Patients with adult hexosaminidase A (Hex A) deficiency may have clinical manifestations similar to amyotrophic lateral sclerosis (ALS). Mutations in the hexosaminidase A (HEXA) gene are common in the Jewish Ashkenazi population in Israel. Serum samples of 115 Israeli patients with sporadic ALS were screened for enzymatic activity to detect “enzyme-based carriers.” Fifteen samples with low (< 50%) enzymatic activity were subjected to mutation analysis, which included the two common mutations in the HEXA gene among Ashkenazi Jews (+1278TATC and IVS12+1G→C). Three “enzymatic carrier” patients of Moroccan origin were checked for two additional mutations (ΔF304/305 and Arg170→Gln), specific to this ethnic group. Two “enzymatic carrier” patients of Iraqi origin were analyzed for the mutation Gly250→Ser, specific to the population. The mutation Gly 269→Ser was found in carriers of Ashkenazi origin only (n = 10). The only abnormalities found were heterozygous +1278TATC mutations in two Ashkenazi patients. Their clinical presentation was not different from that usually encountered in ALS. The frequency of mutations in the HEXA gene among Israeli ALS patients was not higher than in the healthy Israeli population. Therefore, Hex A deficiency seems to be a very unlikely cause of an ALS-mimic syndrome.

Hexosaminidase A (Hex A) is a lysosomal enzyme that participates in the degradation of the ganglioside GM2. Accumulation of this glycolipid, caused by deficiency of the enzyme, leads to degeneration of nerve cells and to a wide spectrum of neurological diseases.18 Hex A deficiency is inherited according to an autosomal recessive pattern. Total deficiency is responsible for a fatal infantile disorder, Tay-Sachs disease. Partial deficiency of enzyme activity is associated with a variety of early adult-onset neurological phenotypes, characterized by upper and lower motor neuron signs, cerebellar disturbances, parkinsonism, and psychosis or dementia in different combinations.7,17 Adult GM2 gangliosidosis is commonly mentioned in the differential diagnosis of amyotrophic lateral sclerosis (ALS), especially in “atypical” cases associated with other neurological disturbances, such as ataxia, stuttering, dementia, psychosis, or polyneuropathy.25 However, a literature survey revealed only four patients in whom the clinical picture was consistent with ALS1,8,11,26; in others additional neurological signs were present.6,14,17,24

Abbreviations: ALS, amyotrophic lateral sclerosis; Hex A, hexosaminidase A; PCR, polymerase chain reaction.
Key words: amyotrophic lateral sclerosis; gene mutations; GM2 gangliosidosis; hexosaminidase A; motor neuron disease.
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Mutations on the HEXA gene are quite rare. The frequency of carriers among Caucasians, as defined by enzyme assay, is 1:260. The frequency is highest among the Jewish Ashkenazi population in Israel and the United States, in which it is 1:270 and 1:30, respectively. Other Jewish ethnic groups with an elevated frequency of HEXA mutations include those of Moroccan (carrier rate 1:110) and Iraqi (1:140) origins, each manifesting specific mutations. In other Jewish ethnic groups, the frequency is 1:280.

Patients with adult-onset GM2 gangliosidosis in Israel are usually compound heterozygotes, bearing one of the two common Ashkenazi “infantile” mutations (+1278TATG or IVS12+1G→C) on one allele, while the second chromosome carries an “adult” mutation, e.g., Gly269→Ser. Among Moroccan Jews, the common mutations are ΔF304/305 and Arg 170→Gln; in Iraqi Jews, the common mutation is Gly250→Val.

In order to determine a possible relationship between ALS phenotype and HEXA mutations, and to determine whether an ALS-minic syndrome is a manifestation of adult-onset GM2 gangliosidosis, we have screened ALS patients for the most prevalent HEXA mutations among the Israeli population.

**Patients and Methods**

The study included 115 patients with sporadic ALS (64 males). Their mean age at onset was 53 years (±12 years; range 21 to 82). Most (n = 74) were of Ashkenazi origin, 15 were Moroccan, 12 Iraqi, and 4 Yemenite. The remaining 10 were of various other origins. Among these patients, 32 had a bulbar form at onset. All patients were diagnosed with definite or probable ALS using the revised El Escorial criteria. Other Jewish ethnic groups with an elevated frequency of HEXA mutations include those of Moroccan (carrier rate 1:110) and Iraqi (1:140) origins, each manifesting specific mutations. In other Jewish ethnic groups, the frequency is 1:280.

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The sera of all patients were analyzed for Hex A activity by a semiautomatic system (Technicon II autoanalyzer, Bran & Luebbe, Norderstedt, Germany) based on the different heat sensitivity of its isoenzymes, using two synthetic substrates: 4-methylumbelliferyl-N-acetyl-glucopyranoside (4-MUG; Glucosynth, Warrington, UK), and the Hex A-specific substrate 4-methylumbelliferyl-N-acetyl-glucopyranoside-sulfate (4-MUGS; Melford Laboratories, Ipswich, UK). Hex A activity was expressed as 4-MUGS/4-MUG ratio (in percent).

Patients who had low activity (<50%) were considered “enzyme-based carriers” (patients who may carry a mutated HEXA allele), and were subjected to mutation analysis. DNA was extracted from their leukocytes and amplified by polymerase chain reaction (PCR). All enzyme-based carriers were screened for the frequent Ashkenazi mutations (+1278TATC and G→C IVS 12+1). Moroccan Jewish patients (n = 3) were additionally screened for the ΔF304/305 and Arg 170→Gln mutations. The mutation Gly250→Val was sought in carriers of Iraqi origin (n = 2), as was the mutation Gly269→Ser in carriers of Ashkenazi origin (n = 10).

