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Original Article

Pilot study of classic galactosemia: Neurodevelopmental impact and other complications urge neonatal screening in Egypt

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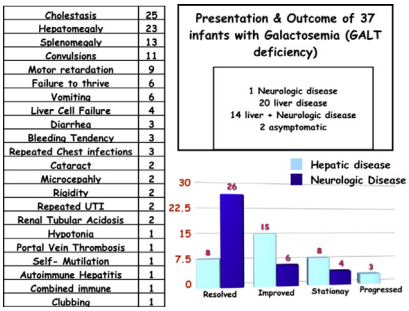
GRAPHICAL ABSTRACT



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ABSTRACT

Classic galactosemia is caused by deficiency of galactose-1-phosphate uridylyltransferase (GALT). It causes serious morbidity and mortality if left untreated. Screening for galactosemia is not included in Egyptian neonatal screening program. The study aimed to define clinical presentation and complications of galactosemia at Pediatric Hepatology Clinic, Cairo University, Egypt. Thus, the clinical presentation, course and outcome of 37 children with documented galactosemia was studied. Jaundice was the main presentation (67.6%). Other presentations included; convulsions (29.7%), motor retardation (24.3%), mental retardation (5.4%), microcephaly (5.4%), failure to thrive (16.2%), hepatomegaly (62.2%), splenomegaly (35.1%), vomiting (16.2%), diarrhea (8.1%), liver cell failure (10.8%), renal tubular acidosis (5.4%), cataract (5.4%), autoimmune hepatitis (2.7%), self-mutilation (2.7%), combined immune deficiency (2.7%) and kernicterus (2.7%). There was no correlation of residual enzyme activity to severity, clinical presentation, liver function tests, liver biopsy findings or outcome apart from highly significant correlation with repeated chest infections ($P = 0.001$). Duration to diagnosis and exposure to galactose in diet correlated with liver pathology severity i.e. hepatocyte necrosis ($P = 0.003$) and cytoskeleton damage ($P = 0.003$), but not to outcome. Galactosemia should be suspected in any child with liver, neurologic disease and/or immunodeficiency. Its complications are potentially preventable. Early detection is mandatory to

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prevent serious morbidity and mortality. Initiation of neonatal screening for galactosemia in Egypt is recommended.

Introduction

Classic galactosemia results from deficiency of galactose-1-phosphate uridylyltransferase (GALT) activity, while partial enzymatic impairment results in the more common clinical variant, Duarte galactosemia [1]. Deficiency of GALT results in accumulation of galactose, production of galactitol, defective galactosylation and glycosylation [2]. If undiagnosed and untreated this metabolic derangement causes progressive morbidities that compromise quality of life and threatens it. The derangement varies from jaundice, liver cell failure, sepsis, minor neurologic mental and motor derangements to severe handicapping, renal tubular dysfunction, ovarian dysfunction, cataracts and death [3–6]. Prompt diagnosis is essential to institute galactose-restricted diet to halt March of galactosemia. While compliance to galactose restricted diet does not promise cure, it is the treatment that reduces acute, short and long-term morbidity and mortality significantly. Galactosemia complications are potentially preventable [7–9]. Some countries provide neonatal screening programs to allow early detection and management of galactosemia [10,11]. The neonatal screening programs for galactosemia allowed early detection of the classic galactosemia, which is fatal, and the Duarte type. It allowed further identification of molecular defects in galactosemia. It allowed identification of classic galactosemia functional severe (G) mutations in each of GALT alleles, hence being referred to as "GG" galactosemia, and identification of the compound heterozygosity for one functionally severe (G) GALT mutation together with a D2 allele in the Duarte galactosemia [12]. Partial GALT deficiency clinical spectrum ranges from clinically silent to milder clinical spectrum with potentially problematic developmental deficits rather than life threatening complications [13].

In countries where newborn screening is not available, health system depend on the diagnosis made by neonatologists or clinicians at large. In Egypt screening for galactosemia is not included in neonatal screening program. This work aimed to define clinical presentation(s) of galactosemia that should raise clinicians high index of suspicion to diagnose galactosemia in communities in which neonatal screening programs are not feasible.

