

# Long-term follow-up and sudden unexpected death in Gaucher disease type 3 in Egypt

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## ABSTRACT

**Objective:** To describe the long-term follow-up and distinct phenotype of a large cohort of patients with Gaucher disease type 3 on enzyme replacement therapy (ERT) in Egypt.

**Methods:** A prospective cohort study of 78 patients on ERT who were followed for up to 9 years with yearly evaluations that included EEG and cognitive testing.

**Results:** Of the patients, 73% were homozygous for the L444P *GBA1* mutation; all but 7 were neurologically symptomatic. Supranuclear gaze palsy with variable but stable cognitive function was present in 91% of patients. Convergent strabismus and bulbar dysfunction were noted in 22% and 37%, respectively. Features of oppositional defiant disorder were present in 54% of patients. Twenty-three patients (30%) developed seizures while on ERT for 1–9 years. Of those, 12 patients (15%) died suddenly and unexpectedly at a mean age of  $6.7 \pm 5.0$  years (range 1.5–18). Sudden death was usually associated with a seizure disorder or a terminal seizure, but 7 of 12 patients had a preceding normal EEG. An additional 11% had background slowing or epileptogenic activity on EEG without clinical seizures. There were 3 familial cases of sudden unexpected death.

**Conclusions:** Despite having the most common *GBA1* genotype known to be associated with neuronopathic Gaucher disease, patients with Gaucher disease type 3 in Egypt have a phenotype and a clinical outcome on ERT that are very different from those observed in other populations. Identifying putative modifying genes of this ethnic group is likely to lead to better therapy for neuronopathic Gaucher disease generally. *Neurol Genet* 2016;2:e55; doi: 10.1212/NXG.0000000000000055

## GLOSSARY

ERT = enzyme replacement therapy; SUDEP = sudden unexpected death in epilepsy.

Gaucher disease is the most common autosomal recessive lysosomal storage disease and is caused by a deficiency of glucocerebrosidase due to pathogenic variants of the *GBA1* gene.<sup>1</sup> Gaucher disease type 1, the nonneuronopathic form, has an incidence of about 1 in 40,000–60,000 in the general population and 1 in 500–1,000 among Ashkenazi Jews.<sup>2</sup> Patients with Gaucher disease type 3 (also called chronic neuronopathic Gaucher disease) constitute about 5% of the population of patients with Gaucher disease in the United States and in Europe, with an estimated incidence of about 1:100,000.<sup>3</sup> However, recent reports suggest that this form of Gaucher disease predominates in countries such as China, Korea, and Egypt.<sup>4–8</sup> Gaucher disease type 3 presents most often with severe systemic disease and supranuclear gaze palsy and often with a cognitive deficit.<sup>9,10</sup> Rarely, these patients may present with myoclonus or seizures that are often associated with mild systemic disease.<sup>11</sup> Before the advent of enzyme replacement therapy (ERT), pulmonary infiltrates and esophageal varices associated with liver cirrhosis were common.<sup>9</sup> ERT has no reported direct effect on the neurologic aspects of the disease.<sup>3,10,12,13</sup>

Supplemental data  
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Therefore, long-term ERT allows for study of the intrinsic neurologic natural history of Gaucher disease type 3.

Here we describe the long-term follow-up of Gaucher disease in patients in Egypt who almost all have a single (and the most common) neuronopathic *GBA1* genotype.<sup>1</sup> We show that, for an unknown reason, their phenotype and clinical outcome are very different from those described in similar patients in other countries.

**METHODS** **Standard protocol approvals, registrations, and patient consents.** Patients were followed prospectively on the International Collaborative Gaucher Group Gaucher Registry, clinicaltrials.gov study number NCT00358943, and enrolled in the Neurological Outcomes Subregistry. All legal guardians of patients gave their written informed consent per protocol. In addition, all studies used standard of care for neuronopathic Gaucher disease.

