Bilateral grey-matter increase in the putamen in primary blepharospasm

T Egen, M Mühlau, C Gaser, D Sander

Background: Primary blepharospasm is a focal dystonia characterised by excessive involuntary closure of the eyelids. The pathology of primary blepharospasm is unresolved. Aim: To pinpoint grey-matter changes that are associated with primary blepharospasm. Methods: 16 right-handed patients with primary blepharospasm (mean age 67.4 (SD 4.3) years; 12 women) were compared with 16 healthy volunteers matched for sex and age. High-resolution T1-weighted magnetic resonance imaging of each participant was obtained and analysed by voxel-based morphometry, a method to detect regionally specific differences in grey matter between patients and control group. To evaluate whether the identified grey-matter changes were correlated with the duration of primary blepharospasm or botulinum neurotoxin treatment (BoNT), separate regression analyses were carried out. Results: In patients with primary blepharospasm, grey-matter increase in the putamina was observed, whereas regression analyses did not indicate a correlation between grey-matter increases and the duration of primary blepharospasm or BoNT. Grey-matter decrease was detected in the left inferior parietal lobule; here regression analyses of grey-matter decrease showed a significant (p = 0.013) correlation of grey-matter decrease with the duration of BoNT. Conclusions: The data suggest structural changes in primary blepharospasm and point to a crucial role of the putamen for the pathophysiology of this focal dystonia.

PARTICIPANTS AND METHODS

Patients and controls

Diagnosis of primary blepharospasm was established by a detailed history and a neurological examination carried out by an expert neurologist of our outpatient clinic for movement disorders (Department of Neurology, Technische Universität München, München, Germany). The severity of primary blepharospasm was assessed with the Blepharospasm Disability Scale and the Severity Rating Scale. Secondary forms of blepharospasm were excluded by history, clinical examination, laboratory tests and neuroimaging. The 16 patients included were right-handed with primary blepharospasm. Table 1 summarises the demographic and clinical details.

All patients had no neurological abnormalities except for primary blepharospasm and were on regular botulinum neurotoxin treatment (BoNT). The 16 right-handed healthy controls were matched for age and sex. The study was carried out according to the Declaration of Helsinki and all participants had given prior written informed consent.

Data acquisition

High-resolution structural data were acquired on a 1.5-T Siemens Magnetom Symphony scanner (Erlangen, Germany) (standard two-channel birdcage head coil; magnetisation-prepared rapid gradient echo sequence; sagittal slices 160; repetition time (TR) 11.1 ms; echo time (TE) 4.3 ms; flip angle 15°; matrix size 224× 256 mm; voxel size 1×1×1 mm). A neuroradiologist, who was blinded to the study, detected neither abnormal nor unusual findings in all the screened images.

Image processing

VBM comprises the following steps:

- Spatial normalisation of all images to a standardised anatomical space to allow for spatial averaging
- Segmentation of images into grey and white matter as well as cerebrospinal fluid

Abbreviations: BoNT, botulinum neurotoxin treatment; FDG, 18F-deoxyglucose; fMRI, functional magnetic resonance imaging; VBM, voxel-based morphometry
thresholded our results at a height threshold of \( p < 0.001 \) and, additionally, at an extent threshold of \( p < 0.05 \), uncorrected and, left (Z = 4.2) putamen (fig 1). In both clusters of grey-matter 

Grey-matter increase was identified in the right (Z = 4.5) and left inferior parietal lobule (Z = 4.7). Here regression analyses showed a trend towards a correlation of grey-matter decrease with the duration of primary blepharospasm (\( p = 0.12 \)) and a significant correlation of grey-matter decrease with the duration of BoNT (\( p = 0.013 \); fig 3).

