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Clinical and laboratory presentation of classical galactosaemia in infants and children at Chris Hani Baragwanath Academic Hospital

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ABSTRACT

Background. Classical Galactosaemia is an autosomal recessive disorder of galactose metabolism due to a deficiency of galactose-1-phosphate uridyltransferase (GALT) enzyme. In the neonatal period it can be a life threatening disease with multi organ involvement and non-specific symptoms and signs. In infancy and childhood, it can present with cataracts and cirrhosis. Long-term complications include verbal dyspraxia, cognitive disability and hypergonadotrophic hypogonadism. Galactosaemia responds to a galactose free diet and early diagnosis reduces morbidity and mortality, especially in early infancy.

Objectives. To determine the number of cases with classical galactosaemia seen at Chris Hani Baragwanath Academic Hospital (CHBAH) Paediatric Gastroenterology, Hepatology and Nutrition Unit (PGHNU) Soweto Gauteng, between January 1994 and December 2013 and to document the clinical, laboratory characteristics and outcome of these patients.

Methods. All children diagnosed at PGHNU with classical galactosaemia between January 1994 and December 2013 were included in the study. Clinical and laboratory parameters were determined and analysed. Outcome and long-term complications were documented.

Results. Twenty-three children with classical galactosaemia were diagnosed during the study period. All patients had severely low or absent GALT enzyme activity. Mean age at diagnosis was 4.6 months (age range 3 -24 months). The commonest presenting symptoms were yellow discolouration of the eyes (74%), abdominal distension (65%) and failure to gain weight (57%). Most frequent clinical features at diagnosis were hepatomegaly (100%), pallor (78%), jaundice (78%), ascites (61%) failure to thrive (52%) and cataracts (55%). Laboratory findings included metabolic acidosis (78%), coagulopathy (65%) and liver derangements (61%). Anaemia was noted in 78% of the patients, which was primarily macrocytic. Eight out of the 23 patients presented with evidence of infection. Long-term complications in those assessed, included visual problems (12/18patients), developmental delay(9/16patients) and speech impairment (4/9patients).

Conclusion. The study provides information on the clinical, haematological and biochemical presentation of galactosaemia thus increasing the awareness of the condition and encouraging strategies aimed at early recognition. This will prevent on- going damage to target organs in postnatal life. The study also documents the presence of long-term complications in the South African black child with classical galactosaemia, encouraging a structured follow up programme to prevent, identify and manage complications such as neurodevelopmental delay and speech impairement.

Background

Galactosaemia is an autosomal recessive inborn error of carbohydrate metabolism, which has been evident in our South African population and the rest of the world for many decades [1,2]. The disorder occurs as a consequence of deficiency of the enzymes involved in galactose metabolism (the Leloir pathway) and its conversion to glucose. The most common form of the disease is caused by galactose-1-phosphate uridyltransferase (GALT) enzyme deficiency. The other two genetic hypergalactosaemias include galactokinase enzyme deficiency and epimerase enzyme deficiency. The Leloir pathway substrates are involved in cell recognition, cell signalling, the immune system and neural development [3,4]. Severe GALT deficiency results in the accumulation of toxic galactose metabolites such as galactose-1-phosphate and galactitol and causes a decrease in UDP-galactose, a sugar required for galactosylation of glycoproteins and glycolipids [5,6,7,8]. The GALT gene is located on chromosome 9p13 with over 100 mutations described of which Q188R is the commonest in the Caucasian population and S135L in the non-Caucasian population [1,3]. In the South African black population the S135L mutation was found to account for 91% of the allele in patients with GALT deficiency galactosaemia [9]. Estimated incidence of this condition in South Africa, is between 1/14400 and 1/21904 as compared to a world incidence of 1/40 000 to 1/60000 [10]. Three phenotypes of GALT deficiency have been described and include classic galactosaemia, clinical variant galactosaemia and biochemical variant galactosaemia (Duarte variant). The division is based on GALT enzyme activity, galactose metabolite levels, genetic testing and the incidence of acute and long-term complications [11] (Table 1). Classic galactosaemia is a profound deficiency in GALT enzyme, which is the most common form of the disease [5, 12]. Clinical variant galactosaemia is thought to occur with the S135 L genotype found in African Americans and South Africans [1,10]. African Americans with this clinical variant are thought to not develop long-term complications if diagnosed and treated early [10]. For the purpose of this report classical galactosaemia will refer to both classic and clinical variant galactosaemia as genetic testing and galactose metabolite levels were not available.

