Phenotypes and mechanisms in myoclonus-dystonia

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Screening for dystonia genes *DYT1*, *11* and *16* in patients with writer’s cramp

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Abstract

Task-specific focal upper limb dystonia can be part of the phenotypic spectrum of different types of hereditary dystonia. We investigated whether writer’s cramp as presenting symptom is associated with mutations in DYT11, DYT16, or with the DYT1 GAG deletion in 43 patients. No DYT11 and DYT16 mutations were identified. One patient carried the GAG deletion in the DYT1 gene. In our cohort, writer’s cramp as presenting symptom is not associated with mutations in DYT11 or DYT16, but it can be the sole manifestation of DYT1 GAG deletion mutation carriers.
Introduction

Focal dystonias form a heterogeneous group of movement disorders characterised by abnormal postures, involuntary twisting, and repetitive movements involving a specific body part. Writer’s cramp is one of the task-specific focal dystonias. The pathophysiological mechanisms are largely unknown. Over the last years, several genes for inherited forms of dystonia have been identified and writer’s cramp can be part of their phenotype. It has been frequently described in patients with myoclonus-dystonia (M-D) carrying a mutation in the DYT11 gene (epsilon-sarcoglycan or SGCE). Up to now, 26 different families with genetically proven M-D have been described, and in 42% (55/130) of the affected members writer’s cramp was part of the phenotype. Another dystonia gene is DYT1 or TOR1A, where a 3-bp deletion causes limb-onset generalised primary dystonia, and incidentally task-specific focal dystonia as presenting symptom has been described (<3%). Recently, a new dystonia-associated gene, DYT16 (PRKRA), was described. Little is known about the phenotypic spectrum and frequency of DYT16 mutations. Mutations in this gene are associated with an autosomal recessive, generalised, young-onset form of dystonia and have been described in eight patients so far. One of these patients developed writer’s cramp and three patients developed dystonia involving the hands.

We examined 43 index patients who presented with writer’s cramp, and sequentially screened them for mutations in DYT11 and for the DYT1 3-bp deletion. Young-onset patients (≤30 years) were also examined for DYT16 mutations.

Methods

Patients. Forty-three index patients (95% Caucasian; 27 men, 16 women) with writer’s cramp were included in our study after obtaining informed consent. All patients were seen in our centre in a period of 18 months and examined and classified by a movement disorder specialist (JHTMK). The patients were classified in two categories: (1) simple writer’s cramp, in which dystonic posturing of the hand and arm occurs only during writing, and (2) complex or dystonic writer’s cramp, in which the dystonia also manifests during other manual tasks and is sometimes spontaneous.

Genotyping. DNA was isolated from white blood cells using standard procedures. All patients were screened for mutations in DYT11 (exon 1-12 except for exon 10, a rare splice variant) and for the 3-bp deletion in the DYT1 gene by sequencing (ABI big dye v3.1 chemistry, ABI 3730 capillary system, Applied Biosystems, Foster City, CA). In addition, we sequenced all exons of DYT16 in patients with young onset (≤30 years, seven patients).
Screening for copy number variations of *DYT11* was performed by multiplex ligation-dependent probe amplification (MLPA) using the commercially available probe set P099B (MRC Holland, Amsterdam, The Netherlands) according to the manufacturer’s instructions.

**Results**

Among the 43 patients, 14 had simple writer’s cramp and 29 a complex form (Table 1). The presence of mirror movements was observed in 14 patients. Mean age at onset was 39 years (±11 years, range 12-65) with seven patients having a young age of onset (≤30 years). Mean disease duration at time of examination was 12 years (±8 years, range 2-37). Twenty-three percent (10/43) of the patients had a positive family history for movement disorders: four patients had first or second degree relatives with writer’s cramp, two with cervical dystonia. In addition, four patients had family members with non-dystonic movement disorders (three with Parkinsonism and one with a tic disorder).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>Gender (female:male)</th>
<th>Mean age at examination (SD, range)</th>
<th>Mean age of onset (SD, range)</th>
<th>Mean disease duration (SD, range)</th>
<th>Positive family history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple writer’s cramp</td>
<td>14</td>
<td>3:11</td>
<td>53 yr (±10, 35-78)</td>
<td>41 yr (±12, 15-65)</td>
<td>11 yr (±9, 15-37)</td>
<td>29% (4/14)</td>
</tr>
<tr>
<td>Complex writer’s cramp</td>
<td>29</td>
<td>13:16</td>
<td>51 yr (±10, 17-64)</td>
<td>38 yr (±10, 12-58)</td>
<td>12 yr (±8, 2-34)</td>
<td>21% (6/29)</td>
</tr>
</tbody>
</table>

No mutations were identified in *DYT11* or *DYT16*. In one patient, the *DYT1* 3-bp deletion (c.904_906delGAG, NM_000113.2) was found. This 32 years old woman with a negative family history for movement disorders suffered from writer’s cramp of her dominant right hand since age 12 years. She adjusted to write with her left hand with success until the age of 26 years. At that age, she developed task-specific dystonia of her left hand, not only with writing, but also with typing. At examination, while writing right handed, a jerky flexion/extension movement is present in the second and third finger resulting in illegible writing. Writing with the left hand results in a dystonic flexion of the wrist. Further neurological examination was unremarkable; especially no hand dystonia was noted during other activities. She is treated with *Botulinum toxin A* every 4 months with a moderate result.
Discussion

We investigated 43 patients with writer’s cramp as presenting symptom for mutations in DYT11, DYT16, and the GAG DYT1 deletion. We did not identify an association between writer’s cramp and DYT11 mutations in our cohort. This is in line with previous studies reporting that DYT11 mutation carriers generally exhibit a combination of dystonic and myoclonic symptoms.\(^6\) One young-onset complex writer’s cramp patient carried the 3-bp deletion in the DYT1 gene. Our observed low frequency of the GAG deletion in patients with writer’s cramp is similar to previous observations.\(^2\) We did not identify DYT16 mutation carriers in the young-onset patients, but did not screen for gene dosage alterations. Therefore, we cannot definitely rule out involvement of the DYT16 gene.

A young age of onset and a positive family history generally attributes to a genetic cause for dystonia. In our cohort, mean age at onset was 39 years including seven young-onset patients. We observed long mean disease duration at examination (12 years), which can account for discrepancies of the reported age of onset. Twenty-three percent of our index patients reported a positive family history. However, in patients with focal dystonia, positive family members may be missed by taking family history alone.\(^7\) Moreover, the reduced penetrance and the occurrence of \textit{de novo} mutations make it difficult to predict a possible role of known genetic factors.

We report a genetic screening of one of the largest series of patients with writer’s cramp as initial symptom. Definite conclusion, that writer’s cramp is not associated with DYT11 or DYT16, cannot be drawn. On the basis of the current knowledge we propose the following guidelines for clinical practice. Genetic testing of the DYT1 gene is indicated in patients with an early onset of disease, complex writer’s cramp, and disease spread. If these features are combined with myoclonic jerks, DYT11 should also be tested. The phenotypic spectrum of DYT16 is still largely unknown, and genetic testing can be considered in young-onset writer’s cramp patients.

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References