RESULTS

Grey-matter increase was identified in the right (Z = 4.5) and left (Z = 4.2) putamen (fig 1). In both clusters of grey-matter

![Image](https://www.jnnp.com)

Figure 1 Grey-matter increase bilaterally in the putamen (Z = 4.5 on the right; Montreal Neurological Institute (MNI) coordinates: \( x = 25, y = -8, z = 6 \), \( Z = 4.2 \); Z value, 4.2 on the left; MNI coordinates: \( x = -26, y = -13, z = 4 \)). Results are projected on (A) coronal and (B) axial slices of the study-specific averaged T1-image in a standard stereotactic space derived from all the 32 study participants.
FDG-PET study showed striatal and thalamic hypermetabolism in patients with primary blepharospasm. Using fMRI, one group reported a greater activation of the anterior visual cortex, anterior cingulate cortex, primary motor cortex, central region of the thalamus and superior cerebellum during spontaneous and voluntary blinking in patients with primary blepharospasm than in controls, whereas another group compared spasms of the orbicularis oculi muscle in patients with primary blepharospasm with voluntary eye blinks of healthy controls and, notably, found spasms of the orbicularis oculi muscles in patients with primary blepharospasm accompanied by putaminal activation exactly at the site of grey-matter increase shown by our study. In summary, several lines of evidence suggest a crucial role of the putamen in the pathophysiology of primary blepharospasm, which is confirmed by our structural data.

A functional putaminal change has been proposed that leads to a disturbance in the resistance of the blink system to environmental triggers and hence to lid spasms. Such a functional putaminal change may go along with an increased number of neurones or synapses and, hence, grey-matter increase as shown by our VBM study. The neuronal correlate of changes in grey matter detectable by VBM is, however, unknown. An alternative explanation has been proposed in a VBM study on another focal dystonia (idiopathic cervical dystonia). Here, changes in grey matter were seen as a result of neuronal plasticity—that is, synaptic remodelling that follows excessive involuntary movements. The major difficulty interpreting not only VBM but also PET and fMRI studies on primary blepharospasm remains the question, whether the putaminal changes reflect the primary cause or the secondary consequences of primary blepharospasm including its treatment.

We, however, assume that the grey-matter increase shown by our study is more likely to reflect a primary putaminal alteration for the following reason: the patients included in our study varied with regard to the duration of primary blepharospasm and duration of BoNT (table 1). If these variables were considerably related to the grey-matter increase of the putamina, we would expect at least some correlation of this increase with the duration of primary blepharospasm or BoNT, but none of the respective regression analyses showed even a trend towards such a correlation. Longitudinal studies on patients with primary blepharospasm may help to finally resolve this question.

Moreover, we found grey-matter decrease in the left inferior parietal lobule in primary blepharospasm. Several case studies have reported unilateral dystonia contralateral to parietal lesions, but we are not aware of unilateral parietal lesions resulting in a symmetric dystonia such as blepharospasm. The finding of grey-matter decrease in the parietal region only on the left side indicates the involvement of functions that are primarily related to the left parietal cortex. Accordingly, cortical sensory processing, which may be presented in the parietal cortex in a leftward-biased manner, has been postulated to be abnormal in dystonia. Several further functions have, however, been related to the parietal cortex in a leftward-biased manner (eg, motor attention and movement selection, integration of time and space, and imitation). Therefore, it is also conceivable that frequent spasms of the eye-closing orbicularis oculi muscles as present in primary blepharospasm lead to neuroplastic changes detectable by VBM. In fact, our data point in this direction, as regression analyses showed a trend towards correlation of the grey-matter decrease with the duration of primary blepharospasm and a significant correlation with the duration of the BoNT. Therefore, we conclude that the grey-matter decrease in the left inferior parietal lobule is more likely to reflect a secondary cause rather than the primary cause of primary blepharospasm.
Our data suggest in vivo morphological changes in the putamen in primary blepharospasm and, hence, support the hypothesis of a pivotal role for the putamen in the pathophysiology of this focal dystonia.

ACKNOWLEDGEMENTS
TE and his colleagues from the Department of Neurology (Technische Universität München) were supported by KKF-Fond 766160. We thank JP Rauschecker for reading an earlier version of this manuscript.

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Competing interests: None declared.

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*J Neurol Neurosurg Psychiatry* 2006 77: 1017-1020 originally published online May 11, 2006
doi: 10.1136/jnnp.2005.087148

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