Patient and methods

Participants

This is an observational study that included a cohort of 37 infants and children who were followed up for 2-years during the period from 2015 to 2017 at the Pediatric Hepatology Clinic New Children Hospital, Cairo University, Egypt. *The trial was approved by Pediatric Department Committee for Post-Graduate Studies and Research, Faculty of Medicine, Cairo University, Egypt. Parents consented to trial.* Inclusion criteria: patients fulfilling the diagnosis of classic galactosemia confirmed by reduced erythrocyte galactose-1-phosphate uridylyltransferase (GALT) activity by C14 radioactive assay [14]. The reduction was reported as 0%, up to 10% and more than 10%, or reported as absent, reduced or not.

Methods

Analysis was performed of all data of recruited children, including history of age at onset of symptoms, age at presentation, presenting symptom, complications and/or associations of liver disease, neurologic disease, age of the patient at the time of the study, weight and height percentiles, and outcome. Anthropometric measures were plotted against Egyptian Percentiles for weight and height [15] and recorded as percentiles for age.

Outcome was graded into: resolved where the condition resolves without sequela, improved where the condition improves but did not resolve completely, stationary, progressive and death.

Statistical analysis

All the statistical analyses in this study were conducted using Statistical Package for Social Sciences version 15 (SPSS, Chicago, Ill). Simple frequency, cross-tabulation, descriptive analysis, tests of significance (t test for parametric data and Chi square χ^2 tests for nonparametric numbers N5), analysis of variance (ANOVA), and correlations were employed. Fisher's exact test (for categorical data with numbers less than 5) was employed in comparing presentations, biopsy findings, reducing substances in urine according to amount of GALT residual activity among the studied cohort with reduced GALT activity.

Results

The studied cohort comprised 37 infants with a male preponderance; 22 (59.4%) were males and 15 (40.6%) were females. Mean ± standard deviation (SD) of age at presentation was 447.8 ± 519.9 days as shown in Table 1. Galactose restricted diet was instituted within 2–8 days from presentation. Eight (21.6%) had a single presenting symptom and 2 (5.4%) were screened immediately after birth, as the older sister suffered from galactosemia, while others had multiple presenting symptoms (Fig. 1). Only one child with galactosemia presented by self-mutilation

Table 1
Descriptive data of studied cohort with galactosemia.

No = 37		Min	Max	Mean	SD
Age at onset of symptoms (days)[a]		1.00	1460	156.9	340
Age at presentation (days)[a]		18.00	1565	447.8	519.9
Age at final visit (days)		126.00	4380	1178.1	1012.4
Disease duration (days)		7.00	2735	596.7	834.3
Duration of follow up (days)		2.00	2821	737.5	835.9
		Frequency		Percent	
Gender	Male	22		59.4	
	Female	15		40.6	

[a] Apart from a child who presented at age of 5 years by portal vein thrombosis, portal hypertension and chronic liver disease.