Classical galactosaemia presents in the neonatal period with non-specific signs and symptoms occurring several days after exposure to dietary galactose from milk. Failure to thrive, jaundice, ascites, diarrhoea and vomiting are some of the clinical presenting features. This was supported by local studies done in the Western Cape and Mpumalanga [1,12]. Laboratory investigations may reveal metabolic acidosis, hypoglycaemia, liver derangement, coagulopathy and sepsis [5,12]. Confirmatory diagnosis of classical galactosaemia is made by measuring GALT enzyme activity, which will be extremely low, or absent [13]. Documented mean age at diagnosis in South Africa was 5.1 months in the Cape metropolitan region as compared to as early as 72 hours in Ireland [1,5]. Neonatal screening is not routinely available in South Africa and this may contribute towards morbidity and mortality of the condition [10,13]. Management of galactosaemia simply involves elimination of dietary lactose and galactose, which reduces the complications such as sepsis, cataracts, growth failure and severe liver disease. Early intervention is vital in our resource limited setting, as this will improve long term survival.

The demographics, clinical and laboratory findings in children with classical galactosaemia presenting to Chris Hani Baragwanath Academic Hospital (CHBAH) Paediatric Department in Gauteng have not been previously documented. The aim of this study is to provide detailed information regarding clinical, haematological and biochemical presentation as well as outcome of South African children with classical galactosaemia.

Methods

The study design was a secondary analysis of the CHBAH Paediatric Gastroenterology, Hepatology and Nutrition Unit database. The study population included all patients diagnosed with classical galactosaemia at CHBAH between January 1994 and December 2013. Both in-patient and out-patients were included in the study. All participants were confirmed as classical galactosaemia as evidenced by a severely low or absent GALT enzyme activity. As the diagnosis was only based on GALT enzyme activity and not Galactose-1-phosphate level or genetic testing, for the purpose of this study, there was no differentiation between classic and clinical variant galactosaemia. The Duarte variant was excluded based on enzyme activity levels. Children with inherited types of galactosaemia other than GALT enzyme deficiency and suspected cases not confirmed by GALT enzyme activity were excluded. Patients with secondary causes for hypergalactosaemia were also excluded from the analysis. World Health Organization (WHO) anthropometry software was utilized for anthropometric measurements.

Study setting

Chris Hani Baragwanath Academic Hospital is a tertiary academic hospital located in Soweto, Johannesburg South Africa. The hospital has sub-speciality paediatric services, including gastroenterology and serves as a referral center for surrounding clinics and district hospitals.

Data collection and analysis

The data was collected from the CHBAH Paediatric Gastroenterology Hepatology and Nutrition Unit database and the National Health Laboratory Services (NHLS) records. Demographic information, anthropometry, history, clinical presentation and laboratory results were collected for each subject. Outcomes and long-term complications were documented where available.

Data was entered into a Microsoft Excel spread sheet and basic statistical analysis was performed using Microsoft Excel. Appropriate descriptive statistical analysis using percentages, medians and ranges were used. Continuous data was presented as medians and interquartile ranges (IQR) by group and categorical data was presented as frequencies and percentages by group. In cases where data was unavailable, participants were excluded from that part of the analysis.

Ethics permission was obtained from the University of the Witwatersrand's Human Research Committee (Clearance number M140535).

RESULTS

Demographics

Twenty-three patients from CHBAH Paediatric Gastroenterology, Hepatology and Nutrition Unit were diagnosed with classical galactosaemia. The mean age at diagnosis was 4.6 months (range 2 days to 24 months), with two of the patients being diagnosed as neonates. Female to male ratio was 1:0,64. Twenty -two (96%) were black and 1 white (4%). Nineteen patients came from Gauteng province, 3 were from North West province and one was from KwaZulu-Natal (KZN) province.

Anthropometry

WHO anthro plus software was used to calculate individual z scores. Twelve (52%) out of the 23 patients were severely underweight for age (weight < -3 z score) and four were underweight (weight -2 to -3 z score). Height for age data was unavailable on 4 of the patients; of the remaining 19 patients, 12(63%) were severely stunted (length < -3 z score) and 2 were stunted (length -2 to-3 z score). Of the 19 patients assessed for weight for height, eight (42%) were wasted (weight for length -2 to-3 z score), four of whom were moderately and four severely wasted (weight for length <-3 z score). Head circumference was available on seven subjects of which six were normal for age and one was macrocephalic due to hydrocephalus (Table 2).

