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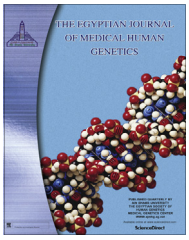

ORIGINAL ARTICLE

Demographic and clinical features of glutaric acidemia type 1; a high frequency among isolates in Upper Egypt

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KEYWORDS

Glutaric acidemia type 1;
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Abstract *Objective:* Glutaric acidemia type 1 (GA1) was thought to be a rare disorder in Arab countries. Recently, a relatively large number of patients with GA1 have been detected in Egypt. The aim of this work was to: (1) find out the commonest clinical characteristics of the disease among Egyptians presenting with GA1; (2) delineate the demographic factors that may lead to a high prevalence of GA1 among Egyptians; (3) Recommend the most suitable strategy to screen for the disease.

Patients and methods: The study included all patients with GA1 who presented at The Genetics Unit, Ain Shams University Hospital (GUASH) during the last three years. The information about patients with GA1 including the epidemiological and clinical data was obtained retrospectively from patients' files.

Results: The authors surveyed data of 26 patients in 23 families who were personally examined and the diagnosis was confirmed by laboratory data. The mean age of onset of symptoms was 5.8 ± 2.2 months: the mean delay in establishing the diagnosis was 11.73 ± 13.97 months. At the onset of symptoms, macrocephaly (85%) was the commonest feature of GAI followed by dystonia (69%), and persistent convulsions (50%). Onset of symptoms occurred during an acute febrile illness in 68% of patients, which was associated with the worst forms of dystonia (X2 = 12.5, $p = 0.14$). The frequency of affected Christian families among all affected families was 43%, which

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is significantly higher than that expected of the Christian minority in Egypt (6–15%). There has been no significant increase in consanguinity among those Christian families ($F = 0.014204$) pointing to a high gene frequency of GA1 in isolated areas in Upper Egypt.

Recommendation: In the absence of mass newborn screening program, continuous Health Education program should be implemented to promote detection of early signs of GA1 such as macrocephaly before the occurrence of acute crisis of encephalopathy especially in families with history of similar patients. We recommend that a nationwide program of extended tandem mass screening should cover all newborns in Egypt to promote early detection of patients with GA1 and to avoid the severe consequences of the delay in diagnosis.

1. Introduction

Glutaric acidemia type 1 (GA1) is an inherited metabolic disorder caused by deficiency of glutaryl-CoA dehydrogenase, which is involved in the degradative metabolism of L-lysine, L-hydroxylysine and L-tryptophan [1]. The defect gives rise to elevated glutaric acid, 3-hydroxyglutaric acid, glutaconic acid, and glutarylcarnitine which can be detected by gas chromatography/mass spectrometry (organic acids) or tandem mass spectrometry (acylcarnitines) [2]. Based on the urinary excretion of metabolites, GA1 patients are classified into high and low excretor groups. The low excretor patients are more difficult to diagnose despite having the same clinical picture and prognosis of high excretor patients.

Untreated patients have dystonia during infancy resulting in a high morbidity and mortality. This is associated with striatal injury, which results from encephalopathic crises precipitated by infectious diseases, immunizations and surgery during a finite period of brain development [3]. In 10% of patients the disease may also occur insidiously without clinically aarent crises [4].

GA1 is generally a rare disorder with an estimated prevalence around 1 in 100,000 newborns [5]. However, some communities have a high prevalence such as the Amish Community [6], Canadian Oji-Cree natives [7] and the Irish travelers [8].

Few patients with GA1 have been reported in Arab countries; These include six Arab families in Israel and West bank [9] and sporadic patients in Kuwait, Oman and Arab Emirates [10,11].

In Egypt, Selim et al. reported one patient with GA1 during screening of 800 clinically suspected patients with neurometabolic disorders [12]. Three other patients have been reported in screening of 170 patients referred for GC–MS of urine due to a suspected metabolic disorder [13]. A larger number of patients with GA1 have been diagnosed by Genetics Unit Ain Shams University Hospital (GUASH) in the last three years.

The aim of this work was to: (1) find out the commonest clinical characteristics of the disease among Egyptians presenting with GA1; (2) delineate the demographic factors that may lead to a high prevalence of GA1 among Egyptians; (3) Recommend the most suitable strategy to screen for the disease.

2. Patients and methods

The study included all patients with glutaric acidemia type 1 who presented at GUASH during the last three years (2010–2012). GUASH is the center recognized by the Ministry of Health in Egypt for management of patients with metabolic disorders. Patients included in this study comprise a representative sample of patients with GA1 in Egypt as they are referred from all over Egypt to GUASH at Ain Shams University in Cairo. The work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human after approval of the ethics committee of Ain Shams University and approval of the parents of the patients.