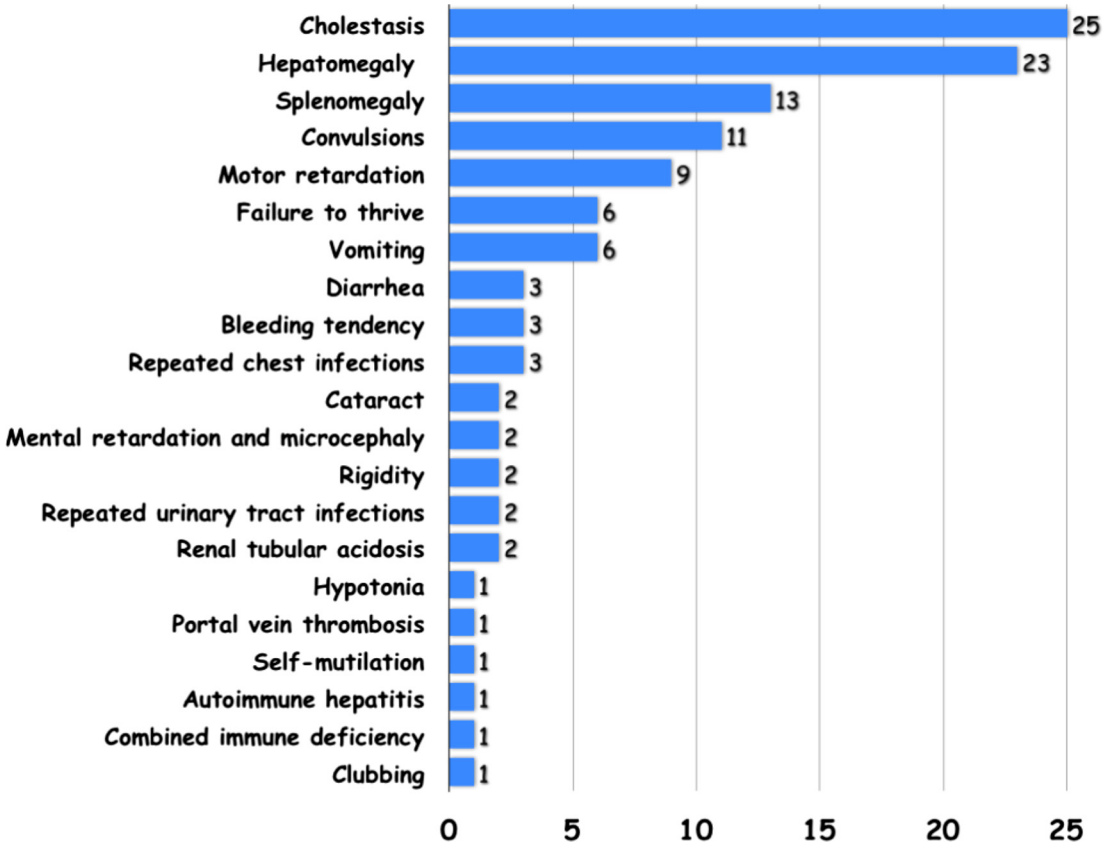

Fig. 1. Frequencies of presenting symptoms and signs of studied cohort with galactosemia.

and mental subnormality, he had normal uric acid level, and was not found to suffer from other causes of self-mutilation apart from galactosemia.

GALT enzyme activity was quantitative in 36 of the cohort, where 10 (43.2%) had 0–10% residual activity and 18 (48.6%) had more than 10% residual activity, while the 37th child had a semi quantitative GALT assessment. There was no significant association between residual GALT activity and type of symptom, sign or complication apart from repeated chest infections ($P = 0.001$) as shown in Table 2. There was no statistically significant association between age at onset, age at presentation with any symptom, sign or complication. 33 (89.2%) patients were investigated for reducing substance in urine as in Table 3. There was no statistically significant association between GALT residual activity and amount of reducing substance in urine or with outcome of neurologic or liver disease as illustrated in Tables 3–5. Nine children underwent liver biopsy as deemed indicated. Duration to diagnosis and longer duration of exposure to galactose in diet correlated with liver pathology severity i.e. hepatocyte necrosis (correlation coeffi cient = 0.997, $P = 0.003$) and cytoskeleton damage (correlation coef ficient = 0.997, $P = 0.003$), but not to outcome.

Outcome after institution of galactose restricted diet

One infant who presented by liver cell failure at one month of life had a complete remission on galactose-restricted diet. The other progressed to death. Among the 7 with portal hypertension, the portal hypertension was not reversible and only one child underwent liver transplantation, while the others had a stationary course. Among the 25 with cholestasis, only 8 resolved the cholestasis completely on galactose-restricted diet as in Table 5. Renal tubular acidosis was not reversible by galactose-restricted diet and was very challenging to control, as phosphorous doses tailored according to needs were difficult to tolerate by the affected children.

Cataract was removed surgically in one child and in the other it resolved completely initially but recurred after a duration of reluctance to compliance to galactose-restricted diet by age of 1 year, and is currently awaiting ophthalmologic intervention.

Among the 11 children who presented by epilepsy that was difficult to control, 4 had a stationary course and 5 were controlled on anti-epileptic medications of them 4 were weaned successfully off anti-epileptic medications. Those with delayed walking, achieved walking by 18–36 months of age.

Four (14.2%) children died; one child died from liver cell failure, two from pneumonia, and there was one unexplained death in a child suffering from poorly controlled epilepsy.

Discussion

Galactosemia associated morbidities and mortality are potentially preventable. Galactosemia results from deficiency of GALT, galactose epimerase and galactokinase. Accumulation of galactose and galactitol –the alcohol of galactose- are toxic to various tissues, including the liver, nervous system and kidneys [2]. While galactosemia morbidity and mortality is amenable to management by galactose-restricted diet, the chronic morbidity in classic galactosemia in not amenable to management by diet. The earlier the institution of galactose-restricted diet the better the prognosis, as children with galactosemia are challenged in their early days by life-threatening amounts of galactose, given that breast milk is rich in lactose that is a disaccharide composed of galactose and glucose [16].

Table 2
Clinical presentations of the study group according to % of reduction of GALT enzyme activity.