Clinical signs and symptoms

The commonest presenting symptoms were yellow discoloration of the eyes or skin (17/23) (74%), abdominal distension (15/23) (65%) and inadequate weight gain (13/23) (57%) (Table 2). None of the patients presented with a history of bleeding. Of the 23 patients with galactosaemia, three had a positive family history of the disease. The most common clinical signs included hepatomegaly (23/23) (100%), pallor (18/23) (78%), jaundice (17/23) (74%), failure to thrive (15/23)(65%), ascites (14/23)(61%) and cataracts (12/22)(55%). The youngest age recorded with cataracts was one month. Neurological impairment was noted at presentation in six of the 23 patients; two had milestone regression, two delayed milestones and two presented with seizures (Table 2). Of note six patients were clinically anicteric and none had signs of coagulopathy such as ecchymosis or active bleeding. All parents of affected children received genetic counselling and the children were discharged on lactose free diet and vitamin supplements. Children were referred to dietetics department for ongoing nutritional advice and growth monitoring.

Laboratory findings

All patients had severely low or absent transferase activity, giving a median of 0.69 units (IQR 0.00; 2.67 units). None of the patients included, had enzyme activity levels in the biochemical variant galactosaemia range (Duarte variant). Blood was obtained from 11 of

the 23 mothers to establish transferase levels in obligate heterozygotes and all were confirmed to be carriers (median 12.63 and IQR 11.80; 14.99 units). One father was tested and confirmed to be a galactosaemia carrier, on GALT enzyme activity. Of note one of the cases was a twin, however the GALT enzyme activity was normal in the sibling. DNA analysis was not considered necessary for diagnosis, however was performed on one mother and she was confirmed to be a carrier of S135L mutation. Two patients who had genetic testing were found to be homozygous for the S135L mutation. Positive urine reducing substances in the urine were confirmed in 21(91%) patients and 2(9%) were unknown. The reducing substance was confirmed to be galactose in those that tested positive.

Haematology

Haematological review showed 78% of the patients to have presented with anaemia (corrected for age). Analysis of the red cell parameters showed 61%(14/23) of the patients to have macrocytosis, mean cell volume (MCV) >100, and the rest were normocytic (Graph 1). The causes of macrocytosis were not investigated. Sixty five percent had deranged coagulation profile as evidenced by International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT) values, with a median INR of 1.51(IQR 1.15; 2.00) and PTT of 55.30 seconds (IQR 40.90; 64.40 Sec) for all patients. Normal laboratory value for INR is ≤1.2 and PTT≤ 40sec (varies with each laboratory).

Electrolytes and acid/base

Eighteen (78%) of the patients presented with metabolic acidosis with a median serum bicarbonate of 13mmol/L (IQR 12-17). Anion gap was raised in 12 and normal in 11 patients with a median value of 18mmo/L. Urine pH was not routinely documented. Six of the patients were initiated and discharged on oral sodium bicarbonate due to persistent acidosis. Two out of the 23 patients (9%) presented with prerenal dysfunction that subsequently corrected during first presentation.

Eighteen of 23(78%) had elevated alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT) was raised in one patient but not sufficiently to suggest biliary obstruction. Hypoalbuminaemia (albumin <30g/l) was noted on 7(30%) of the patients and all presented with ascites. Glucometer was used for glucose reading. Hypoglycaemia (HGT<2.6mmol/L) was noted in 39%(9/23) of the patients and 13%(3/23) were hyperglycaemic (Table 3). Three patients had acholic stool on presentation with normal gamma-glutamyl transferase.

Infants with classical galactosaemia may present with rickets. Alkaline phosphatase was raised in 18 of the 23 patients (78%). Median values of calcium and phosphate were 2.3 mmol/L and 1.12 mmol/L respectively. It was difficult to confirm a diagnosis of rickets, as there was limited availability of parathyroid hormone levels and wrist x-rays, due to the retrospective nature of the study. However, two patients were reported to have clinical signs of rickets on presentation.

Infection

Twenty patients (87%) were retroviral disease negative, 2(9%) were positive and 1(4%) was unknown. Nine of the 23 patients were HIV exposed. One of the HIV positive patients demised at first presentation with suspected sepsis.

All patients were investigated for sepsis using cultures on blood (23), urine (21) and cerebral spinal fluid (CSF) (15). Positive cultures were confirmed on eight patients. Blood cultures were positive in two patients, one for coagulase negative Staphylococcus (CNS) and the other Klebsiella pneumonia. Six of the 21(29%) urine cultures were positive; two grew Escherichia coli (E. coli), one Klebsiella pneumonia, 1 Candida albicans, 1 Enterobacter species and 1 mixed growth. All urine results demonstrated significant number of leucocytes. Two of the 15(13%) CSF cultures were positive and both grew CNS, the significance of which was unclear, as the CSF white cell count and protein were not raised. Of note one patient grew CNS on blood and cerebrospinal fluid and E. coli in the urine. C-Reactive Protein (CRP) was raised in eight of the 23 (35%) patients, three of which had positive cultures; two positive urine cultures (E. coli and Candida albicans) and one positive blood culture (Klebsiella pneumonia). Bedside urine dipsticks were obtained in some of the patients on admission but unfortunately many of the indices were not recorded which made it difficult to interpret.