All patients have been personally examined at the GUASH metabolic clinic. The diagnosis was confirmed by elevated level of C5-DC carnitine in blood using LC MS/MS and/or elevated 3-hydroxyglutaric acid in urine.

The epidemiological and clinical data were obtained retrospectively from patient's files. This included family history, origin, religion and consanguinity of parents. The clinical history was reviewed with emphasis on the age of onset, the presenting symptoms and signs, duration of illness before referral to our hospital.

A statistical study of the relation between the commonest clinical findings and the laboratory profile of patients at presentation was done using SPSS program using Pearson Chi square test and Kruskal–Wallis for association study and Wilcoxon Rank Sum to study the correlation between the clinical findings and the level of C5-DC in blood [14].

3. Results

Twenty six patients from 23 families were included in this study. There were 9 families (39.1%) in which multiple siblings were affected, of which 3 were included in this study. The remaining 6 siblings were deceased and not included in this analysis.

The mean age of patients was 41.85 months ± 15.5. Sixteen of the 26 patients were males. The mean age of onset of the disease was 5.8 ± 2.2 months. The delay between onset of symptoms and establishing the diagnosis varied from one month to 12 years (Fig. 1). The mean time needed to establish the diagnosis of GA1 was 11.73 months ± 13.97.

Twenty two patients (84.6%) had macrocephaly including a single patient who received treatment following newborn screening of siblings of patients (Table 1). He has no other symptoms or signs of the disease till the age of 9 months (at the time of preparing this study). The next commonest clinical feature was severe dystonia (69%). Rapid deterioration within few days of onset of the disease (acute onset of the disease) occurred in 68% of patients; the associated intercurrent infection and persistent convulsions occurred in half of patients.

The level of C5-DC varied in patients from 0.36 to 6.4 μmol/L with a mean of 1.97 ± 0.84 μmol/L (normal value ⩽ 0.34 μmol/L). GC-MS of urine showed a high level

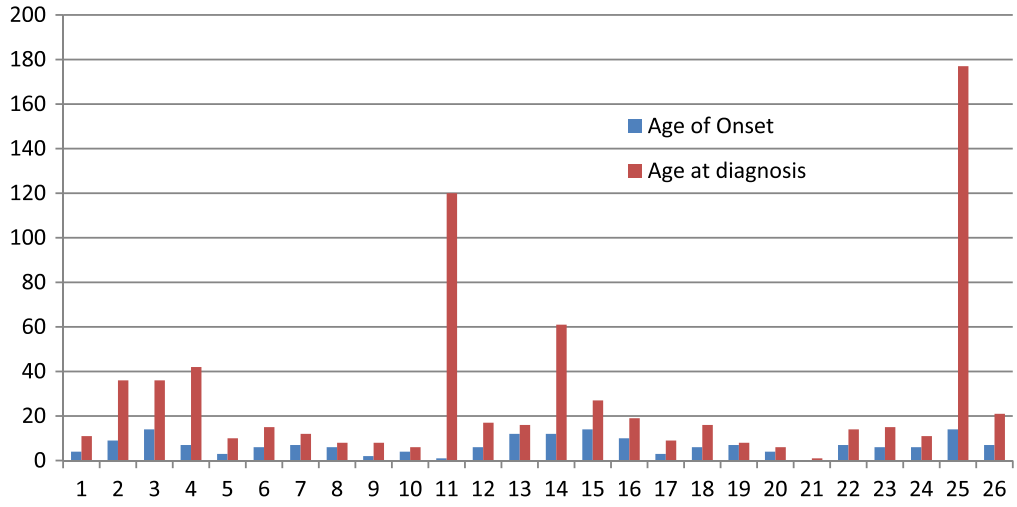

Figure 1 Distribution of the age of onset and age at diagnosis of patients showing a marked delay in the diagnosis of cases with GAI in Egypt.

Table 1 Summary of main clinical features in patients with GA1.