Total number of cases = 36[a]	Number		GALT			*P*
			0% n = 2	1–10% n = 16	>10% n = 18	
Weight (Percentile)	Mean ± SD		14 ± 15.5	47.8 ± 33	23.5 ± 24.9	0.056
Height (percentile)	Mean ± SD		14 ± 15.5	28 ± 26.7	15.3 ± 14.2	0.235
Age of symptoms onset[a]	Mean ± SD		0.5 ± 0.69	4.87 ± 10	9.98 ± 18.9	0.518
Age at presentation[a]	Mean ± SD		8.02 ± 7.04	15.1 ± 17.1	16.12 ± 19	0.830
Age at final visit[a]	Mean ± SD		64.4 ± 39.24	36.7 ± 28.86	40.7 ± 37.8	0.561
Disease duration[a]	Mean ± SD		63.9 ± 38.54	15.2 ± 19.7	17.8 ± 28.9	0.066
Duration of follow up[a]	Mean ± SD		59.4 ± 36.4	21.7 ± 23.9	24.6 ± 28.9	0.192
Vomiting	No	30	1	15	14	0.197
	Yes	6	1	1	4	
Diarrhea	No	33	1	15	17	0.09
	Yes	3	1	1	1	
Failure to thrive	No	31	1	14	16	0.313
	Yes	5	1	2	2	
Jaundice	No	12	1	6	5	0.732
	Yes	24	1	10	13	
Hepatomegaly	No	13	0	6	7	0.548
	Yes	23	2	10	11	
Splenomegaly	No	23	0	10	13	0.129
	Yes	13	2	6	5	
Bleeding tendency	No	33	2	14	17	0.695
	Yes	3	0	2	1	
Cataract	No	34	2	14	18	0.266
	Yes	2	0	2	0	
Liver cell failure	No	32	1	14	17	0.161
	Yes	4	1	2	1	
Convulsions	No	25	2	12	11	0.427
	Yes	11	0	4	7	
Post-kernicterus, mental retardation, microcephaly & rigidity	No	34	2	15	17	0.936
	Yes	2	0	1	1	
Delayed motor milestones	No	27	2	11	14	0.584
	Yes	9	0	5	4	
Hypotonia	No	34	2	15	17	0.936
	Yes	2	0	1	1	
Repeated chest infections	No	33	0	16	17	0.001
	Yes	3	2	0	1	

One child had semi-quantitative assessment of GALT, and was not included in this comparison.
[a] Ages are in months.

Table 3
Reducing substances in urine of the study group according to % of reduction of GALT enzyme activity.

Reducing substance in urine		GALT		Total	*P*
	0	1–10%	>10%		
None	0	1	1	2	0.703
Trace	0	0	2	2	
Positive	1	9	11	21	
Strong positive	1	4	1	6	
Very strong positive	0	1	1	2	
Total	2	11	13	24	

Galactose-restricted diet should be implemented as early as possible in children with galactosemia to prevent the early morbidity and mortality associated with early exposure to galactose in nursing milk –whether breast or artificial milk**.** The countries that developed neonatal screening programs for galactosemia secure prompt initiation of galactose-restricted diet [17], which has a remarkable acute effect in halting pathogenesis, and if instituted before symptoms appear it prevents the early neonatal mortality and morbidity that is known to occur during the first 8 days of life [18].

This work provides evidence that studies of prevalence and incidence of galactosemia in Egypt are mandatory, and inclusion of galactosemia in neonatal screening is urged. Egypt neonatal screening program does not include neonatal screening for galactosemia. Thus full-blown picture of galactosemia is still being encountered in Egypt. The study aimed to search for a "typical" clinical presentation to raise index of suspicion for prompt diagnosis of galactosemia in absence of neonatal screening program in Egypt.

The studied cohort exhibited serious complications of galactosemia, ranging from failure to thrive, motor development retardation, epilepsy, microcephaly, mental retardation, jaundice, hepatosplenomegaly, portal hypertension, autoimmune hepatitis, portal vein thrombosis, liver cell failure, cataract, renal tubular acidosis, self mutilation, and a severe form of combined immune deficiency that was investigated as severe combined immunodeficiency and death.

The studied cohort represent the "late presenters", as their age of onset of symptoms was about 6 months (mean ± SD = 156 days ± 340 days). No correlation was found between residual GALT activity and clinical picture.

This work studied clinical presentation spectrum of known cases of classic galactosemia and not incidence, as the studied

Table 4
Liver functions of the study group according to % of reduction of GALT enzyme activity.

