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RESTORATION OF BLADDER FUNCTION BY BONE MARROW CELL TRANSPLANTATION IN RATS WITH UNDERACTIVE BLADDER BY BLADDER OUTLET OBSTRUCTION.

Aims of study
In generally, storage disorders are mainly treated with medications such as anticholinergic agents. However, if bladder contractility has already been impaired by bladder outlet obstruction (BOO), it is difficult to improve the symptoms by such medications. On the other hand, it has been reported that bone marrow stem cells have the potential to differentiate into various cells, and autologous bone marrow transplantation has been used for the reconstitution of bone, muscles, and blood vessel. In this study, we tried to restore bladder function by bone marrow cell transplantation in rats with underactive bladder due to BOO.

Materials and methods
Twelve female Sprague-Dawley rats (recipients) were anesthetized with halothane, and the bladder and proximal urethra were exposed through a lower abdominal incision. A polyethylene catheter (PE-50; outer diameter 0.96 mm) was placed under the urethra, and a 4-0 silk ligature was tied around both the urethra and catheter to create partial BOO. After the ligature had been secured, the catheter was pulled out. Bone marrow cells were collected from the femurs of green fluorescent protein (GFP) transgenic Sprague-Dawley rats (n = 2, donors) under halothane anaesthesia, and were cultured in minimal essential medium supplemented with 10% fetal bovine serum. After 1 month, urethral obstruction was removed in the recipient rats under halothane anaesthesia, and 1×10^7 GFP-labeled bone marrow cells (0.2 ml) was directly injected into the bladder walls of rats in the transplant group (n = 6). Rats (n = 6) in the sham-operated group were injected with culture medium (0.2 ml) by the same procedure. One month after transplantation, isovolumetric cystometry was performed in intact control rats (n = 6) and rats from the sham-operated group and the transplant group. Then the bladders were removed to examine the existence of green fluorescence-positive cells and anti alpha-smooth muscle actin (alpha-SMA) antibody-positive cells.

Results
Residual urine volume was significantly increased in the sham-operated group (6.1±2.4 ml, p = 0.002) and the transplant group (3.2±2.1 ml, p = 0.014) compared with that of the intact control rats (0.2±0.1 ml), but it was significantly smaller (p = 0.047) in the transplant group than the sham-operated group. During continuous cystometry, the amplitude of bladder contraction pressure was significantly lower in the sham-operated group (31.9±4.3 cmH_2O) compared with the intact control group (51.3±11.7 cmH_2O p = 0.007) and the transplant group (50.9±13.9 cmH_2O p = 0.018), but there was no significant difference between the control and transplant groups. On immunohistochemistry, numerous green fluorescence-positive cells were found in the smooth muscle layer and submucosal layer, and a part of these cells were also labeled by anti alpha-SMA antibody in the transplant group.

Interpretation of results
The amplitude of bladder contraction was significantly decreased and residual urine volume was increased by BOO, suggesting that the decrease of contractility was caused by bladder wall stretching that impaired contraction by bladder smooth muscle. Decreased bladder activity due to BOO recovered after bone marrow cell transplantation, and transplanted cells in the bladder wall were also positive for anti alpha-SMA antibody staining. These findings suggest that bone marrow cells injected into the bladder wall differentiated into smooth muscle cells and improved detrusor muscle contractility.

Concluding message
It is suggested that bone marrow cell transplantation can improve micturition disorders related to underactive bladder.

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