Histology

Liver biopsies were not routinely performed as part of the work up for classical galactosaemia. In total four patients underwent a closed biopsy, three were done due to worsening liver function or suspected progression to cirrhosis while one was a diagnostic post mortem biopsy. Two out of the four biopsies had the histological triad of pseudo acinar transformation, cholestasis and steatosis. The other two patients had two out of the three features. Three out of the four patients had some degree of fibrosis and although not histologically graded, were reported as bridging fibrosis in one patient (3 months old), incipient cirrhosis on the other (2months old) and micro nodular cirrhosis on the third (8 months old). Other features seen on histology included portal triaditis, extra medullary haematopoiesis and giant cell transformation.

Follow up

Up to May 2017 six of the 23 classical galactosaemic patients (26%) were still under the care of the PGHN Unit and followed up annually. Regarding follow up; three patients demised at presentation with suspected sepsis and one was lost to follow up a month post diagnosis. Sixteen patients were followed up to the age of 1 year, eight up to 5 years and two until adolescence (Graph 2). There were 12 patients with cataracts, eight of which required surgery, nine patients had developmental delay, seven had learning difficulties and four had speech impairments. Two patients presented with hydrocephalus one of which required a VP shunt. The other patient showed no progression of the hydrocephalus and did not require surgery. One patient was reported with craniosynostosis and one with

dextrocardia. On assessing growth, there was one patient with a pathological short stature whose endocrinological investigations did not reveal a cause for the short stature (Table 4).

Discussion

A total of 23 patients with classical galactosaemia were reviewed over a 20-year period at CHBAH in Soweto Gauteng. The study focuses on the documentation of the clinical and laboratory findings of classical galactosaemia upon presentation. The diagnosis is usually made early in the neonatal period following exposure to dietary galactose from milk [1]. In this study, the mean age of presentation was 4.6 months, which is indicative of delays in the detection. Internationally diagnosis is as early as 3 days due to the availability of neonatal screening programmes in some countries [2,4]. Severity at presentation varies amongst each patient depending on the age at presentation and advancement of the disease. In our population, late presentation may be attributed to the lack of neonatal screening programmes, financial constraints for transportation to hospital and lack of parental awareness and education [12]. Improved clinical vigilance could also assist in earlier diagnosis.

Similarly as the study done in Cape Town, the drainage area of CHBAH consists primarily of a black population explaining the racial profile of the study. The GALT deficiency conditions are known to be inherited as autosomal recessive traits. The data suggested a gender bias, showing the condition to be more common in females. In our study female to male ratio was 1:0,64 versus 1:1,6 of the local study done at the Cape metropolitan region [1]. However, combining and analysing data for the same period of patients with galactosaemia from all provinces of South Africa may reveal no gender bias as shown in American studies [6]. The majority of the patients were from Gauteng province mainly from Soweto, 3 were referred from North West province as CHBAH serves as their referral hospital and 1 was from KZN province who happened to be on vacation at the time of presentation. The diverse location of residence of the study population made it difficult to suggest incidence in the population. Only three of the 23 patients (13%) had a positive family history for galactosaemia. This assisted in making an early diagnosis and providing genetic counselling to those families.

Human immunodeficiency virus (HIV) is highly prevalent in our setting making it prudent to screen all patients for this disease [14]. In addition, the clinical features of an HIV positive infant with or without sepsis may be indistinguishable from a child with galactosaemia and sepsis. These reasons explain the high testing rate even in the early years of the study. Of the nine HIV exposed patients, two were confirmed positive, one of which died on presentation from suspected sepsis while the other was initiated on highly active antiretroviral therapy (HAART) prior to discharge.

It is vital that the diagnosis of galactosaemia be considered in children presenting with common suggestive features including hepatomegaly, pallor, jaundice, failure to thrive, ascites, cataracts and neurodevelopmental delay. Of interest, all the patients presented with hepatomegaly, a finding in keeping with other local study [1]. However, less than 50%

of the patients had hepatomegaly upon presentation when looking at international studies [15]. Nearly a quarter of patients were clinically anicteric and this created a challenge in making the diagnosis. Cataracts was diagnosed on presentation in about half of the patients that is comparable to 66% in the study done in Cape Town [1]. The youngest was a one month old, demonstrating the early manifestation of cataracts in this condition and the urgency for diagnosis [16]. Significant number of patients were failing to thrive whom 70% were underweight, 74% stunted and 42% wasted as compared to 29% of the patients failing to thrive in the survey done in United States of America (USA)[17]. Ascites was noted in two thirds of the patients and could be most likely attributed to liver dysfunction. A number of clinical conditions were documented that are not commonly associated with galactosaemia. These included diverse conditions like dextrocardia, craniosynostosis and hydrocephalus. The hydrocephalus may occur secondary to a meningitis, as patients with galactosaemia are prone to infections, or as a complication of a hypoxic insult during a seizure from a hypoglycaemic event.

