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SHORT COMMUNICATION

Accessory mammillary bodies formed by the enlarged lateral mammillary nuclei: cytoarchitecture

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Abstract

Post mortem examination of the hypothalamus of a 79-year-old woman, deceased in cardiac arrest without recorded neurological symptoms, revealed well-defined spherical protrusions located rostro-laterally to the mammillary bodies that appear to be regular size when compared to normal. Cytoarchitectonically, these accessory mammillary bodies are formed by the enlarged lateral mammillary nucleus that is normally a thin shell over the medial. The mammillary nuclei appear to function synergistically in memory formation in rats; however, the functional consequences of the present variation are difficult to interpret due to lack of human data. Most importantly, in addition to the possible functional consequences, lateral mammillary bodies can be falsely identified as various neuropathological processes of the basal diencephalon including gliomas; therefore, it is extremely important to disseminate this unique morphological variant among clinicians.

Keywords Mammillary · Hypothalamus · Cytoarchitecture · Morphology · Brain · Human

Introduction

The mammillary bodies and the related nuclei occupy the basal hypothalamic region in the posterior hypothalamus. The mammillary bodies are formed primarily by the medial mammillary nucleus in humans, dorsolaterally surrounded by significantly smaller lateral mammillary nucleus (Saper 2004). Surrounding the mammillary nuclei, there is a shell of relatively large, darkly stained cells which is referred as tuberomammillary nucleus. The neurons occupying the tuberomammillary nucleus indeed resemble the cells of the magnocellular system of the paraventricular and supraoptic nuclei; however, they are not immunoreactive for oxytocin or vasopressin, instead they secrete histamine, galanin and melanin-concentrating hormone (Airaksinen et al. 1991; Gai et al. 1990; Mouri et al. 1993; Panula et al. 1990).

The medial and lateral mammillary nuclei are separated by a thin white matter plate. Normally, the medial mammillary nucleus is extremely large and dwarfs the lateral mammillary nucleus (LeGros Clark 1936; Saper 2004; Mai et al. 2008). Although there is a thin layer of darkly stained neurons at the lateral border of lateral mammillary nucleus that is considered to be the part of the nucleus, the morphology of the cells in the medial and lateral mammillary nuclei is virtually indistinguishable. Based on this morphological similarity, and on the concern that the lateral mammillary nucleus in humans does not appear to be analogous with the same-named nucleus in rats exhibiting larger and more distinctly stained neurons with definite projection fields, the functional subdivision of the nuclei was questioned previously (Saper 2004).

In the present study, we intend to provide a cytoarchitectonical overview of a unique phenomenon of an accessory pair of mammillary bodies. In addition to the extremely important aspect of this morphological feature during the radiological evaluation, the morphological arrangement

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of the mammillary nuclei in this distinctive case may provide an understanding of the relationship between the medial and lateral mammillary nuclei in the normal human hypothalamus.

Methods

The hypothalamic sample with the unique case of accessory mammillary bodies was found by coincidence during autopsy and of a 79-year-old woman, who died in cardiac arrest. This sample was compared with a hypothalamus that exhibited normal-sized and -shaped mammillary bodies, obtained from a 90-year-old woman, deceased in acute myocardial infarct. The tissue samples were harvested at less than 12 h *post mortem* period, in accordance with the regulations of the Institutional Review Board of Lake Erie College of Osteopathic Medicine (LECOM). The clinical records of the individual did not indicate any neurological or neuroendocrinological disorders. The block containing half of the hypothalamus was split by the midsagittal line and it was fixed by immersion in 0.1 M phosphate-buffered (pH 7.4; PB) 4% formaldehyde at 4 °C for 2 weeks. The sample was cryoprotected with 30% sucrose in phosphate buffer containing 0.9% sodium chloride (PBS) supplemented with 0.15% sodium-azide and then sectioned on a freezing microtome at 30 µm intervals in coronal planes. The sections were collected in three series of wells of plastic 12-compartment plates with PBS containing 0.2% sodium-azide, and stored at 4 °C until processing.

Sections were mounted on slides, dehydrated on a warming plate for 60 min and defatted in Safe Clear II (Fisher Scientific 044–192). Then the sections were treated with descending alcohol series and stained with hematoxylin (Sigma GHS216, 5 min), washed in tap water for 10 min and stained with eosin (Sigma HT1101162, 2 min). Staining was followed by 95% and 100% ethanol treatment (2 times 5 min, respectively), xylene treatment (2 times 5 min) before coverslipping.

