East African Medical Journal Vol. 76 No 5 May 1999
GALACTOSAEMIA IN BLACK SOUTH AFRICAN CHILDREN
P.J. Ojwang, MBChB, FRC. Path (UK), T. Manickum, BSc, MSc, PhD, (Natal) and W.M. Deppe BSc, MSc, (Natal), Department of Chemical Pathology, Faculty of Medicine, University of Natal, Durban, South Africa

Request for reprints to: Dr. P.J. Ojwang, Department of Chemical Pathology, Faculty of Medicine, University of Natal, Private Bag 7, Congella, 4013 Durban, South Africa

GALACTOSAEMIA IN BLACK SOUTH AFRICAN CHILDREN

P.J. OJWANG, T. MANICKUM and W.M. DEPPE

ABSTRACT

***Objective*: To evaluate the clinical and biochemical features of all black children confirmed to have galactosaemia from the KwaZulu Natal Province of South Africa.**

***Design:* Prospective laboratory study.**

***Subjects*: These included all black children with the presenting clinical features suggestive of the diagnosis of galactosaemia.**

***Setting:* Department of Chemical Pathology, King Edward VIII Hospital, Durban, South Africa.**

***Method:* In each case, urine was screened for the presence of a reducing substance using urinary dipstick followed by thin layer chromatography to establish the presence of galactosaemia. The diagnosis of galacotosaemia was then confirmed by analysis of galactose-1 phosphate uridyl transferase (GALT) activity in the erythrocytes using the established Beutler enzyme assay procedure. Age and sex-matched samples were used as controls for GALT activity. The presenting clinical features of each patient on admission were also recorded.**

***Interventions*: Patients confirmed to have galactosaemia were immediately placed on a galactose free diet.**

***Results*: The age distribution of affected individuals varied from six weeks to 27 months with 60% of the children being males. The most common presenting clinical features were jaundice in 77% of the patients, failure to thrive 62%, and cataracts 54%. Four patients had complete absence of GALT activity. Two infants who displayed acute toxicity symptoms and positive urine galactose, exhibited normal GALT activity.**

***Conclusion*: GALT deficiency is the most common form of galactosaemia in black children in the KwaZulu Natal region. Cases of galactokinase or epimerase enzyme deficiency appear to be present. Further investigation is required to establish the occurrence and prevalence of the latter in affected individuals in this region.**

INTRODUCTION

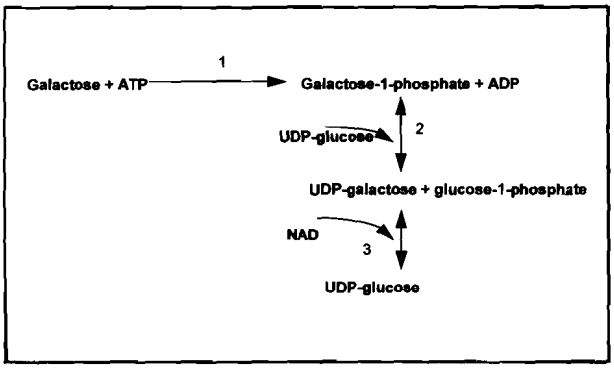
Galactosaemia is not uncommon among black children in Southern Africa yet it is rarely reported in the medical literature. The earliest report by Bernstein in 1965(1) described seven cases from South Africa. Macfarlane *et al* described three cases of black infants from Southern Rhodesia (now Zimbabwe) in 1979(2) and more recently, four cases were described from the Gauteng Province of South Africa by van den Berg *et al* in 1993(3). Presently, we are unable to obtain any recorded information on the incidence of galactosaemia in Kenya and other East and Central African countries.