All study participants had a severely low or absent transferase activity. Attempts were made to establish the carrier status on twelve parents by doing red cell enzyme activity and all were confirmed to be carriers. Of note negative results in the parents do not entirely exclude the diagnosis. DNA analysis is not routinely performed and parental unavailability and financial limitations were some of the reasons why not all parents were tested. Although GALT genotypes were not tested in all patients, we would have expected the majority to test positive for the S135L mutation as shown by local studies in the Western Cape and studies in African Americans in the USA [1,12,18]. To confirm the assumption subsequent genetic testing in the active follow up patients of this study and patients diagnosed after 2013 may be performed.

Conjugated hyperbilirubinaemia and metabolic acidosis at presentation correlate with the findings of the other local study [1]. Liver derangement was a common presenting clinical finding with the majority of patients having conjugated hyperbilirubinaemia and predominantly raised liver transaminases. Of interest three of the twelve patients were reported as having acholic stool on presentation but a normal gamma-glutamyltransferase, made causes of cholestasis such as biliary atresia unlikely. The majority of patients with galactosaemia presented with metabolic acidosis, with a third having persistent acidosis despite being changed to a lactose free diet. These patients required bicarbonate supplements and were discharged on oral bicarbonate. Once maintained on galactose free diet, the majority were weaned off the bicarbonate within the first year. Hypoglycaemia is one of the common known presenting signs however, 3 of the 23 patients were hyperglycaemic on glucometer reading at presentation, making it difficult for the clinician to consider galactosaemia as a differential diagnosis early on. It is known that high plasma galactose levels can cause overestimation of glucose readings by glucose meters as shown in the local and international studies [11,12]. This may not only lead to misdiagnosis but also to unnecessary administration of insulin with fatal consequences. It is critical that high glucose meter readings are confirmed with laboratory blood glucose levels. [19]

More than half of the patients, had macrocytosis associated with anaemia on presentation and four had MCVs between 95fl and 99fl, which fell on the higher side of normal (age

related). Macrocytosis has been previously documented in various causes of parenchymal and obstructive liver disease although not specifically in galactosaemia. The PGHN Unit noted an anecdotal higher prevalence in galactosaemia as compared to other liver diseases in infancy and the study wanted to document this. Investigations for possible causes were not routinely conducted so substrate deficiencies could not be excluded. The macrocytosis in liver disease is thought to be due to cholesterol and/or phospholipid deposition on the membrane of circulating red blood cells. The macrocytosis in galactosaemia needs to be further investigated and statistically compared with MCV values in age comparable cholestastic children, with causes other than galactosaemia. Deranged coagulation profile is associated with the condition but based on the study, appears to not be significant enough to present with active bleeding or ecchymosis, in keeping with international studies [15]

Due to the predisposition of children with classical galactosaemia to sepsis, blood, urine and cerebrospinal fluid cultures should be done as routine investigations as it is generally difficult to determine which galactosaemic neonate is septic on the basis of clinical findings [6,20]. Infection amongst patients with galactosaemia is commonly noted during the second week of life and is usually bacterial. A study done in Massachusetts revealed E. coli to be the commonest organism where three of the four septic galactosaemic patients cultured E. coli [20]. In this study, the patients that were proven septic, cultured a variety of organisms including gram positive bacteria, gram negative bacteria and fungal organisms. Even though according to the literature E. coli accounts for about 36% of all neonatal sepsis in patients with galactosaemia, the study suggests that other organisms should also be considered and therapy adjusted as microbiologically indicated [20]

In the present review, patients who deteriorated despite feed change and medical intervention underwent a liver biopsy for histological evaluation. Biopsy revealed features in keeping with galactosaemia as evidenced by pseudo glandular transformation, cholestasis and steatosis. However, liver biopsy is not routinely done as it is not diagnostic and the histologic picture can present in other inborn errors of metabolism. Histology can however assess the degree of fibrosis and progression to cirrhosis. Even though the study numbers were small, significant fibrosis was noted as early as two months, which demonstrated the need for early diagnosis and management.