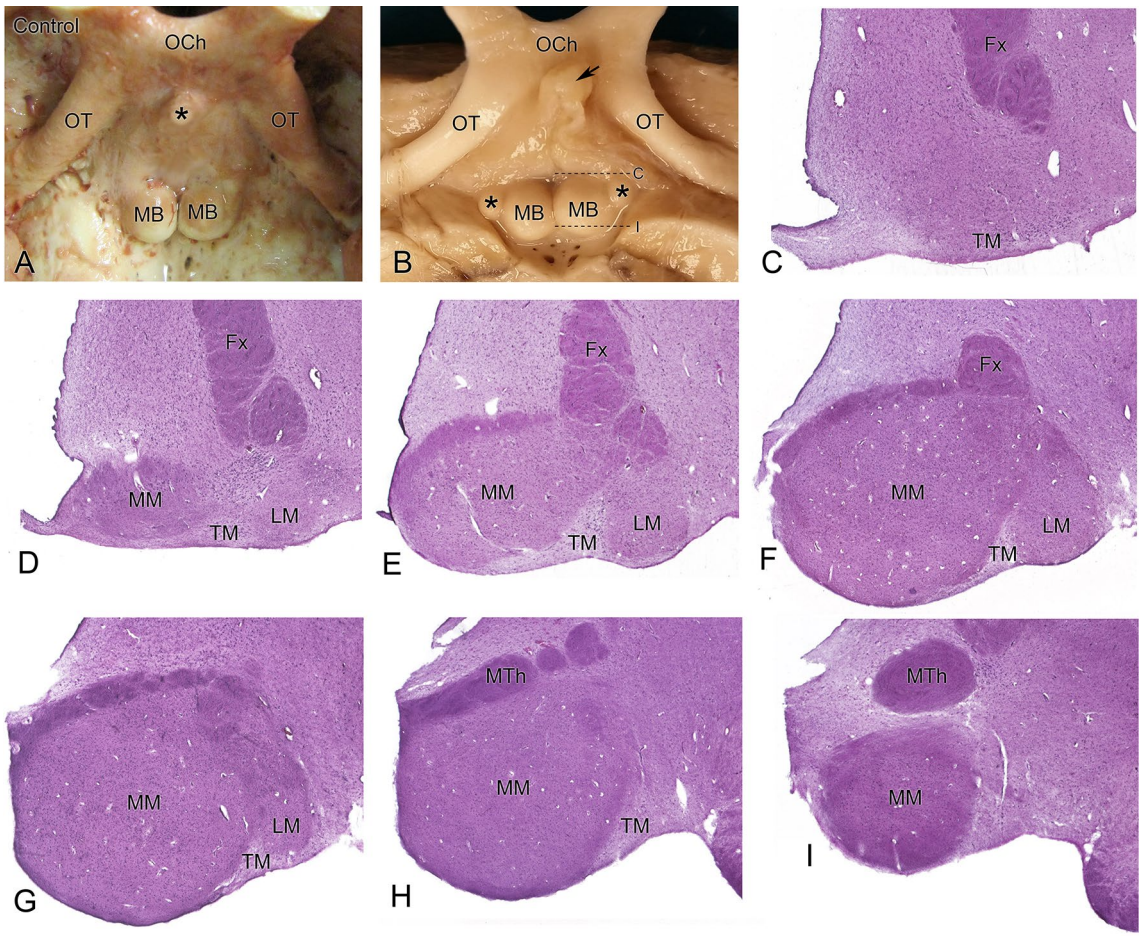

Fig. 1 Accessory mammillary bodies (asterisks, **b**) are formed by the abnormally massive lateral mammillary nucleus (LM; **d**–**g**). Normal anatomy is depicted on **a** (Control). The plane of sections **c** and **i** is labeled with dashed lines on **b**. *Fx* fornix, *OCh* optic chiasm, *OT* optic tract, *LM* lateral mammillary nucleus, *MM* medial mammillary nucleus, *MTh* mammillothalamic tract, *TM* tuberomammillary nucleus; arrow, infundibulum. Magnification of the micrographs **c**–**i** ×25

Results

In the present unique case, *post mortem* examination of the hypothalamus revealed an additional set of accessory mammillary bodies at the rostro-lateral border of the mammillary bodies (Fig. 1b) that appear to be normal size when compared to a normal anatomical layout (Fig. 1a). To determine the cytoarchitecture of these structures, the sections of the posterior hypothalamus were stained with hematoxylin and eosin (Figs. 1c–i, 2a–f).