All patients with Gaucher disease type 3 and neurologically asymptomatic patients with the L444P/L444P *GBA1* genotype (c.1448T>C) who were on ERT were included in this study. All patients were diagnosed by glucocerebrosidase deficiency followed by *GBA1* genotyping. Analysis for common mutations was performed by PCR followed by Sanger sequencing. Full sequencing of the *GBA* gene was performed as previously described.<sup>14,15</sup> In addition, for some patients, a strip hybridization-based assay for Gaucher disease was used for the detection of 8 commonly reported mutations in the *GBA* gene (c.84dupG (84GG), c.115+1G>A (IVS2+1G>A), c.1226A>G (p.N370S), c.1297G>T (p.V394L), c.1342G>C (p.D409H), c.1448T>C (p.L444P), c.1504C>T (p.R463C), and c.1604G>A (p.R496H)) and 2 recombinant alleles (RecNci-1 and RecTL) according to manufacturer's protocol (Vienna-lab Diagnostics, Vienna, Austria). However, *GBA1* genotyping was not performed in some patients (designated as unknown in tables e-1 and e-2 at Neurology.org/ng).

Neurologic evaluation included performing 21-channel standard EEG and IQ testing when the patient's overall health was sufficiently improved to permit meaningful measurement. Assessment varied according to age; Vineland Adaptive Behavioral Scale was used for children <4 years and Wechsler intelligence scales were used for preschool, school-age, and adult groups. Neurocognitive impairment is mild if IQ is 55–70, moderate if IQ is 35–55, and severe if IQ is <35.

ERT dose ranged from 20 to 60 IU/kg of body weight every 2 weeks. Some patients were given a trial of higher ERT doses when possible to better control their symptoms (table e-1).

**Statistical analysis.** Summary statistics for continuous and categorical variables are reported with mean ( $\pm$  SD) and percentages, respectively. Time-to-event analyses were conducted using Kaplan-Meier survival curves with Hall-Wellner 95% confidence intervals.

**RESULTS** **Patient description.** A total of 78 patients were followed over 1–9 years. Their mean  $\pm$  SD age when last examined was  $9.5 \pm 5.5$  years (range, 1.5–22.5). Twenty-three patients developed seizures (table e-1), 9 patients had EEG abnormalities without

clinical seizures (table e-1), and 46 patients had no EEG abnormality or seizures (table e-2).

***GBA1* genotype and phenotype.** Patients, their genotype, and clinical characteristics are presented in tables e-1 and e-2. In the group with seizures, all but 3 patients were L444P homozygous: 1 patient was D409H homozygous, and the mutations in the other 2 were unknown. In the group without seizures and with normal EEG, 2 patients with D409H/D409H had aortic root and valvular calcifications and regurgitation, whereas 1 patient (patient 6) had a newly observed anomaly consisting of ectatic proximal coronaries. These patients had increased reflectivity of the cornea and asymptomatic hydrocephalus. In the group with EEG abnormalities, 6 patients were L444P homozygous and 3 were unknown. Among those with no EEG abnormalities or seizures, 31 patients were L444P homozygous and the genotype in 9 was unknown. Eighty percent of all patients were homozygous for L444P. Virtually all patients had consanguineous parents. There was considerable intrafamilial heterogeneity, and siblings often had discordant neurologic and systemic disease severity (tables e-1 and e-2).

Seven patients, all in the normal EEG and no seizures group, had no neurologic abnormalities on clinical examination, including normal horizontal saccades. Six of them were homozygous for L444P and 1 was L444P/D409H; 3 patients had a splenectomy at a very early age. The other 71 patients all had supranuclear gaze palsy in isolation or in combination with variable developmental delay but often had improved motor skills over time. Patients with seizures (table e-1) had lower cognitive function than those with no seizures and normal EEG (table e-2). If one imputes an IQ of 100 to those with clearly normal cognitive function, the Full-Scale IQ of the former group was  $68 \pm 15$  and that of the latter group was  $85 \pm 13$  ( $p < 0.0001$ ). Our patients tended to remain cognitively stable over the years. Convergent strabismus was noted in 22% overall (11% without and 37% with seizures or EEG abnormalities). Bulbar dysfunction was reported in 37% overall (28% without and 50% with seizures or EEG abnormalities) (tables e-1 and e-2). Features of oppositional defiant disorder<sup>16</sup> were observed in 54% overall (48% without and 62% with EEG abnormalities). EEG abnormalities consisted of a persistent generalized slow and disorganized background, often seen in diffuse encephalopathies (table e-1). EEG abnormality was not always associated with clinical seizures; on the other hand, no epileptogenic activity was detected with surface EEG in some patients with seizures. Seizures were reported in about 30% of patients with Gaucher disease type 3 who were on ERT (table e-1), and their cumulative incidence is

