Japan Society of Neurovegetative Research

Onuf-Mannen's Nucleus

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Onuf's Anatomical Description

In the anatomical study of the human sacral spinal cord, an American anatomopathologist, Onuf described a small but distinct group of motor neurons in the anterior horn of the second sacral segment, and named it Group X, which he ascribed to motor neurons innervating the perineal muscles such as the ischiocavernosus, bulbo-cavernosus or erector clitoridis muscles[1,2] (**Fig. 1**). He also described cell columns of vegetative neurons consisting of three groups, namely, dorsolateral, ventrolateral and central groups in the sacral cord.[1,2] Onuf's study, however, was purely anatomical and he gave no evidence of functional significance.

Negative Tetrad of Amyotrophic Lateral Sclerosis

Toyokura[3] discussed the clinical features of amyotrophic lateral sclerosis (ALS), mentioning the importance of four negative clinical signs that are characteristic with this intractable disease: absence of a sensory deficit, absence of vesico-rectal incontinence, absence of external ophthalmoplegia and absence of bedsores. He named these negative signs the "negative tetrad of ALS," which, he thought, was quite suggestive to solve the problem of highly selective involvement of somatic motor neurons in ALS. Stimulated by Toyokura's comment, Mannen carried out a series of pathology studies on the sacral cord of ALS patients and found that the motor neurons of Onuf's Group X in the second sacral anterior horn were well preserved in ALS, in spite of the severe depopulation of the other motor neurons of the entire sacral anterior horn[4] (**Fig. 2**). He examined the histopathology of the external sphincter muscles of the anus and urethra, which are striated muscles, and found that they are quite intactly preserved in ALS. Mannen also found that Onuf's Group X was almost totally depopulated in patients with multiple system atrophy showing the clinical pictures of Shy-Drager syndrome, in which the external sphincter muscles of both anus and urethra were severely degenerated and ano-rectal incontinence was one of the characteristic clinical features[5] (**Fig. 2**). From these clinico-pathological studies, Mannen concluded that the neurons of Onuf's Group X were innervating the anal and urethral external sphincter muscles.

Functional Significance of Onuf's Nucleus

To confirm this hypothesis proposed by Mannen, several animal experiments were subsequently done mostly in Japan and the experimental data clearly confirmed that the small group of motor neurons of the sacral anterior horn corresponding to the human Onuf's Group X were innervating the striated sphincter muscles of the anus and urethra.[6–8] Animal studies further demonstrated the somatotopic localization of motor neurons innervating the external sphincter of the anus and those innervationg the external sphincter of the urethra; the former is situated in the dorsomedial portion and the latter in the ventrolateral portion of Onuf's Group X.

Animal experiments also confirmed that the columns of the vegetative neurons of the caudal sacral cord described by Onuf were innervating the internal sphincter muscles of the anus and urethra, which were composed of smooth muscles.

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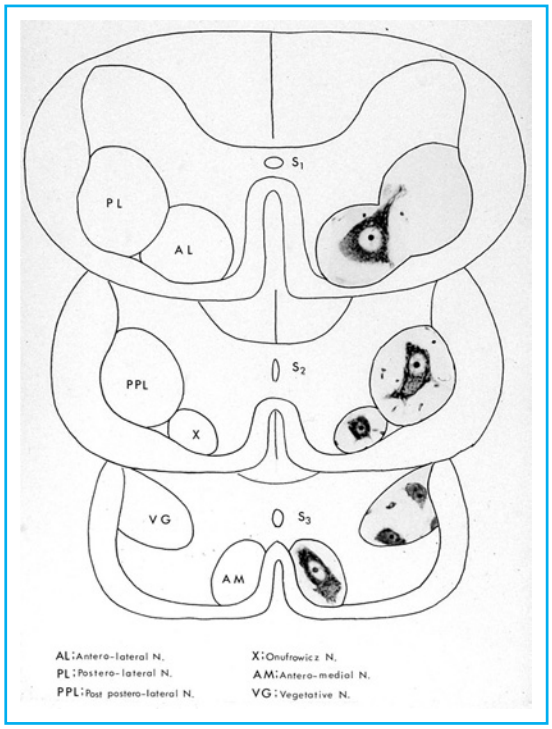

Fig. 1 Motor neuron groups in the sacral spinal cord according to Onuf's naming, with microscopic pictures of typical motor neurons stained by the Nissl method in each group under the same magnification

In animals, the vegetative neurons going to the anal internal sphincters are located in the dorsal group and those to the vesico-urethral smooth muscles are situated in the ventral portion.[8]

We carried out cytometrical studies of human Group X in various degenerative disorders with or without vesico-rectal incontinence[9] and showed that the number of remaining neurons in Group X, in cases with incontinence, was less than 13% of the normal neuronal population, while a case with 37% remaining neurons of the normal did not show any incontinence clinically.[10] These findings suggested that the critical number of Group X neurons for preserving continence might be between 13 and 37% of normal.