Histological examination revealed that the accessory mammillary body is formed entirely by the abnormally massive lateral mammillary nucleus (Figs. 1d–g, 2a, b) while the medial mammillary nucleus (Fig. 1d–i) populates the medially located mammillary body (Fig. 1b) whose size is comparable to normal (Fig. 1a). The tuberomammillary nucleus is located superior to the groove between the medial and lateral mammillary nuclei (Fig. 1c–h).

The morphology of cells in the medial and lateral mammillary nuclei was near identical in both hypothalami; however, in the case of dual mammillary bodies, the cells appeared to have slightly more distinctive outline with more

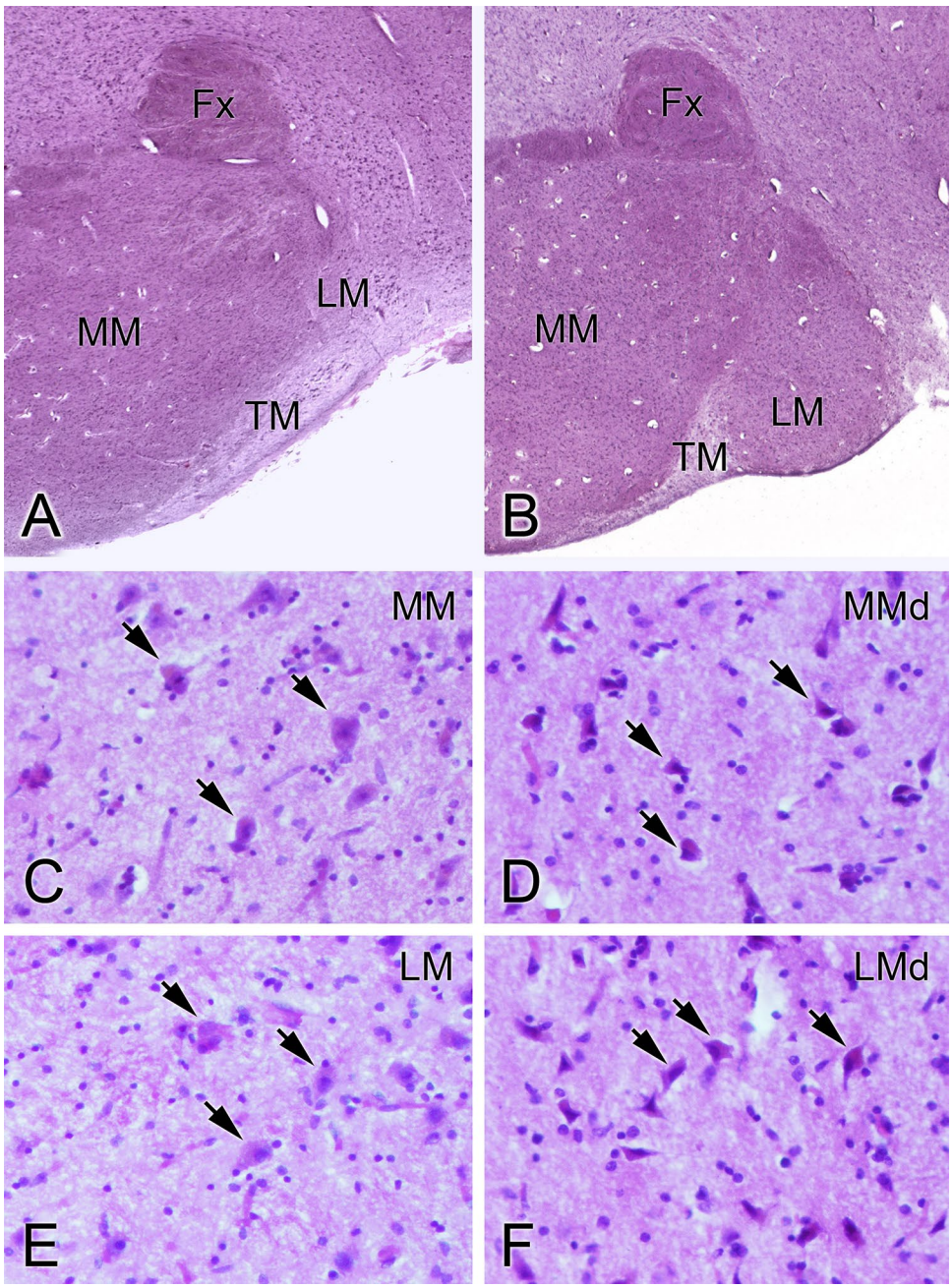

Fig. 2 Cytoarchitectonics of the mammillary nuclei in normal case (**a, c, e**) and in case of the accessory mammillary bodies (**b, d, f**). The morphology of the cells of the medial mammillary nucleus (**c, d**, arrows) is nearly identical to that of the cells of the lateral nucleus (**e, f**, arrows). However, cells appeared to have more well-defined perikarya and processes in case of the dual mammillary bodies (**d, f**, arrows) when compared to normal (**c, e**, arrows). *Fx* fornix, *LM* lateral mammillary nucleus, *LMd* lateral mammillary nucleus in case of dual mammillary bodies, *MM* medial mammillary nucleus, *MMd* medial mammillary nucleus in case of dual mammillary bodies, *TM* tuberomammillary nucleus. Arrows depict characteristic neurons in the mammillary nuclei. Magnification: **a, b**, ×25; **c–f** ×400

well-defined processes (Fig. 2d, f, arrows) when compared to normal mammillary bodies (Fig. 2c, e, arrows).

Discussion

The record of the patient did not contain any neurological and neuroendocrine disorders; therefore, the functional significance of dual mammillary bodies is hard to speculate and requires further comparative immunohistochemical studies. Lesions of the mammillary bodies are linked with amnesia, and it has been suggested that the medial and lateral mammillary nuclei function in a synergistic way in memory formation controlling theta rhythm and head direction information, respectively (for review see Vann and Aggleton 2004). However, it is extremely difficult to extrapolate animal data, outlining the functions of the medial and lateral mammillary nuclei, to human, since cytoarchitecturally the human lateral mammillary nucleus does not appear to be equivalent with the same-named structure in rats (Saper 2004; Vann and Aggleton 2004).