presented in figure 1. Seizures were focal, focal with secondary generalization, or generalized at onset. Six patients had their first seizures just before sudden death. Patients with a chronic seizure disorder were treated with valproic acid at a dose of up to 60 mg/kg/day, with variable results (table e-1).

**Patient outcome.** Twelve patients died unexpectedly at a mean age of  $6.7 \pm 5.0$  years (range 1.5–18). The cumulative incidence of sudden death in patients with seizures, in those with seizures and EEG abnormalities, and in the overall study population is presented in figure 2. Most patients died after a seizure. Of note, 7 of the 12 patients who died suddenly had a preceding normal EEG (table e-1). Patients were followed for a total of 476 years, which is an incidence of sudden death of 25 per 1,000 patient-years in this population of patients with Gaucher disease. There was no clear relationship between sudden unexpected death and the severity of the systemic disease, ERT dose, or cognitive level. There were 3 cases in which sudden unexpected death occurred in 2 affected siblings in a family—patients 6 and 7; the identical twin and cousin of patient 21 died suddenly with seizures; and patient 22 and his sibling both died suddenly after seizure.

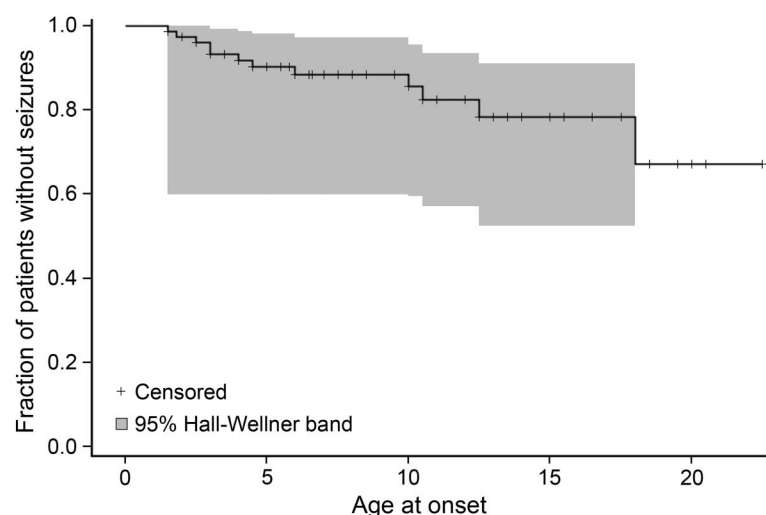
**DISCUSSION** Here we present a large and genetically homogeneous patient cohort with Gaucher disease type 3, most of whom (about 80%) had the common neuronopathic Gaucher genotype L444P/L444P. This cohort shows the entire clinical spectrum of this genotype—from normal neurologic phenotype to severe neurologic manifestations. We included only patients on ERT in this

study because general health and cognitive performance in patients with Gaucher disease type 3 are known to be influenced by the visceral disease.<sup>3,13</sup> Therefore, the neurologic outcome of patients with Gaucher disease type 3 on long-term ERT reflects only their intrinsic cerebral dysfunction. The phenotype observed in our patients consisted of marked behavioral abnormalities; common bulbar dysfunction (dysarthria, dysphagia, or stridor); epilepsy; and frequent sudden unexpected death, usually with epilepsy or an isolated seizure, in the face of stable cognitive function in most patients. Remarkably, their phenotype was more severe and different from that described for the same genotype in other countries.<sup>13,17–19</sup> It should be noted that 31% of patients in the study analyzing the Neurological Outcomes Subregistry of the International Collaborative Gaucher Group Gaucher Registry as of June 1, 2007, were from Egypt, but their phenotype was not specifically described.<sup>19</sup> Patients with Gaucher disease type 3 in China and Japan seem to have more severe neurologic disease than patients in Europe and the United States.<sup>6,7</sup> However, none of these studies have described sudden death, even in patients receiving long-term ERT. Behavioral problems have not been described in patients with Gaucher disease type 3. A 17-year-old Arab Israeli female patient with the L444P/L444P genotype developed epilepsy that devolved into myoclonic seizures and a more rapid cognitive decline.<sup>20</sup>