The study was only able to comment on outcomes on the children that were followed up long enough for complications to manifest. Three patients died at presentation with suspected sepsis, concurring with other studies regarding the severity of the condition. The high attrition in follow up numbers may have been due to financial constraints, lack of transport but also perhaps inadequate education of parents by medical staff, on long term complications. Emphasis needs to be placed by doctors on the necessity for follow up to puberty and adolescence, as many of the long-term complications are known to arise even when there is compliance with diet. Seven patients were developmentally delayed based on formal assessment by a neuro developmental paediatrician, neurologist and occupational therapist. Recommendation for remedial schooling was advised in 4 of the 7 children in view of their learning difficulties. This is in keeping with international studies, which estimates that 38% to 65% of children with galactosaemia have neurodevelopmental

speech disorders [15,21]. Of note in one international study, IQ less then 85 was found in 25% of galactosaemic patients despite dietary compliance [22]. Of the 9 patients assessed for speech impairment (childhood apraxia and dysarthria), four are receiving long-term speech therapy. This demonstrates the importance of early assessment and monitoring of speech development and early referral for speech therapy. Ovarian dysfunction is a well-documented complication associated with galactosaemia. The recommendation is to screen for hypergonadotropic hypogonadism if by twelve years of age there is delay in secondary sexual characteristics or if by fourteen they still have irregular menses. Two female patients ages 16 and 17 years were followed to adolescence and screened for ovarian dysfunction. The 16-year-old experienced irregular menstrual cycles, which settled within the next year. Both patients had normal follicle stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol levels. International studies report an incidence of premature ovarian insufficiency (POI) in 81 % of females with galactosaemia therefore ongoing screening is highly recommended [11]. One patient had short stature and was referred to Endocrine Unit who attributed the cause to galactosaemia. All patients who attended follow up clinic were formally screened by the ophthalmology department for cataracts and were regularly followed up until cataracts fully resolved. Of the twelve patients with cataracts, two thirds eventually required surgery despite dietary compliance. International studies report incidence of cataracts in galactosaemic patients as 30% versus our study incidence of 55% which may be attributed to late presentation and/or non compliance [11]. Patients non-compliant with diet should be referred for re-assessment. However compliance with the diet does not entirely prevent the formation or cause resolution of cataracts thus requiring ongoing ophthalmologic assessment [11].

Management of classical galactosaemia requires a multidisciplinary approach and places financial and emotional burden on the caregiver. It also places a financial burden on a resource poor healthcare system. Early diagnosis and dietary intervention has a positive impact on complications associated with galactosaemia especially those presenting in infancy. The study contributes information on early clinical presentation, thus increasing clinical awareness of the condition. Increasing awareness will drive strategic developments towards early screening programmes, as routine screening has not yet been implemented in South Africa except as part of research studies [12]. In terms of screening we would recommend a combined galactose level and GALT enzyme activity as methods such as urinary reducing substances and blood galactose are not reliable especially on the S135L homozygous classical galactosaemia [23]. This study is the first local study to document the presence of long-term complications in the South African black patients. Literature from the rest of Africa is lacking. The patient who according to local studies predominantly has the S135L genotype and subsequently belongs to the group that is thought to have the disease with less long term complications [10]. This study also encourages the development of a more structured programme in terms of monitoring patients with galactosaemia from infancy to adolescence. These strategies will improve follow up rates and assist in formally documenting and managing long term complications.

Study Limitations

The retrospective nature of the study resulted in some information being unavailable for analysis. In addition, due to the lack of a neonatal screening programme, it is not known how many neonates or infants with galactosaemia were missed during the study period. Due to financial constraints and because it would not impact on management, genetic testing was not routinely performed, so the study was unable to confirm previous South African data of the high prevalence (>90%)of the S135L genetic mutation in black patients with galactosaemia.

Conclusion

Diagnosis of classical galactosaemia needs to be suspected in sick infants as signs and symptoms are non-specific on presentation. Classical galactosaemia should be considered in any child with cholestatic jaundice, hypoglycaemia and sepsis especially in the neonatal period. Early diagnosis can reduce mortality and morbidity by preventing complications such as failure to thrive, cataracts, cirrhosis, sepsis and neurodevelopmental insults. However even with early intervention, some complications cannot be entirely prevented such as poor cognitive function and speech impairment. The study proves the presence of long term complications such as neurodevelopmental delay and speech impairment in the black South African population. Emphasis should be placed on long term follow up of the patients with classical galactosaemia, as suggested by international clinical guidelines for the management of classical galactoseamia [24]. By documenting local experience, the study contributes to a heightened awareness of this potentially lethal condition and emphasizes the need for long term follow up of the South African black patient with classical galactosaemia..