Intranuclear Somatotopic Localization

In order to directly confirm the innervation of the external sphincter of the anus by the neurons of Group X that Onuf has described, Mannen examined the pathological change of these neurons in a case of anorectal amputation for rectal cancer.[11] He discovered that the motor neurons in Group X showed marked central chromatolysis, a sign of retrograde change caused by axonal injury of the motor neurons. The Mannen case

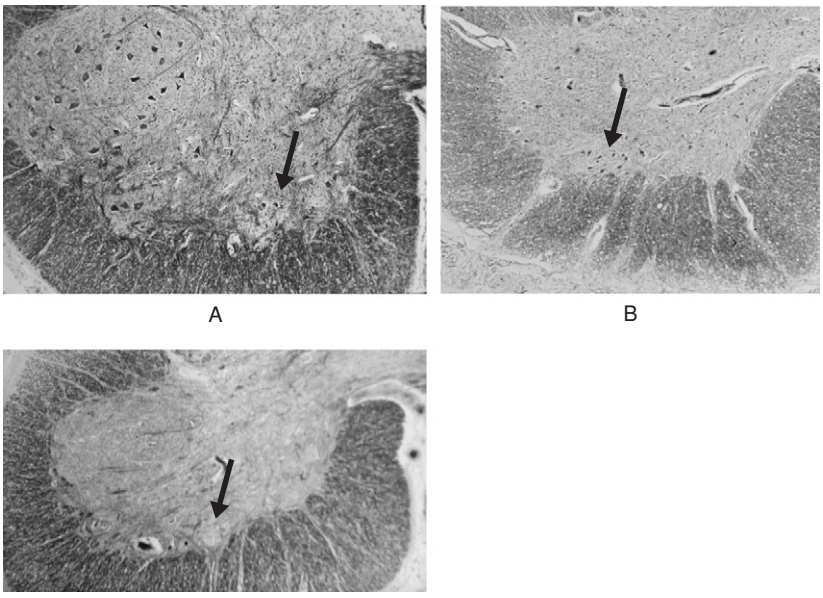

Fig. 2 Second sacral anterior horn in normal people (A), ALS (B) and Shy-Drager syndrome (C), stained by the Klüver Barrera method

Neurons in Onuf-Mannen's nucleus (arrow) is normally preserved in ALS, but depopulated in Shy-Drager syndrome.

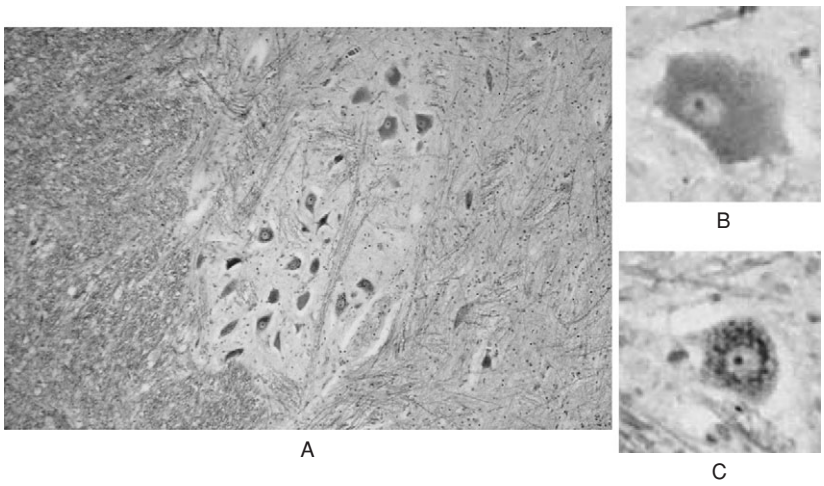

Fig. 3 Onuf-Mannen's nucleus in a case with ano-rectal amputation (A), stained with chromatolytic neuronsin of the dorso-medial portion (B) and a normal-looking neuron in the ventrolateral portion (C) (Klüver Barrera staining)

was further examined several years later with regard to the somatotopic localization within the nucleus.[12] The study revealed that the chromatolytic neurons were found only in the dorsomedial portion of Group X, and the neurons situated in the ventrolateral portion of it were normally preserved (**Fig. 3**). The finding confirmed the somatotopic localization of motor neurons within Group X discovered by animal experiments; those of the dorsomedial portion of Group X innervate the external anal sphincter muscle, while those of the ventrolateral portion innervate the urethral external sphincter muscle. The somatotopic localization of vegetative neurons in S3, which had been elucidated in animal experiments, was also confirmed in humans. Only the vegetative neurons in the ventromedial portion of the intermediolateralis nucleus at S3 showed central chromatolysis in the case of anorectal amputation.

The Onuf-Mannen Nucleus in Human

The above mentioned results of the studies with regard to the functional significance of Group X described by Onuf, both in men and in animals, were all inspired by the series of papers by Mannen. Most of the subsequently published papers on anatomical and pathological studies of this small motoneuron group have been done by Japanese scientists, all of whom unanimously confirmed Mannen's notion that the motoneurons of Onuf's Group X are innervating the external sphincter muscles of the anus and urethra. That is to say, although Group X, a special motor neuronal group in S2 had been anatomically described by Onuf, the functional significance of it was discovered and confirmed by Mannen 75 years later. In order to commemorate the anatomical description by Onuf and the discovery of functional significance by Mannen, Toyokura proposed to call the Group X of Onuf, the Onuf-Mannen nucleus.[13] His proposal is based on the fact that the discovery of the functional significance of this small motor neuron group in the second sacral spinal cord were derived from the classical clinico-pathological observations that are still quite efficient to elucidate the fundamental problems in the field of basic neuroscience.

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