The causes of death of our patients are unknown, but in most cases death occurred shortly after an epileptic seizure. In these cases, sudden unexpected death in epilepsy (SUDEP) can be invoked.<sup>21,22</sup> The incidence of SUDEP in our study population is much higher than that described in various epilepsy populations (0.35–9.3 per 1,000 person-years).<sup>23,24</sup>

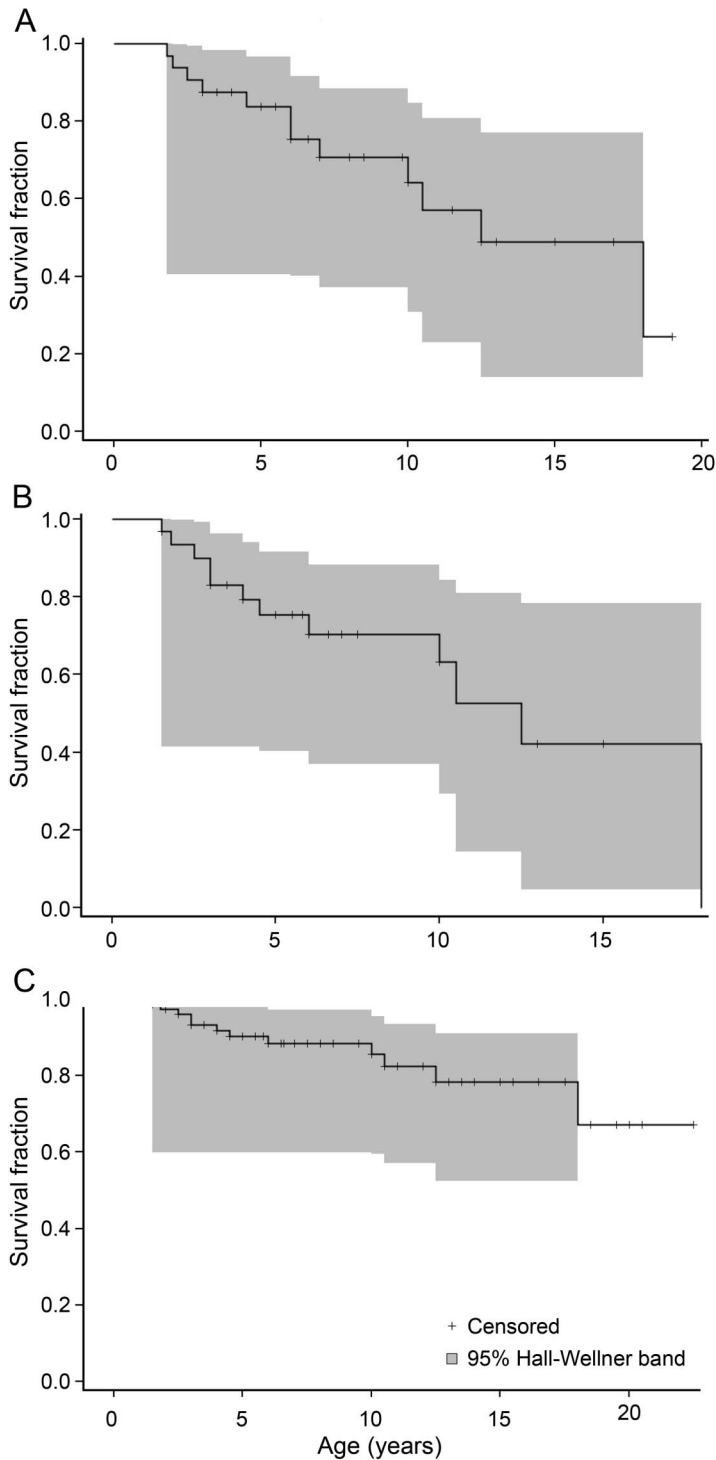
The epileptic seizures in many cases were phenotypically partial complex, with possible temporal lobe epileptogenic foci in some patients. Involvement of the temporal lobes in neuronopathic Gaucher disease is not surprising because a specific pattern of hippocampal neuropathologic abnormalities has been described.<sup>25</sup> Our data suggest that epilepsy in Gaucher disease type 3 is associated with a risk for sudden unexpected death, but a normal EEG does not preclude sudden death. In the general population, the incidence of SUDEP is inversely related to remission of epilepsy.<sup>23</sup> The lowest incidence of SUDEP is in patients with well-controlled epilepsy or patients in remission.<sup>26</sup> Therefore, seizure control is likely to be the most direct way of preventing SUDEP in this population of patients with Gaucher disease. It remains to be seen whether