The term galactosaemia refers to an inherited autosomal recessive disorder associated with a defect in the metabolism of galactose. The main pathways for galactose metabolism are represented in Figure 1. As indicated, the three key enzymes involved in the conversion of galactose to glucose are galactokinase, galactose-1-phosphate uridyl transferase (GALT) and uridine diphosphogalactose-4-epimerase. The deficiency of any one of these enzymes may lead to galactosaemia, but GALT deficiency is the most common disorder and often leads to severe clinical manifestations. The gene for GALT is located on chromosome 9 and several mutations have now been cloned and sequenced(4-6). These mutations seem to have a variable impact on the biochemical and clinical manifestations of transferase-deficient galactosaemia in affected individuals. Approximately 70% of all Caucasians with transferase-deficient galactosaemia have the Q188R missense mutation in which arginine is substituted for glutamine

on exon 6. These patients exhibit no detectable GALT activity in their erythrocytes and often present with severe acute toxicity symptoms(7).

Figure 1

Scheme showing metabolic pathways in galactose metabolism



Enzymes:
1. Galactokinase
2 Galactose-1-phosphate uridyl transferase (GALT)
3 UDP - Galactose-4-epimerase

Previous studies have shown that only 12.5% of transferase deficient blacks have the alleles for Q188R missense mutation, with impaired enzyme activity similar to the one seen in Caucasians(7). Some blacks however, demonstrate the ability to metabolise small amounts of galactose. While no GALT activity is detectable in their erythrocytes, minimal enzyme activity is present in the liver and intestine. This is the 'Negro' variant of galactosaemia, commonly associated with a mild form of the disease. In the Duarte' variant, GALT activity is diminished but the affected individuals manifest no clinical disorder(8).

Most patients with galactosaemia will present with acute or long-term toxicity symptoms if no treatment is instituted. These range from the life-threatening hypoglycaemic attacks, severe diarrhoea and vomiting to those that are equally severe but not necessarily acute, such as failure to thrive, liver dysfunction with jaundice and cirrhosis, cataracts and mental retardation.

This paper presents our observations on some clinical and biochemical aspects of galactosaemia in 15 black children from the Kwa Zulu Natal province of South Africa. This, to our knowledge, represents the largest series of galactosaemia ever reported in black children from sub-Saharan Africa.

MATERIALS AND METHODS

A total of 15 black children with galactosaemia referred to our laboratory at the King Edward VIII Hospital in Durban over a four year period from October 1994 to September 1998 were studied.

In each case, the clinical diagnosis of galactosaemia was confirmed by a positive identification of galactose in the urine, by thin layer chromatography and analysis of GALT activity in the erythrocytes using the fluorometric Beutler procedure(9). In this method, the rate of the transferase reaction is followed by measurement of the formation of glucose-1-phosphate. Red cells are incubated with galactose-I-phosphate, UDP-glucose and NADP. Fluorescence due to NADPH is measured and compared with known dilutions of NADPH. A correction is made for the amount of haemoglobin. The haemoglobin content is determined by absorbence against known dilutions. Samples from age and sex matched controls were also analysed for GALT activity.

The presenting clinical features on admission were recorded as shown in Table 1. These included failure to thrive as determined by the consulting paediatrician, evidence of hypoglycaemic attacks, presence of jaundice, diarrhoea and vomiting, inanition, cataracts and general developmental delay. Also recorded, were biographical data relating to age and sex on first admission. Similarly, we recorded the corresponding results for GALT activity and urine screening for galactose as shown in Table 2.

Table 1

Frequency of clinical features among galactosaemic infants

Acute toxicity syndrome	No. of cases	% Prevalence
Hypoglycaemia	0	0
Cataracts	7	53.9
Inanition	0	0
Failure to thrive	8	61.5
Vomiting	3	23.1
Diarrhoea	4	30.8
Liver disease/jaundice	10	76.9
Developmental delay	2	15.4