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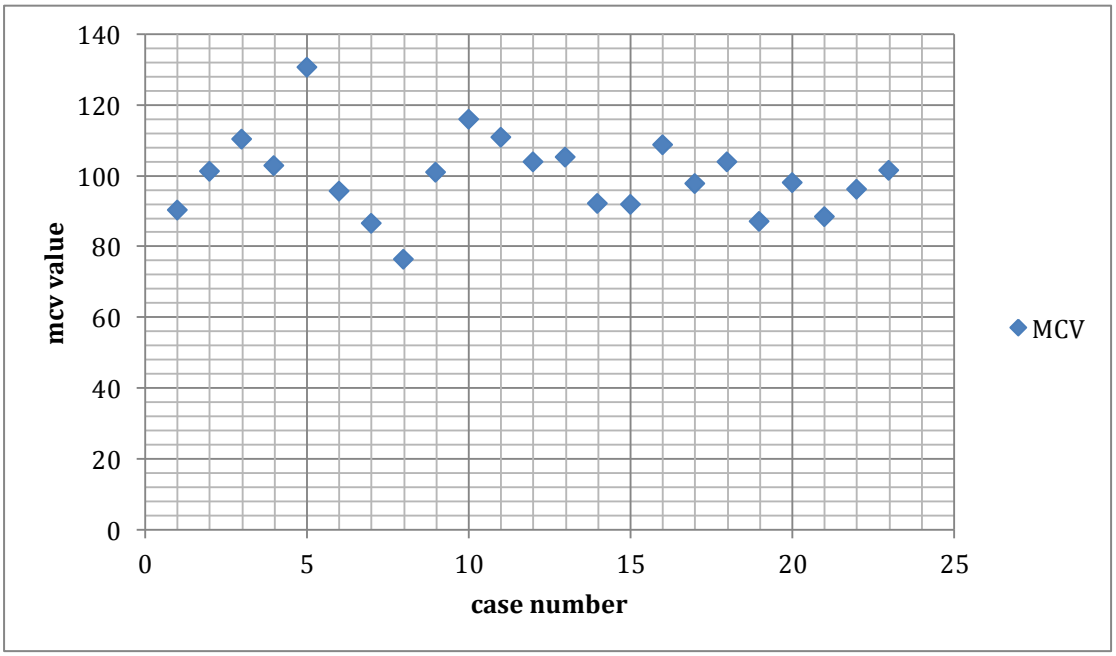
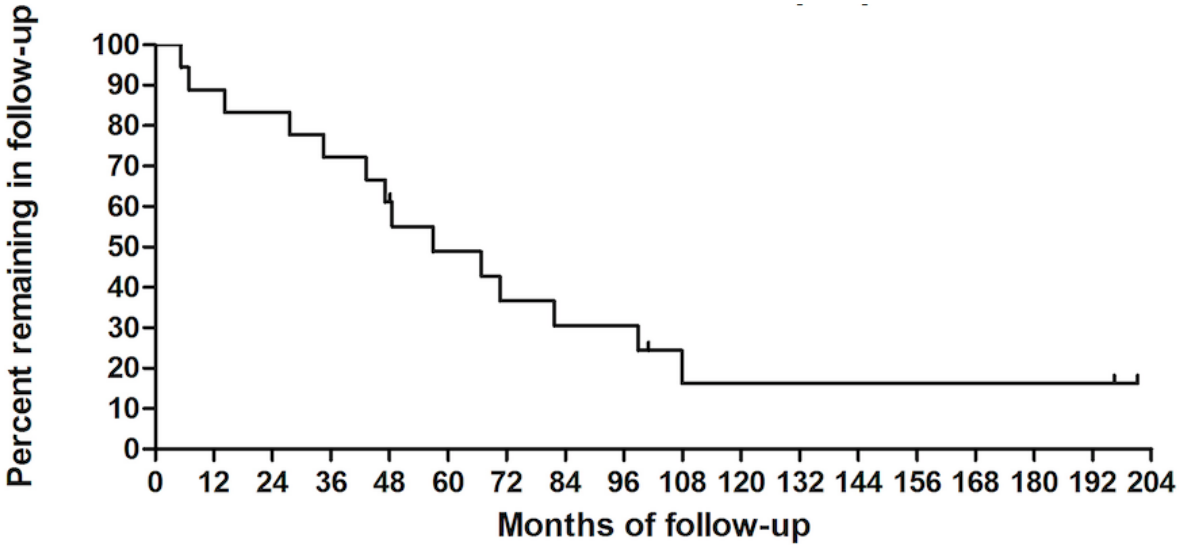
Graph 1: Mean cell volume (MCV) for each patient



Graph 2: Months of follow up after diagnosis



Every drop on the graph indicates events either due to death or lost to follow up. However the phenotypic nature of the disease is most likely to be due to lost to follow up rather than death.