Case No.	Age of onset[a] (months)	Acute onset	Associated intercurrent infection	Macrocephaly (>95th centile)	Persistent convulsions	Severe dystonia	3-OH glutaric in urine	C5-DC μMol/L
1.	4	–	–	+	–	–	+ + +	1.91
2.	9	+	+	+	+	+	+ + +	1.42
3.	14	+	+	+	+	+	+ + +	NA[b]
4.	7	–	–	+	–	–	+ + +	1.45
5.	1	–	–	+	–	–	+ + +	1.57
6.	6	+	+	+	+	–	+	0.5
7.	7	+	–	+	–	+	+ + +	1.34
8.	7	–	–	+	–	+	+ + +	NA
9.	2	+	–	+	+	–	+ + +	NA
10.	4	+	+	+	+	+	+ + +	0.62
11.	2	–	–	+	+	+	+ + +	0.76
12.	6	+	+	+	+	+	+ + +	0.36
13.	2	+	+	+	+	–	+ + +	1.38
14.	2	+	+	+	–	+	+ + +	0.37
15.	14	+	+	–	–	+	+ + +	NA
16.	10	+	+	+	–	+	+ + +	6.4
17.	3	+	+	+	+	+	+ + +	4.48
18.	1	–	–	–	–	+	+ + +	5.5
19.	7	+	–	–	–	+	+ + +	0.9
20.	4	–	–	+	–	+	+ + +	2.49
21.	0[c]	N/A	N/A	+	–	–	+ + +	2.7
22.	7	+	+	+	+	+	+ + +	3.05
23.	6	+	–	–	–	–	+ + +	NA
24.	6	+	+	+	+	+	+ + +	0.43
25.	14	+	+	+	+	+	+ + +	3.42
26.	7	–	–	+	+	+	+ + +	0.4
	5.8 ± 2.2[d]	17(68%)	13 (52%)	22(84.6%)	13(50%)	18(69%)	26(100%)	1.97 ± 0.84[d]

[a] The age at which the clinical features of the disease were first reported by parents.
[b] N/A = Not Available.
[c] Patient was diagnosed during screening of sibs of affected cases.
[d] Mean and range with 95% statistical confidence.

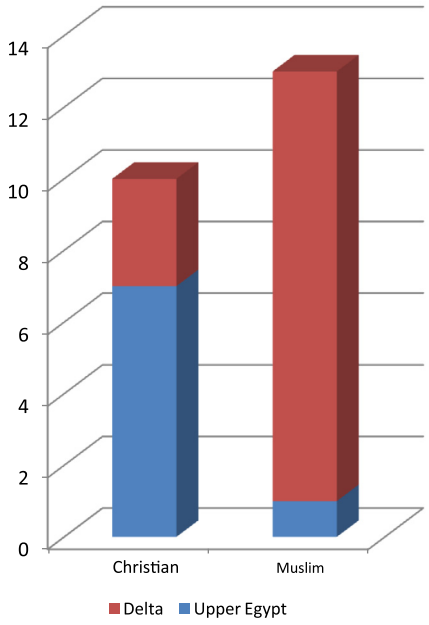

Figure 2 Distribution of cases in delta and Upper Egypt.

of 3-hydroxy glutaric acid in urine in all 26 patients. However, it was mildly elevated in one patient that was reported as a low excretor GA1 (Table 1).

Pearson Chi-Square test for the association of the mode of onset with different clinical features, showed no significant association with macrocephaly or convulsions. On the other hand, there was a significant association between associated intercurrent infection and the occurrence of severe dystonia ($X2 = 12.5$ $p = 0.14$).

The Kruskall Wallis test showed non-significant difference between all categories of onset as regards the level of C5-DC carnitine in blood. Wilcoxon Rank Sum test also showed no significant correlation between the level of C5-DC carnitine and the occurrence of macrocephaly, acute febrile onset, severe dystonia or convulsions.

Ten families out of total 23 families were Christians; most of those families came from Upper Egypt (7/10) around the area of Asyut Governorate. In contrast, 12 of the remaining 13 Muslim families were from the Delta region of the Nile (Fig. 2).

Fourteen families showed variable degrees of consanguinity with a total coefficient of inbreeding 0.027174 ± 0.01220998 in the whole sample. This is significantly higher than the coefficient of inbreeding among Egyptians which is as high as 0.01010 [15]. The high coefficient of inbreeding was mainly due to consanguinity in Muslim families (0.3125); On the contrary, the coefficient of inbreeding (0.014204) among Christian families was not significantly different from that of the coefficient of inbreeding among Egyptians.

4. Discussion

Following the establishment of a centralized facility for the management of metabolic disorders at GUASH, a relatively large number of patients with GA1 have been referred from all over Egypt. This raised questions about the possibility of a high prevalence of GA1 among Egyptians, the commonest clinical features in those patients, and the most suitable method for early diagnosis of the disease.