Table 2

Summary of biochemical findings

Serial number	Age (months)	Sex	GALT activity[a] Subject	GALT activity[a] Control	Galactose in urine	Reducing substance in urine
1	1.6	M	0.00	23.03	+	+
2	3	F	0.00	55.75	+	+
3	5	M	0.00	29.5–42.6	+	+
4	18	F	0.00	32.25	+	b
5	27	M	0.95	30.67	+	+
6	6	F	1.50	33.10	+	+
7	12	F	2.13	39.07	+	+
8	3	M	2.50	34.9	+	+
9	6	M	3.09	23.78	+	+
10	4	F	6.55	23.78	+	b
11	6	M	9.52	31.12	+	+
12	2	M	12.3	27.1	+	+
13	2	F	16.69	38.18	+	+
14	2	M	35.8	25.7	+	+
15	2	M	65.4	29.8	+	+

a Units: µmol UDP-glucose/g Hb/hr
b Urine screening not done

RESULTS

The age distribution of the patients on first admission was variable. The oldest was 27 months, two were 18 and 12 months and 12 (80%) were six months or less. The youngest infant was six weeks. There were nine males (60%) and six females (40%).

Jaundice was the most common presenting clinical feature in 77% of the patients, followed by failure to thrive (62%) and cataracts (54%) (Table 1). None of the patients were reported to have had features suggestive of hypoglycaemia.

Two of the patients with cataracts had galactose in the urine, with normal GALT activity in the erythrocytes. One of the children with cataracts was also positive for cytomegalovirus infection. Although diarrhoea and vomiting were severe in some children, none of them exhibited any features of inanition.

Four patients (26.6%) had complete absence of GALT activity while nine had reduced but variable activity compared to controls (Table 2). Two infants, No 14 and No 15, presenting with acute toxicity symptoms, had galactose present in the urine strongly supporting a clinical diagnosis of galactosaemia but GALT activity was detectable in each case. Facilities were not available for analysis of galactokinase or uridine diphosphogalactose-4-epimerase.

DISCUSSION

King Edward VIII Hospital in Durban is the main referral hospital providing specialist paediatric care for the whole province of Kwa Zulu Natal. During the four years between October 1994 and October 1998, we confirmed the diagnosis of galactosaemia in 15 cases out of the 929 patients that were referred to us for the investigation of inborn errors of metabolism. Since the Kwa Zulu Natal birthrate for blacks is estimated as 256,000 live births per annum (Health Systems Trust - Durban), the estimated incidence of galactosaemia in the black population of this province is 1:11145. This figure is relatively high compared to that of 1:52000 reported from the black community of Mashonaland in Zimbabwe(2) and is also much higher than Caucasian figures reported from New Zealand 1:37000(10), Switzerland 1:50 000 (10) and the United States, 1:40000 (11). It also implies that galactosaemia is a much more common inherited metabolic disorder among the black community of this region of South Africa than was hitherto believed.

Although our numbers are relatively small, we have found a male to female distribution of 3:2 which confirms the male predominance observed in previous studies(12,13).

The variability of the clinical manifestations of

galactosaemia has previously been described by Hsia *et al*(13). As a result of the limited number of cases so far detected in southern Africa, detailed analysis of the clinical manifestations has previously not been undertaken in this region. In our patients, as in previous studies, the clinical manifestations have ranged from the acute life-threatening conditions such as diarrhoea and vomiting to the equally severe complications such as hepatic dysfunction and cataracts.

None of our patients presented with hypoglycaemia even in those in which GALT activity was undetectable. It is likely that those who suffered hypoglycaemic attacks died before reaching hospitals if they were in rural areas where health facilities are most often not readily available. The most frequent clinical manifestations seen in our patients were hepatobiliary dysfunction with jaundice (76.9%), and failure to thrive (61.5%).

Cataracts were present in approximately 54% of the cases. Whilst the majority of these were transferase deficient, in two patients, GALT activity was normal suggesting either galactokinase or uridine diphosphogalactose-4-epimerase deficiency. In one patient, the diagnosis of galactosaemia was delayed because of the initial finding of a positive test for cytomegalovirus which can also be a cause of cataracts at birth and early infancy. The pathogenesis of cataracts in galactosaemia is attributed to the accumulation of galactose-1-phosphate or galactitol in the lens tissue.