**Figure 1** Cumulative incidence of seizures in 78 patients with Gaucher disease type 3 receiving enzyme replacement therapy



The shaded area represents the 95% confidence interval.

**Figure 2** Cumulative incidence of sudden death



Cumulative incidence of sudden death (A) in patients with seizures, (B) in those with seizures and EEG abnormalities, and (C) in the overall study population. The shaded area represents the 95% confidence interval.

prophylactic use of certain antiepileptic medications can decrease the likelihood of SUDEP in this patient population.

The reason for such a unique Gaucher disease type 3 phenotype, which includes behavioral abnormalities, frequent bulbar dysfunction, epilepsy, and

sudden unexpected death, in patients in Egypt is unknown. It is likely that modifier gene variants common in this population contribute to this phenotype. These may include ion channels that are directly or indirectly influenced by cellular levels of glucosylceramide.<sup>27</sup> Increased sensitivity of hippocampal neurons to glutamate-induced neurotoxicity has been described.<sup>28</sup> The higher the level of glucosylceramide in neurons, the greater the toxicity.<sup>28</sup> Therefore, certain glutamate receptors may play a role in the phenotypic expression of neuronopathic Gaucher disease. Defective calcium homeostasis mediated by overactivity of the ryanodine receptor that correlated with glucosylceramide levels was also described.<sup>29</sup> The ryanodine receptor is particularly expressed in the most affected hippocampal areas, CA2–CA4.<sup>25</sup> Therefore, this calcium receptor may also be a potential phenotype modulator in neuronopathic Gaucher disease. A yet-unidentified cardiovascular risk factor may be an important contributor to SUDEP in Egyptian patients with Gaucher disease type 3.<sup>30</sup>

The detailed clinical spectrum and long-term follow-up of Gaucher disease type 3 in Egypt presented here should be useful for the development and assessment of primary therapy for this disease and for identifying genetic modifiers. Such genetic variants may help identify the best antiepileptic medications or other medical interventions to either use or omit in this condition. It may also lead to using other disease-altering agents that are not currently under consideration.

#### AUTHOR CONTRIBUTIONS

M.A. recruited and studied the patients and gathered all data, interpreted and analyzed the data, and edited the manuscript. D.B. performed the statistical analysis and edited the manuscript. R.S. interpreted and analyzed the data and wrote the manuscript.

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#### DISCLOSURE

M.A. has received travel support and/or honoraria from Genzyme. D.B. reports no disclosures. R.S. has served on scientific advisory boards and received funding for travel and/or speaker honoraria from Protalix Biotherapeutics and Amicus Therapeutics; has applied for and/or holds patents for triheptanoin diet for adult polyglucosan body disease treatment, use of tetrahydrobiopterin as a marker and a therapeutic agent for Fabry disease, use of tetrahydrobiopterin as a marker and a therapeutic agent for Fabry disease (Europe), urinary triaolylceramide (gb3) as a marker of cardiac disease (Europe), and gene encoding a new TRP channel is mutated in mucopolipidosis; has consulted for Gerson Lehrman Group Councils Guidepoint Global; has served on speakers' bureaus for Genzyme Corporation; and has received research support from Protalix Biotherapeutics,



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