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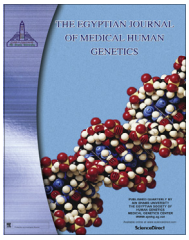

ORIGINAL ARTICLE

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

Osama K. Zaki [a,*], Heba Salah Elabd [b], Shaimaa Gad Ragheb [b], Dina A. Ghoraba [a], Ahmed Essam Elghawaby [a]

[a] *Ain Shams University Hospital, College of Medicine, Cairo, Egypt*
[b] *College of Medicine, Ain Shams University, Cairo, Egypt*

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KEYWORDS

Glutaric acidemia type 1;
Inborn errors of metabolism;
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Genetics;
Consanguinity;
Newborn screening

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

* Corresponding author. Address: Ain Shams University Hospitals, 3 Kamal Raslan St., Heliopolis, Cairo 11771, Egypt. Tel.: +20 1005188879; fax: +20 226824170.
E-mail addresses: ozaki@medical-genetics.net, okzaki@gmail.com (O.K. Zaki).

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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