X-linked recessive spina and bulbar muscular atrophy: clinical and molecular study of a large family

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Background: SBMA or Kennedy’s disease, is a disorder of the motor neurons characterized by the adult onset and slow progression of proximal muscle weakness and atrophy associated with fasciculations, tremor and muscle cramps. SBMA occurs only in males. Patients often show gynecomastia, testicular atrophy, and reduced fertility due to androgen insensitivity. All patients with SBMA have expansion of CAG trinucleotid repeats (>35 CAGs) in the androgen receptor (AR) gene.

Methods: In this study, DNA was extracted with standard method, then AR gene’s CAG region was amplified with PCR. PCR products were evaluated with agarose gel electrophoresis.

Results: The proband (patient 1) had expanded allele (with 50 CAG repeats), his son had normal allele (18 CAG). His daughters had one normal allele (20 CAG), one expanded allele (47 CAG) and one normal allele (18 CAG), one expanded allele (50 CAG), respectively. His sister had one normal allele (21 CAG) and one expanded allele (52 CAG), his father had normal alleles (21 CAG). Son of aunt of proband had 56 CAG repeats (patient 2). Other aunt’s sons had 25 and 56 CAG repeats (patient 3).

Conclusion: To our knowledge, this is the first report SBMA from Turkey and clinical findings were confirmed with molecular genetic diagnosis.

Key words: Spinal and bulbar muscular atrophy, clinical aspects, androgen receptor gene, CAG repeats


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individuals of a SBMA family together with their clinical and neurologic features.

Materials and Methods

Patients

**Patient 1:** A 47 year-old male wind instrument player. Approximately 20 years ago while he was playing his lips started to loose his instrument. 5 years later he got hand tremor, difficulties with swallowing and got tired easily. Those complaints increased in severity within 3-4 years. Then, when he is tired he could hardly talk, control his chin and whatever he eats comes out of his nose. His mother died at 62. His mother and father were not consanguineous. He has four sisters and two brothers. All his sisters and brothers are healthy.

**Patient 2:** A 36 year-old man, presented with weakness of legs at age 30. He feels pain at his leg and waist while climbing up and down on stairs. He has gynecomastia. He has difficulty in breathing while walking. He doesn’t have any difficulty with swallowing and producing sound. His mother died at 52. His mother and father were not consanguineous. Approximately 15 years before her death, she started having difficulty with walking and in the last couple of years she was unable to meet her daily needs. She also had difficulties with swallowing. He has one sister, who is 34 year-old and healthy.

**Patient 3:** A 41 year-old male farmer presented with difficulty in sitting and standing four months ago. A gynecomastia was observed at age 28. He had tremor in his hands and lips for ten years. His mother died at 65. His mother and father were not consanguineous. His two sisters and two brothers, were all healthy (Figure 1).

Methods

Genomic DNA was extracted from peripheral blood leukocytes by salting-out method and CAG repeat lengths were determined as described Young et al. Electromyographic recordings were done with Nihon Cohten Neuropac.

Results

Neurologic and genetic results

Neurologic symptoms and CAG repeat lengths of the patients are summarised in Table 1. EMG findings are given in Table 2.

**Patient 1:** Neurologic examination indicated fasciculations of the tongue, chin, deltoid, and quadriceps. There was muscular atrophy and weakness of the

### Table 1

<table>
<thead>
<tr>
<th>Patient no / Age</th>
<th>Age at onset of disease</th>
<th>No of CAG repeats</th>
<th>Symptoms at onset</th>
<th>Present symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/47</td>
<td>27</td>
<td>50</td>
<td>Facial weakness</td>
<td>Hand tremor, dysphagia, dysarthria, dysphonia, GM</td>
</tr>
<tr>
<td>2/36</td>
<td>30</td>
<td>56</td>
<td>Pain of legs, proximal weakness</td>
<td>Premature exhaustion GM</td>
</tr>
<tr>
<td>3/41</td>
<td>31</td>
<td>56</td>
<td>GM, tremor</td>
<td>Paralysis of the extremities</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Patient no / Age</th>
<th>SNAP</th>
<th>CMAP</th>
<th>SCV</th>
<th>MCV</th>
<th>DML of</th>
<th>Needle EMG finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/47</td>
<td>Normal</td>
<td>Normal</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Increase</td>
<td>Denervation</td>
</tr>
<tr>
<td>2/36</td>
<td>Normal</td>
<td>Normal</td>
<td>Decrease</td>
<td>N</td>
<td>Increase</td>
<td>Denervation</td>
</tr>
<tr>
<td>3/41</td>
<td>Normal</td>
<td>Normal</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>Denervation</td>
</tr>
</tbody>
</table>

