Sonographic Alteration of Lenticular Nucleus in Focal Task-Specific Dystonia of Musicians

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Key Words
Musican’s cramp · Task-related dystonia · Lenticular nucleus · Substantia nigra · Transcranial ultrasound

Abstract
Background/Aims: In distinct movement disorders, transcranial sonography detects alterations of deep brain structures with higher sensitivity than other neuroimaging methods. Lenticular nucleus hyperechogenicity on transcranial sonography, thought to be caused by increased local copper content, has been reported as a characteristic finding in primary spontaneous dystonia. Here, we wanted to find out whether deep brain structures are altered in task-specific dystonia. Methods: The frequency of sonographic brain-stem and basal ganglia changes was studied in an investigator-blinded setting in 15 musicians with focal task-specific hand dystonia, 15 musicians without dystonia, and 15 age- and sex-matched nonmusicians without dystonia. Results: Lenticular nucleus hyperechogenicity was found in 12 musicians with task-specific dystonia, but only in 3 nondystonic musicians (Fisher’s exact test, p = 0.001) and 2 nonmusicians (p < 0.001). The degree of lenticular nucleus hyperechogenicity in affected musicians correlated with age, but not with duration of music practice or duration of dystonia. In 2 of 3 affected musicians with normal echogenic lenticular nucleus, substantia nigra hyperechogenicity was found.

Conclusions: Our findings support the idea of a pathogenetic link between primary spontaneous and task-specific dystonia. Sonographic basal ganglia alteration might indicate a risk factor that in combination with extensive fine motor training promotes the manifestation of task-specific dystonia.

Introduction
Focal task-specific dystonia in musicians presents as a loss of voluntary motor control of extensively trained movements while playing an instrument [1, 2]. Approximately 1% of all musicians are affected [2]. Although the specific pathophysiology of the disorder is still unclear, it appears that its etiology is multifactorial with contributions from genetic, neurophysiological, physical and en-
vional factors [3]. While standard structural magnetic resonance imaging (MRI) studies have not revealed any gross pathology in patients with primary dystonia, transcranial sonography (TCS) and voxel-based morphometry MRI detected changes in the globus pallidus of 75% of patients with primary spontaneous dystonia [4, 5]. Increased echogenicity (‘hyperechogenicity’), mainly in the medial part of the lenticular nucleus (LN), was detected on TCS in more than 75% of patients with spontaneous cervical or upper-limb dystonia [4, 6]. To find out whether basal ganglia changes are also present in task-specific dystonia, we studied musicians with focal task-specific hand dystonia, unaffected musicians and unaffected nonmusicians with TCS.

Materials and Methods

Study Subjects

Altogether 45 subjects were studied with TCS: 15 were professional musicians suffering from focal task-specific hand dystonia while playing their instrument (6 guitar, 3 piano, 1 organ, 2 violin, 3 woodwind players), 15 were professional musicians without dystonia (5 guitar, 4 piano, 2 violin, 1 brass, 3 woodwind players), and 15 were age- and sex-matched nonmusicians without dystonia (table 1). Diagnosis of task-specific primary dystonia was established (or excluded) by a neurologist specialized in movement disorders in musicians (E.A.) after elaborate investigation of all musicians involved in this study [3]. No subject had signs of Parkinsonism. Secondary dystonia caused by structural brain lesions, endocrine or metabolic disorders, Wilson's disease, basal ganglia calcification, head trauma, anoxia, or prior neuroleptic exposure were excluded by standardized records of the patients' history, cranial MRI and laboratory workup. The severity of the musicians’ hand dystonia was assessed on the Arm Dystonia Disability Scale (ADDS) [7]. For this, the musicians were asked to rate the disability (0: normal; 1: mild difficulty; 2: moderate difficulty; 3: marked difficulty) for each of the following 7 items: playing their instrument, writing, buttoning, eating, shaving, teeth brushing, grasping, and gardening (maximum ADDS score: 21). The severity of the musicians’ hand dystonia in the affected musicians studied here was 3.7 ± 1.6 on the ADDS. The study was approved by the local ethics committee, and written informed consent was obtained from each subject participating in this study.