The study showed that the diagnosis of GA1 has been delayed in most patients despite the clear clinical history of the metabolic disorder, presence of consanguinity and a positive family history in one third of the families. Patients 4 and 11 were salient examples of unjustified delay in diagnosis: Patient 4 was only diagnosed, at the age of 40 months, after having another affected sib despite history of consanguinity and similar affected cousin; the diagnosis of patient 11 was made at the age of 10 years despite clear history of severe dystonia and a stroke like attack following acute febrile illness and a similar affected sib and uncle. This shows the urgent need to train health workers to detect alarming signs of the metabolic disorder especially in the presence of consanguinity and a family history suggestive of the GA1.

The only significant predictive parameter in this study for the prognosis was the association between the occurrence of severe dystonia and the acute onset of the disease associated with intercurrent infection. A similar finding was reported by Strauss and coworkers who found that stroke like attack with abrupt puatminal necrosis is the most distinctive and crippling manifestation in GA1, and the major determinant of morbidity and mortality [16]. Several studies also showed that morbidity and mortality are high in patients who have had acute encephalopathic crisis precipitated by Intercurrent febrile illness, immunization, or surgical intervention [3,17]. Other clinical and laboratory parameters, that were studied in this work, did not have a significant effect on the prognosis of the disease including the level of C5-DC in blood and 3-hydroxyglutaric acid in urine.

The geographic distribution of patients did not show a significant variation between regions of Egypt that referred GA1 patients to our clinic. However, a significant variation in the geographic distribution was detected when the religion of the families was considered; most of the Christian patients were from Upper Egypt (six out of 10 families) while the Muslim families were distributed in Cairo and Delta region (12 out of 13 families).

The overall frequency of affected Christian families was 43%, which is significantly higher than the expected for the proportion of the Christian minority in Egypt (6–15%) [18,19] (Fig. 3).

The significantly high coefficient of in breeding in the whole sample shows that consanguinity played a major role in the occurrence of GA1 in Egypt in the Delta region where 65% of affected families were consanguineous. Health education against the traditional first cousin marriage and screening of newborns of consanguineous couples are recommended

On the contrary, the consanguinity rate among Christian families was not significantly different from that in the general population [20]. In addition, the coefficient of inbreeding was far less than that among Muslim families with GA1. These observations point to the possibility of a genetic drift that led to the widespread of carriers among small Christian isolates in Upper Egypt (villages in Upper Egypt that developed through inbreeding of Christian families living in the same village); however, consanguinity was not a prerequisite for the occurrence of disease in such isolated areas.

In the absence of a national screening program, selective screening is recommended in such populations [3]. This should cover several provinces in Upper Egypt to detect patients with

Figure 3 The distribution of Muslim (red) and Christian (yellow) families with ga1 in Egypt generated by Epi-info program [23].

GA1 before the occurrence of symptoms to prevent the deleterious neurologic complications in the endemic area.

Measuring the level of 3-hydroxyglutaric acid in urine using GC/MS was diagnostic in all cases. However, GC/MS study of urine is difficult to apply as a screening procedure. This is due to the difficulty of sampling and the lengthy procedure that requires special laboratories that are not available in Egypt.

Out of 26 patients with GA1, only one patient had a low excretory GA1 profile in urine; but, the level of C5DC was still high in blood in that case. Thus, Tandem mass screening for C5DC should be the most suitable method to screen newborns for GAI in Egypt; the possibility of false negative cases will be low compared to populations with a high incidence of low excretory phenotype. The latter require DNA screening for prevalent mutations to avoid false negative results [21]. A major advantage of tandem mass screening is that several other metabolic disorders are detectable using the same sample with high throughput machines that are readily available in several laboratories in Egypt. The same blood sample that is collected in the national screening program for hypothyroidism may be used without any added cost for sampling [22].

Until such a screening program is applied in Egypt, all efforts should be directed to raising the level of awareness of physicians to the alarming features that are commonly associated with GA1 such as macrocephaly, acute onset of neurological signs with our without intercurrent infection and dystonia. Physicians should give more time to recording of family history of consanguinity and occurrence of similar cases; it is unacceptable to diagnose two or three sibs as having encephalitis without ordering a metabolic workup. Primary care physicians should immediately refer suspected patients to tertiary care center that has access to diagnostic procedures such as MS/MS and GC/MS.

Recommendation: The study shows that extended tandem mass screening for IEMs should cover all newborns in Egypt to prevent the severe consequences of the delay in diagnosis; this is especially important in Upper Egypt and isolated rural areas where founder effect and consanguinity may lead to high prevalence of IEMs. In addition molecular study is required to characterize the prevalent mutations. This will pave the way to premarital and prenatal screening of couples in endemic areas. Until screening programs are available, every effort should be directed to educating physicians in demoted areas to pick up early signs of the disease such as macrocephaly. This will prevent deterioration of patients and pave the way for early detection in sibs of affected cases.

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