	GALT 1–10% n=15	GALT >10% n=17	t	*P*
Initial ALT[a]	5.925 ± 14.119	3.633 ± 5.815	0.570	0.574
Follow up ALT[a]	1.658 ± 2.012	1.853 ± 2.577	−0.197	0.846
Final ALT[a]	1.234 ± 0.905	1.751 ± 2.487	−0.625	0.539
Initial AST[a]	11.020 ± 29.860	3.946 ± 5.073	0.906	0.374
Follow up AST[a]	2.552 ± 3.0322	2.756 ± 3.250	−0.174	0.879
Final AST[a]	1.751 ± 1.444	3.1001 ± 5.482	−0.755	0.458
Initial ALK[a]	1.049 ± 0.675	1.779 ± 1.487	−1.136	0.272
Follow up ALK[a]	1.805 ± 2.611	1.008 ± 0.541	0.992	0.334
Final ALK[a]	0.910 ± 0.891	0.678 ± 0.349	0.876	0.391
Initial GGT[a]	3.993 ± 5.998	1.623 ± 1.950	1.124	0.297
Follow up GGT[a]	1.832 ± 2.515	0.493 ± 0.460	1.273	0.225
Final GGT[a]	1.525 ± 1.954	1.003 ± 1.288	0.608	0.554
T. Bil initial	2.840 ± 1.851	3.969 ± 3.519	−0.918	0.369
T. Bil follow up	2.387 ± 2.289	4.890 ± 7.015	−0.964	0.350
T. Bil final	1.333 ± 1.549	4.200 ± 6.735	−1.245	0.227
D. Bil initial	2.236 ± 3.292	2.100 ± 2.404	0.906	0.374
D. Bil follow up	0.798 ± 1.195	1.930 ± 3.658	−0.891	0.384
D. Bil final	1.333 ± 3.478	2.221 ± 4.852	−0.475	0.640
Albumin initial	3.185 ± 2.918	2.958 ± 1.275	0.237	0.815
Albumin follow up	1.533 ± 2.484	2.211 ± 1.622	−0.556	0.590
Albumin final	2.725 ± 1.848	2.600 ± 1.794	0.118	0.908
Glucose initial	114.000 ± 8.482	85.000 ± 18.312	2.040	0.111
Glucose final	81.00 ±	78.142 ± 8.970	0.298	0.776

ALT: alanine aminotransferase.
AST: aspartate aminotransferase.
ALK: alkaline phosphatase.
GGT: gama glutamyl transferase.
T. Bil: total bilirubin.
D. Bil: direct bilirubin.
SD: Standard deviation.
[a] Calculated in folds of upper level of normal. *P* value was calculated according to *t*-test. Values are expressed as Mean ± standard deviation.

Table 5
Liver disease pathology and outcome of the study group according to % of reduction of GALT enzyme activity.

Outcome		GALT			Total	*P*
		0	1–10%	>10%		
Hepatocytes in biopsy	Ballooning degeneration	0	1	4	5	0.405
	Necrosis	0	2	2	4	
Cytoskeleton in biopsy	Normal	0	1	5	6	0.226
	Fibrosis	0	2	1	3	
Abnormal cells in biopsy	None	0	0	1	1	0.268
	Infiltration	0	1	4	5	
	Piecemeal necrosis	0	2	1	3	
Total number of biopsies			3	6	9	
Jaundice and liver condition	Resolved	2	4	2	8	0.347
	Improved	0	6	9	15	
	Stationary	0	4	4	8	
	Progressive	0	1	2	3	
Total		2	15	17	34	
Neurological	No impairment	2	12	12	26	0.782
	Improved	0	3	3	6	
	Stationary disease	0	1	3	4	
Total		2	16	18	36	

The child with jaundice who had semi-quantitative assessment of GALT resolved the jaundice. Biopsy was performed in only 9 children as indicated by clinical condition.

cohort was recruited from only those presenting to Cairo University Children Hospitals. Data about spectrum of presentations of "early" presenters is lacking, as the study was not structured to screen for incidence or prevalence, and Egyptian literature that describe the contribution of galactosemia in early neonatal period mortality is also lacking. The limited number of studies that report incidence of galactosemia in Egypt, reported an incidence that ranged from 1:1794 to 1:3000 [19–21]. The current study demonstrated that GALT residual activity is not a determining factor of clinical phenotype of children with untreated galactosemia. Moreover, it is neither possible to define the attributes responsible for development of liver disease or development of nervous system disease or overlap presentation, nor to determine attributes for timing of onset of disease.