Transcranial Sonography

TCS was performed through the preauricular acoustic bone windows using a color-coded phased-array ultrasound system equipped with a 2.5-MHz transducer (Sonoline; Siemens, Erlangen, Germany). The ultrasound parameters chosen were: penetration depth 16 cm, dynamic range 50 dB, high persistence, real-time capability, image persistence, and depth persistence windows using a color-coded phased-array ultrasound system equipped with a 2.5-MHz transducer (Sonoline; Siemens, Erlangen, Germany). The ultrasound parameters chosen were: penetration depth 16 cm, dynamic range 50 dB, high persistence, reject 7. Substantia nigra (SN) echogenic size measurements were performed on the ultrasound machine on axial TCS scans automatically after manually encircling (trace) the outer circumference of SN’s echogenic area. SN echogenic sizes of 0.25 cm² and above were classified as hyperechogenic [8]. The echogenicity of LN and heads of caudate nuclei was classified as hyperechogenic when it was more intense than the surrounding white matter [4, 8]. Classification of subjects with respect to echogenicity of SN, LN and caudate nuclei was based on the most affected side of the investigated brain structure. LN echogenic size measurements were performed on axial TCS scans through the basal ganglia in the same way as described above for measurements of SN echogenic size. Musicians with task-specific dystonia and unaffected nonmusicians with TCS.

Table 1. Demographic variables and TCS findings of 15 musicians with task-specific hand dystonia (MD), 15 healthy (nondystonic) musicians (HM) and 15 healthy (nondystonic, nonmusician) controls subjects (HC) studied with transcranial brain sonography

<table>
<thead>
<tr>
<th>Feature</th>
<th>MD</th>
<th>HM</th>
<th>p</th>
<th>HC</th>
<th>p</th>
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<tbody>
<tr>
<td>Demographic variables</td>
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<tr>
<td>Number</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, F/M</td>
<td>3/12</td>
<td>2/13</td>
<td>3/12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>46.9 ± 10.5</td>
<td>42.9 ± 17.2</td>
<td>0.67c</td>
<td>46.9 ± 13.8</td>
<td>1.0c</td>
</tr>
<tr>
<td>Age at start of practicing music, years</td>
<td>10.6 ± 4.2</td>
<td>8.4 ± 3.2</td>
<td>0.12c</td>
<td></td>
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</tr>
<tr>
<td>Age at onset of dystonia, years</td>
<td>36.8 ± 11.6</td>
<td>N/A</td>
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<tr>
<td>Duration of dystonia, years</td>
<td>9.1 ± 5.5</td>
<td>N/A</td>
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<tr>
<td>Cumulative time of music training, h</td>
<td>21,276 ± 11,478</td>
<td>21,961 ± 11,596</td>
<td>0.89</td>
<td></td>
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<tr>
<td>Duration of having practiced music without dystonia, years</td>
<td>26.4 ± 11.3</td>
<td>34.5 ± 17.1</td>
<td>0.15c</td>
<td></td>
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<tr>
<td>Transcranial sonography findings</td>
<td></td>
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<tr>
<td>Substantia nigra hyperechogenicity</td>
<td>5 (33)</td>
<td>1 (7)</td>
<td>0.084d</td>
<td>2 (13)</td>
<td>0.20d</td>
</tr>
<tr>
<td>Lenticular nucleus hyperechogenicity</td>
<td>12 (80)</td>
<td>3 (20)</td>
<td>0.001d</td>
<td>2 (13)</td>
<td>&lt;0.001d</td>
</tr>
<tr>
<td>Caudate nucleus hyperechogenicity</td>
<td>2 (13)</td>
<td>1 (7)</td>
<td>0.50d</td>
<td>0 (0)</td>
<td>0.24d</td>
</tr>
</tbody>
</table>

Values are means ± SD or n (%).

* Comparison of group MD vs. group HM; \( b \) comparison of group MD vs. group HC; \( \text{t test} \); \( d \) Fisher’s exact test (\( p < 0.05 \) in bold).
subjects were investigated in a randomized order by one experienced sonographer (U.W.) who was blinded to the diagnoses and clinical data. TCS images were digitally stored, made anonymous and reassessed by the same reader in random order. Subsequently, the TCS images were independently assessed by a senior radiologist (A.G.) blind to clinical data. A brain structure was only regarded as hyperechogenic if ratings of both investigators agreed.

Statistics
For comparison of means, a t test for independent samples was performed. Categorical data were analyzed by Fisher’s exact test. Spearman’s correlation test was used for comparison of LN echogenic sizes with age, disease duration and ADDS score.

