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Apostolidis A[1], Jacques T S [2], Freeman A [3], Ghazi-Noori S[1], Kalsi V[4], Popat R[4], Gonzales G[4], Beckett A[1], Datta S[4], Elneil S[4], Dasgupta P[5], Fowler C J [4]
1. Institute of Neurology, UCL, London, 2. Institute of Child Health, UCL, london, 3. Department of Histopathology, UCLH, london, 4. The National Hospital for Neurology and Neurosurgery, UCLH, London, 5. Guy's and St. Thomas's Hospitals and The National Hospital for Neurology and Neurosurgery, UCLH, Lon

HISTOLOGICAL CHANGES IN THE HUMAN BLADDER UROTHELIUM AND SUBUROTHELIUM FOLLOWING INJECTIONS OF BOTULINUM NEUROTOXIN TYPE A (BONT/A) FOR THE TREATMENT OF NEUROGENIC VERSUS IDIOPATHIC DETRUSOR OVERACTIVITY (NDO/IDO)

Hypothesis / aims of study

With the increasing use of BoNT/A injected into the detrusor muscle it is important to understand if it might be having local adverse effects in addition to its acknowledged benefits on patients' symptoms.

To date, only one study has investigated effects of intradetrusor BoNT/A on human bladder histology. In excised neurogenic overactive bladders, those previously treated with BoNT/A at unspecified intervals from injections showed significantly less fibrosis, but no differences in inflammation and oedema, compared to untreated ones.

No study has reported to date on the effect of BoNT/A on histological markers in patients with idiopathic detrusor overactivity (IDO)

We examined, for the first time in a prospective study, the histological changes in the urothelium and suburothelium of patients with neurogenic (NDO) compared to idiopathic detrusor overactivity after one or repeat treatments with intra-detrusor BoNT/A.

Study design, materials and methods

Flexible cystoscopic bladder biopsies were obtained from a consistent bladder area from patients with intractable spinal NDO or IDO before and after treatment with intradetrusor injections of BoNT/A. Neurogenic patients had been treated with 300U BOTOX® and idiopathic with 200U. Follow-up biopsies were obtained 4 and 16 weeks after each treatment session and during clinical relapse, the latter confirmed by resurgence of DO on cystometry and symptom deterioration in voiding diaries.

All specimens were post-fixed in 4% paraformaldehyde, and frozen 10µm-thick sections were stained for haematoxylin-eosin and analysed blindly by 2 pathologists for inflammatory changes, fibrosis, hyperplasia and dysplasia in the urothelium/suburothelium. A 0-3 grading scale was used to score inflammation and fibrosis (0=none, 1=mild, 2=moderate, 3=severe). Results are expressed as mean ± standard error. Parametric t tests were used for statistical analysis.

Results

A total of 179 biopsies were examined from 79 treated patients (113 from 51 NDO patients – 56 from 28 IDO patients); 157 biopsies were taken before and after 1st injection, the remaining 22 after repeat injections. Urothelium was present in all but 2 biopsies (98.9%), but smooth muscle only in 33/179 (18.4%).

Signs of chronic inflammation were present in 125/179 (69.8%) biopsies, whereas acute inflammation in only one (0.5%). Inflammatory changes were identified in the lamina propria in 123/125 (98.4%) biopsies and in the urothelium in 22/125 (17.6%). Inflammation was found in 19/22 biopsies (86.4%) after repeat injections, 73/108 biopsies (67.6%) after the 1st injection and 29/49 baseline biopsies (59.1%). A progressive, but not statistically significant, increase was seen in inflammation score at 4, 16 weeks and relapse time post 1st injection (0.73±0.1 v 0.81±0.1 v 0.92±0.1 v 1.2±0.4, p=0.58, 0.09 and 0.07 respectively).

No difference existed between NDO and IDO in degree of baseline inflammation (0.77±0.1 v 0.67±0.2, p=0.59), but it was more commonly seen in NDO patients (65.6% v 50%). In the NDO group a trend for increase in inflammation score was seen at 4, 16 weeks and relapse time post 1st injection (0.77±0.1 v 0.89±0.1 v 1.2±0.1 v 1.5±0.3, p=0.3, 0.07 and 0.06 respectively). In contrast, in IDO patients it remained unchanged or slightly decreased at the same time points (0.67±0.2 v 0.65±0.2 v 0.40±0.2, p=0.75 and 1.0, respectively; numbers were inadequate for analysis at relapse time).

Eosinophils were identified in 20 biopsies from 18 patients and were more commonly seen in follow-up biopsies (18/130 - 13.8%), especially those from repeat injections (6/22 or 27.3%), than in baseline (2/49 – 4.1%). Eosinophils were also more common in NDO (17/113 biopsies - 15.0%) than IDO bladders (3/56 - 5.3%).

Mild fibrosis was found in 4/179 (2.2%) of all biopsies examined. No fibrosis was found after repeat injections. Also, no dysplasia or hyperplasia was identified.

Interpretation of results

Significant differences in post treatment self-catheterisation rate (NDO 92.4% v IDO 17.5%) may partly explain the post BoNT/A increased inflammation in patients with NDO compared to those with IDO. The presence of eosinophils might be drug-related since they were mostly found in post-treatment biopsies, although not consistently seen in the further follow-up biopsies from these same patients, when available.

Fibrosis also was inconspicuous: it was mild and not associated with repeat treatments.

Concluding message

BoNT/A injections do not appear to be producing significant inflammatory changes, fibrosis or dysplastic changes in the human bladder urothelium/suburothelium.

Differences in degree of inflammation between NDO and IDO bladders may merely be due to increased post-treatment self-catheterisation rates in NDO patients, but further studies are needed to explore the significance of this finding.

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