The identification of galactose in the urine allows for the presumptive diagnosis of galactosaemia. The definitive diagnosis is however provided by the determination of GALT activity in the erythrocytes and where this is normal, determination of galactokinase or epimerase activity must be done to confirm the diagnosis. In the present series, we have shown that transferase deficiency is also the most common form of galactosaemia in black children. We have also shown, albeit indirectly, that galactokinase and/or epimerase deficiency also occur in the black community of this region. To our knowledge, this has previously not been reported.

Variable GALT activity has been demonstrated in the present series thus lending further support to the genetic heterogeneity of galactosaemia. While four of our patients had no detectable GALT activity suggesting homozygosity for this disorder, the majority of the cases had low but significant residual GALT activity compatible with the heterozygous state.

The mainstay of treatment for galactosaemia is the elimination of galactose (or lactose) from the infant's diet. This will cause significant regression even in clinical situations where symptoms and signs of acute toxicity have become apparent. Early diagnosis and institution of galactose-free diet is therefore critical. While neonatal screening appears to be an attractive option, it may not be practicable among our black communities the majority of whom live in remote rural areas.

ACKNOWLEDGEMENTS

We wish to thank the consultant staff of the Department of Paediatrics, Faculty of Medicine, University of Natal for referring suspected cases of galactosaemia to us for further biochemical investigation. We also express our sincere gratitude to Mrs. Noleen Henson and Mrs. Pauline Periasamy for secretarial assistance in the preparation of this manuscript.

REFERENCES

1. Bernstein, R.E. Studies on metabolism and nutritional therapy of the galactosaemic infant and child. *S. Afr. Med. J.* 1965; **39:** 1170.
2. Macfarlane, C.M., Berger, G.M.B. and Axton, J.H.M. Galactosaemia in three Rhodesian infants. *S. Afr. Med. J.* 1979; **55**: 303.
3. Van den Berg, I.C.T., Ubbink, J.B., Bissbort, S. and Vermaak, W.J.H. Clinical and laboratory approach for the diagnosis of Galactosaemia in Africa. *E. Afr. Med. J.* 1993; **70:** 26-30.
4. Reichardt, J.K.V. and Berg, P. Cloning and characterisation of cDNA encoding human galactose-1-phosphate uridyl transferase. *Mol. Biol. Med.* 1988; **5**: 107.
5. Flach, J.E., Reichardt, J.R.V. and Elsas, L.J. II. Sequence of a cDNA encoding human galactose-1-phosphate uridyl transferase. *Mol. Biol. Med.* 1990; **7**: 365.
6. Leslie, N.D., Immerman, E.B,, Flach, J.E., Florez, M. Keil-fridovich, J.L. and Elsas, L.J. The human galactose-1-phosphate uridyl transferase gene. *Genomics.* 1992;**14**:474.
7. Elsas, L.J., Fridovich-Keil, J.L. and Leslie, N.D. Galactosaemia: a molecular approach to the enigma. *Int. Paediat.* 1993; **8**: 101.
8. Levy, H.L., Sepe, S.J. and Walton, D.S. *et al.* Galactose-1-phosphate uridyl transferase deficiency due to Duarte/galactosaemia combined variation: Clinical and Biochemical Studies. *J. Paediat.* 1978; **93:** 399.
9 Beutler E. Red cell metabolism. pp 79-85. New York: Grune and Strathon, 1971.
10. Lyon, I.C.T., Chapman, C.J., Houston, L.B. and Veale A.M. Galactosaemia: estimate live birth incidence in New Zealand. *Hum. Genet.* 1975; **27**: 737.
11. Levy, H.L., Hammersen, G. Newborn screening for galactosaemia and other galactose metabolic defects. *J. Paediat.* 1978; **92:** 871-877.
12. Hugh-Jones, K., Newcomb, A. and Hsia, D.W. The genetic mechanism of galactosaemia. *Arch. Dis. Childhood.* 1960; **35**: 521.
13. Hsia, D.W., Frank, A. and Walker, M.D. Variability in the clinical manifestations of galactosaemia. *J. Paediat.* 1961; **59:** 872-883.