SNAP: Sensory nerve action potential, CMAP: Compound muscle action potential, SCV: Sensory conduction velocity, MCV: Motor conduction velocity
tongue and facial, deltoid and quadriceps muscles. Tendon reflexes were hypoactive. Pharynx reflexes were hypoactive bilaterally. No ambiguous genitalia were noted, nor was sterility, as the patient has two daughters and one son.

We studied by PCR the length of the CAG repeat on genomic DNA from the patient and his family. The PCR products were analyzed on ethidium-stained agarose gels. The patient had a single band that was much larger (50 CAG repeat) in size than the control suggesting the expansion of the CAG repeat number. His son had normal allele while both of his daughters had normal and expanded alleles. His sister had one normal allele and one expanded allele. His father had normal allele. The remaining sisters and brothers did not consent to testing.

**Patient 2:** Neurologic examination indicated fasciculations of the masseter, chin, tongue and amyotrophy of upper limbs and tongue. Pharynx reflexes were normoactive bilaterally. There was muscular atrophy and weakness of the deltoid, bicep and iliopsoas muscles with hypoactive tendon reflexes.

The patient had 56 CAG repeats. His sister did not consent to testing.

**Patient 3:** Neurologic examination revealed fasciculations in the chin and the tongue. Uvula was in the middle and pharynx reflex could not be obtained on the right. There was muscular atrophy and weakness of the tongue and pectoral muscles. Tendon reflexes could not be obtained.

All of the patients sensory examination was normal.

The patient had an expanded allele with 56 CAG repeats, his brother had a normal repeat number. His sisters did not consent to testing (Figure 1).

**Discussion**

The AR gene permitted confirmation of the diagnosis of SBMA by showing the expanded number of CAG repeats within exon 1. In SBMA neurologic symptoms typically begin between the ages of 20 and 50. In our study, onset of neurologic symptoms in our patients began at ages 27 (Patient 1), 30 (Patient 2) and 31 (Patient 3). The clinical findings were similar to those reported by Kennedy et al. Almost 60-90% of the affected males shows gynecomastia. Our patients also had gynecomastia. Testicular atrophy, feminisation and infertility can be seen in 40%
of males. Our patients were fertile. Diabetes mellitus can be seen in 10-20% of SBMA males. Neither the patients nor any of their family members presented with diabetes.

Sperfeld et al have found sensory impairment in half of the 34 SBMA patients. All the patients showed abnormal somatosensory evoked potentials (SSEP). None of our patients showed any sign of sensory impairment. We saw slowing of sensory conduction velocity in 2 of our patients and normal sensory nerve action potential (SNAP) amplitude in all of them patients. Normal SNAP of our patients was compatible with their clinical findings. There are reports in the literature showing slowing of sensory conduction velocity and marked decrease of potential amplitude indicating axonal sensory neuropathy. Sural nerve biopsies consistent with axonal atrophy were also documented.

Mother of the patient 2 had walking and swallowing difficulties starting from 15 years before her death. This finding probably shows that mother had skewed X-inactivation. In X-linked recessive disorders, few female carriers become symptomatic. Recent evidence implicates skewed X-chromosome inactivation in such female carriers.

Disease diagnosis was confirmed by molecular studies. The increased size of the CAG repeats was demonstrated in three affected males and in three female carriers (Figure 1). After confirming the clinical diagnosis, the three carriers have been given proper genetic counselling about the disease and its inheritance.

CAG repeat expansions that cause disease in SBMA have the property of genetic instability, meaning that they often change length when transmitted from parent to offspring. Repeat instability with male transmission of the expanded allele has been described.

All daughters of affected males are obligate carriers. Each child of a carrier female has a 50% chance of inheriting the CAG repeat expansion mutation. To our knowledge the family studied by us is the first family with Kennedy’s disease reported from Turkey. Sons who inherit the AR CAG repeat expansion will be affected, while daughters are carriers.

In conclusion, molecular analysis of the CAG repeats in the AR gene is a valuable tool used for the diagnosis of patients and carriers of Kennedy’s disease. Furthermore, molecular studies are of particular importance for carrier diagnosis.

References