Cytoarchitectonical examination of the medial and lateral mammillary nuclei revealed that the cells that form the nuclei are nearly identical. However, the cells appeared to have more well-defined perikarya and processes in case of the dual mammillary bodies. Whether this morphology may be the result of functional differences or *vice versa*, is entirely speculative considering the uniqueness of the sample and the case in the medical literature; nevertheless it is likely that the projection areas of the enlarged lateral mammillary nucleus may involve additional targets in the central nervous system. The distended lateral nucleus, with a medial mammillary nucleus that appears to be normal size may also settle the long-standing debate whether the distinction between the lateral and medial mammillary nuclei are artificial as suggested by Saper (2004), indicating also that rat mammillary morphology cannot be extrapolated to humans. Additionally, the enlarged lateral mammillary nucleus indicates that this nucleus is an individual complex probably with distinct function(s) and not simply a lateral shell of the medial mammillary nucleus, as suggested by other authors. Finally, in addition to the possible functional consequences, lateral mammillary bodies can be falsely identified as various neuropathological processes of the basal diencephalon including gliomas; therefore, it is extremely important to disseminate this unique morphological variant among clinicians.

Author contributions TC, acquisition of data and critical revision of manuscript for intellectual content. GG, acquisition of data and critical revision of manuscript for intellectual content. RK, acquisition of data and critical revision of manuscript for intellectual content. IM, critical revision of manuscript, interpretation of data, and study supervision. BD, study concept and design, critical revision of manuscript for intellectual content, analysis and interpretation of data, and study supervision.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research Involving Human Participants The brain utilized in these studies was harvested 12 h *post mortem* period in accordance with the regulations of the Institutional Review Board of Lake Erie College of Osteopathic Medicine (LECOM). See materials and methods.

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