**Results**

Fifteen patients (13%) had a low enzyme activity (<50%). On average, this group of patients was not different from patients with normal Hex A activity regarding mean age at onset, form of disease at onset, or ethnic distribution (Table 1). The percent of males was higher in the group with normal Hex A activity than in those with low activity, but this difference was not statistically significant (P = 0.06, chi-square test). The mean duration of the disease to death or tracheostomy (calculated for patients who died or until tracheostomy was performed) was 33.9 ± 25.8 months for the group with normal Hex A activity and 33.9 ± 8.7 months for the group with low Hex A activity.

<table>
<thead>
<tr>
<th>Hex A activity</th>
<th>Normal</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (n = 100)‡</td>
<td>54</td>
<td>5</td>
</tr>
<tr>
<td>Bulbar onset (n)</td>
<td>24</td>
<td>3</td>
</tr>
<tr>
<td>Ashkenazi (n)</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
<td>Mean age at onset (years)</td>
<td>56 ± 12</td>
<td>61 ± 16</td>
</tr>
<tr>
<td>Mean duration of disease (months)‡</td>
<td>33.9 ± 25.8</td>
<td>33.9 ± 8.7</td>
</tr>
<tr>
<td>Mean Hex A activity in serum</td>
<td>61.7 ± 5.7</td>
<td>40.5 ± 6.4</td>
</tr>
</tbody>
</table>

*Values are given ± standard deviations. The two groups were not significantly different in gender distribution, disease form, ethnicity (chi-square test), age at disease onset, and disease duration (t-test).
† Calculated for patients who died or until tracheostomy was performed.
‡ Including two patients with mutations (see text).
The studied population included patients usually regarded as atypical and therefore suspected for ALS-mimic syndromes, as adult GM2 gangliosidosis: early onset (below age 30, \(n = 6\)) or long survival (more than 60 months, \(n = 19\)). These atypical features were not correlated to serum Hex A levels or the existence of mutations.

**DISCUSSION**

The frequency of HEXA mutations in our 115 Israeli ALS patients was found to be 1:58. Among the Ashkenazi ALS patients, the frequency was 1:42, which is somewhat less than expected in the Ashkenazi population in Israel.\(^{23}\) We were not able to detect any patient with a clinical diagnosis of ALS and an enzymatic or genotypic picture compatible with adult type GM2 gangliosidosis. Among cases described in the literature, the motor neuron dysfunction was usually accompanied by other neurological signs that are not common in ALS, thus facilitating the diagnosis. In only four cases was the clinical description compatible with ALS: a 39-year-old woman and 24-year-old man of Jewish Ashkenazi descent with a pure lower motor neuron syndrome\(^{8,11}\) and a non-Jewish 45-year-old woman\(^1\) and a 22-year-old Ashkenazi man with combined upper and lower motor neuron signs.\(^{26}\) All had a slow progression of neurological symptoms over many years.

If Hex A deficiency is indeed a potential cause of motor neuron syndromes, the high frequency of the gene in the Israeli population should cause the prevalence of ALS in Israel to be higher than elsewhere. In fact, however, the ALS frequency in Israel is not higher than that encountered worldwide.\(^{10}\)

Our study is in agreement with two others\(^{5,13}\) that failed to reveal significant Hex A deficiency among ALS patients. In one study,\(^5\) screening for carriers was done by determining Hex A activity in patients’ peripheral white blood cells. In the other,\(^{13}\) Hex A activity level was measured in the plasma, which is less accurate, and the study population was small (\(n = 17\)). We assessed an enriched subgroup of patients by screening directly for mutations, therefore alleviating pitfalls of enzymatic testing.

Other hereditary diseases have also been implicated in the differential diagnosis of ALS-mimic syndromes, including adult-type spinal muscular atrophy and spinobulbar muscular atrophy (Kennedy’s syndrome). Genetic testing for the corresponding gene showed, as in the present study, that such misdiagnoses of ALS are rare: among 54 sporadic and 10 familial ALS patients, mutations in the survival motor neuron gene or neuronal apoptosis inhibitory protein gene as found in spinal muscular atrophy were not detected.\(^{19}\) In another study involving 177 sporadic and 66 familial ALS patients, no survival motor neuron gene mutations were found.\(^{15}\) Conversely, in a study looking for misdiagnosis of spinobulbar muscular atrophy as ALS,\(^{20}\) among 147 sporadic and 100 familial male ALS patients, 5 (2%) showed the CAG repeat expansions in the androgen receptor gene that is diagnostic for spinobulbar muscular atrophy.

In conclusion, this study shows that in an ethnic group with a high frequency of mutations in the HEXA gene, ALS was not associated with Hex A deficiency, even if atypical cases were included and using accurate determination of mutations by genetic testing. Therefore, adult type Hex A deficiency is only rarely a potential cause for ALS-mimic syndromes. Screening for Hex A deficiency in motor neuron syndromes should thus be reserved for individual patients at particular risk, e.g., those with a protracted disease course, additional neurological signs, or a questionable family history of neurological disorders, and need not be performed routinely in each patient. Using these criteria, all cases of misdiagnosed Hex A deficiency published in the literature would have been identified.

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**REFERENCES**