Table 1: The three phenotypes of Galactoseamia caused by deficiency of GALT enzyme

Classic	***Clinical variant***	***Biochemical variant***
Q188R/Q188R Genotype	S135L/S135L Genotype	N314D/Q188R Genotype
Caucasians	Non Caucasians	Caucasians
Absent or barely detectable GALT activity	1 to 10 % residual GALT activity	15 to 33% GALT enzyme activity
Gal-1-P high >10mg /dl	Gal-1-P high >10mg/dl	Gal-1-P high to normal
Free galactose high >10mg/dl	Free galactose>10mg/dl but not as high as classic	Normal free galactose
Positive breath test	Normal breath test	Normal breath test
Long term complications	No long term complications	No overt disease

Gal-1-P (galactose-1-phosphate)

Table 2: Demographic and clinical characteristics of patients with galactosaemia

Age at presentation	***Number***		
Race			
Black	22(96%)		
White	1(4%)		
Sex			
Male	9(39%)		
Female	14(61%)		
Retroviral disease			
Negative	19(83%)		
Positive	2(9%)		
Unknown	1(8%)		
Provincee			
Gauteng	19(83%)		
North West	3(13%0		
Kwazulu Natal	1(4%)		
Growth parameters z scores			
Weight for age(WFA)	4.10,(9.5;3.0)Median,(IQR)		
>-2	7(31%)		
-2- -3	4(17%)		
<-3	12(52%)		
unknown	0		
Height for age (HFA)	55,(50.0;60.3)Median,(IQR)		
>-2	5(27%)		
-2 - -3	2(10%)		
<-3	12(63%)		
unknown	4		
Weight for height(WFH)	-1.3,(-1.84;-0.38)Median,(IQR)		
>-2	11(58%)		
-2- -3	4(21%)		
<-3	4(21%)		
unknown	4		
Clinical symptoms	Yes	No	Unknown
Yellow eyes and skin	17(74%)	6(26%)	0
Abdominal distension	15(65%)	8(35%)	0
Not gaining weight	13(57%)	10(43%)	0
Poor feeding	7(30%)	16(70%)	0
Fever	5(22%)	18(78%)	0
Diarrhoea	5(22%)	18(78%)	0
Irritability	4(44%)	5(56%)	14
Lethargy	3(21%)	11(79%)	9
Clinical signs*			
Hepatomegaly	23(100%)	0	0
Pallor	18(78%)	5(22%)	0
Jaundice	17(74%)	6(26%)	0
Failure to thrive	15(65%)	8(35%)	0
Ascites	14(61%)	9(39%)	0
Cataracts	12(55%)	10(45%)	1
Sepsis	8(35%)	15(65%)	0
Neurological	6(26%)	17(74%)	0
Acidotic breathing	3(43%)	4(57%)	16

*As per clinician finding

Table 3: Laboratory findings in patients with galactosaemia

Laboratory Test	**Median (interquartile range)**
FBC	
WCC Hb(g/dl) MCV(fL) Plat	16.3x10/L (10.20;20.30) 10.6 (8.90 ;11.4) 101.0 (91.9;105.3) 231.0x10/L (188.0;335.0)
CRP(mg/L)	8.35 (2.50;18.00)
U& E	
Na (mmol/L) K (mmol/L) Cl (mmol/L) CO2 (mmol/L) Urea (mmol/L) Creat (umol/L)	139 (133;143) 4.4 (4.1;5.0) 109 (105;112) 13 (12;17) 3.7 (1.9;5.1) 25 (21.0;38.0)
LFT	
Total bilirubin(umol/L) Direct bilirubin(umol/L) Indirect bilirubin(umol/L) Total protein(g/L) Albumin (g/L) Globulins(g/L) Alkaline phosphatase(U/L) Gamma GT(U/L) ALT(U/L) AST(U/L)	89 (31;269) 50 (9;140) 28 (11;89) 52 (45;60) 32 (25;39) 20 (14;25) 709 (406;1213) 27 (21;43) 66 (47;108) 156 (85;315)
Glucose(mmol/L)	3.17 (1.95;3.30)
INR∗	1.50 (1.15;2.00)
PTT∗(sec)	55.3 (40.9;64.4)
Ca∗(mmol/L)	2.3 (2.09;2.41)
Mg∗(mmol/L)	1.0 (0.9;1.1)
PO4∗(mmol/L)	1.12 (1;1.29)
GALT enzyme(units)	0.69 (0.0;2.67)

∗Available on 22 patients

Table 4: Complications on follow up

	Yes	No	Unknown
Neurodevelopmental delay	9	7	3
Learning difficulties	7	2	10
Ovarian dysfunction	0	2	10*
Cataracts	12	6	1
Speech impairment	4	5	10
Other associations	5: Short stature (1) Dextrocardia (1) Craniosynostosis (1) Hydrocephalus (2)		

* Lost to follow up before puberty or have not reached pubertal age yet