Results

Ratings of both TCS readers disagreed only in one musician with dystonia in whom reader 1 assessed left medial LN hyperechogenic while reader 2 assessed LN bilaterally normal. In this case, LN was regarded as bilaterally normal. In musicians with dystonia LN, hyperechogenicity was more frequent than in nondystonic musicians (80 vs. 20%; Fisher’s exact test, p = 0.001) and non-musicians (13%; p < 0.001), while other TCS findings did not differ (table 1; fig. 1). LN hyperechogenicity was unilaterial in 8 and bilateral in 4 affected musicians; its laterality was not related to laterality of dystonia (p > 0.5). The extent of LN hyperechogenicity in affected musicians (sum of bilateral echogenic sizes, 0.63 ± 0.60 cm²) correlated with age (Spearman’s test, r = 0.66, p = 0.008; larger of bilaterally measured LN echogenic sizes, r = 0.70, p = 0.003), but not with cumulative time (hours) of music training, duration (years) of practicing music, duration (years) of practicing music without dystonia, duration of dystonia or dystonia severity on the ADDS score (each, p > 0.1). In 2 of the 3 musicians with dystonia with normal echogenic LN, SN hyperechogenicity was found. Only one of the musicians with dystonia had completely normal TCS findings, compared to 10 of the musicians without dystonia (Fisher’s exact test, p = 0.001) and 11 of the nonmusicians (p < 0.001).

Discussion

Data obtained in this study show that LN hyperechogenicity, previously reported as a characteristic TCS feature in idiopathic spontaneous dystonia, is also frequent in idiopathic task-specific focal dystonia of musicians. Our findings support the idea that there are common pathogenic mechanisms in primary spontaneous and task-specific dystonia [9]. Previously reported accumula-
tion of musician dystonia and other forms of task-related dystonia, mainly writers’ cramp but also of spontaneous focal dystonia in some families, suggest a possible genetic contribution to idiopathic dystonia with phenotypic variability including focal task-specific and spontaneous dystonia [3, 9, 10].

In postmortem studies of patients with spontaneous dystonia, increased levels of copper and manganese were found in the globus pallidus and putamen [11]. This finding was linked to a decreased content of the copper-transporting Menkes protein in the basal ganglia and leukocytes of patients with idiopathic dystonia [12, 13]. The proposition that moderate copper or manganese accumulation causes LN hyperechogenicity despite normal LN MRI has been underpinned by TCS findings in patients with Wilson’s disease and welding-related Parkinsonism [14, 15]. As copper modulates synaptic function and acts as inhibitor of several receptor types, an increase of copper levels in the LN could explain disinhibition of the thalamus via disturbed function of neurons of the globus pallidus internus [16]. Hitherto, genetic studies failed to prove pathogenic mutations of genes related to copper transporting enzymes in idiopathic dystonia [17]. Therefore, the disturbance of copper metabolism might also represent a secondary phenomenon. The positive correlation of the extent of LN hyperechogenicity with increasing age in the affected musicians studied here suggests that trace metal accumulation within the LN occurs very slowly. On the other hand, the missing correlation between LN echogenic size and duration of music practice in the musicians studied here argues against the idea that the intense fine motor training itself causes the basal ganglia changes detected with TCS. Findings of the present study, together with previous TCS findings in spontaneous dystonia, suggest that LN hyperechogenicity reflects rather a – possibly genetically determined – risk factor of dystonia. The combined presence of this risk factor and other pathogenic cofactors such as extensive fine motor training might promote the manifestation of focal task-specific or spontaneous dystonia [3, 9].

LN hyperechogenicity is also frequently found in atypical parkinsonian syndromes [18]. Although dystonia may be present in these syndromes, it is unclear whether the underlying pathology leading to LN hyperechogenicity is similar to that in idiopathic dystonia. It seems more likely that in these entities LN hyperechogenicity is caused by neurodegenerative processes with gliosis and iron accumulation mainly in the putamen [19]. Indeed, the hyperechogenic signals in the anatomic area of the LN are, especially in patients with multiple-system atrophy, usually more lateralized compared to patients with dystonia (unpubl. data).

Interestingly, in 2 of the 3 musicians who had dystonia but normal echogenic LN, SN hyperechogenicity was found. Considering all musicians with task-specific focal dystonia, SN hyperechogenicity was more frequent than in musicians without dystonia, even though this difference was not statistically significant (table 1). SN hyperechogenicity, known to be present in about 9% of the healthy population, is associated with subclinical impairment of nigrostriatal dopaminergic function and is thought to represent a risk marker of Parkinson’s disease [8]. SN hyperechogenicity in non-parkinsonian subjects correlated with mild motor asymmetry [20, 21]. This correlation was most pronounced in motor tasks demanding highly repetitive finger movements [21]. Therefore, one may speculate that a dysfunction of the nigrostriatal dopaminergic system might contribute to motor impairment in some musicians with manifestation of task-specific dystonia when performing highly repetitive finger movements.

Currently, studies are under way to elucidate the relation between sonographic brainstem and basal ganglia changes, genetic status, and affected body regions in patients with different forms of spontaneous and task-related dystonia.

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References