The studied cohort had a late mean age at onset of symptoms and presentation, they might represent the survivors, or "late" presenters, or that complications develop around this age in Egyptian population. It is suspected that detectable residual activity even if scarce could explain why the studied cohort survived the early neonatal period, and did not suffer early demise, i.e. may be an attribute that protects against early death. Yet this assumption needs a bigger sample size for verification.

Incidence and prevalence studies of galactosemia in Egypt will provide answers to questions, pave way for cost-effectiveness

studies, and aid in decision making for inclusion of galactosemia in neonatal screening program.

Until then it is important to note that incremental cost effectiveness studies in different countries varied, and justified neonatal screening programs for galactosemia [10,17,22,23] with the exception of United Kingdom that stopped its galactosemia newborn screening program. One of the arguments that lead to this decision was the low incidence of galactosemia among their population 1:44000 [24–25].

The current work supports that established morbidities of galactosemia are not reversible but are amenable to improvement or control when galactose restricted diet is initiated. Yet, it is quoted that "without treatment, mortality in infants with galactosemia is about 75%" [6]. Despite the lack of a flawless completely curative treatment, galactose-restricted diet reduces morbidity and mortality [26].

The numbers or incidence of early deaths due to galactosemia in Egypt are not known, yet the currently studied cohort of neonates and infants with galactosemia had a later age at onset and later age at presentation. Early restriction of galactose from diet improves mortality and trades sepsis, liver cell failure, epilepsy and renal tubular acidosis with possibility of delayed puberty, ataxia, intention tremor, microcephaly, declined intelligence and other neurologic abnormalities in some children [26].

Neonatal screening for galactosemia is one step for a better outcome of galactosemia. As adherence to galactose-restricted diet needs legislative steps to secure documentation of information about galactose content of foods and food products and needs compliance from community, to allow affected subjects the information that is necessary for their meal planning. Family counseling for families with index cases and genetic testing for future pregnancies are other valuable tools.

Residual GALT activity does not protect against complications of untreated- galactosemia. The current work supports that GALT residual activity is not a determining factor of outcome of children with galactosemia challenged by galactose in diet. The age dependent endogenous galactose, galactose 1 phosphate formation and galactitol might be an explanation [27–30]. Moreover, the currently studied cohort does not represent the whole spectrum of disease [31], as the study assessed the clinical spectrum in known cases with galactosemia only. Effect of amount of galactose exposure i.e. ingested galactose on phenotype awaits further delineation. Again the cohort small size did not allow further stratification according to amount of activity and not range of activity (>10%) and sound statistical analysis. More insight is needed to define clinical spectrum of Duarte galactosemia in Egyptian children and factors affecting the phenotype and need for galactose- restriction in those with residual activity.

Cataract is not a common presentation of galactosemia. Self-mutilation is a rare presentation of Galactosemia. Classic galactosemia phenotypic presentation is diverse, involving a system or more including central nervous system, hepatic, renal and immune system. Cataract was not a common presentation among the studied cohort with galactosemia as only 5.4% of the studied cohort had cataract. Self-mutilation is a presentation of galactosemia, thus galactosemia should be suspected in any child presenting by any neurologic symptom or sign including self-mutilation.

Gene mutation analysis of galactosemia and its specific phenotype in the studied cohort awaits further research. While the analysis of gene mutations was out of scope of the current study, it is of paramount value to study type of mutations in Egyptian children with galactosemia. The mutation-phenotype is different ethnic groups [32–37], and the functional correction of gene defect is currently studied. The specific gene mutation analysis and functional correction expands the management opportunities of galactosemia from galactose restriction to gene therapy [38].

Conclusions

Neonatal screening programs for galactosemia are necessary to allow prompt early diagnosis, thus prevent the serious morbidity, mortality and improve health related quality of life associated with galactosemia but not the chronic morbidities. Early detection of index cases allows best achievable quality of life. [25] The lack of specific clinical picture and irreversibility of damage inflicted by galactose and galactitol stand as a very strong argument in favor of neonatal screening programs for galactosemia. Yet, incidence of galactosemia in Egypt should be studied initially, to allow for projection of anticipated cost effectiveness in planning neonatal screening for galactosemia in Egypt.

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Conflict of Interest

The authors have declared no conflict of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jare.2018.02.001.

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