date: 26.01.2018