# Mammillary Body Volume Loss in Patients with Congenital Central Hypoventilation Syndrome

**R. Kumar[1], K. Lee[1], P. M. Macey[2], M. A. Woo[2], and R. M. Harper[1]**

[1]Neurobiology, David Geffen School of Medicine at UCLA, University of California at Los Angeles, Los Angeles, CA, United States, [2]School of Nursing, University of California at Los Angeles, Los Angeles, CA, United States

## Introduction:

Congenital central hypoventilation syndrome (CCHS) patients show reduced ventilatory responses to $CO_2$ and $O_2$, loss of respiratory drive during sleep, impaired autonomic regulation, and affective and cognitive problems, including learning and memory deficits, likely due to hypoxic injury or mal-development. Several rostral brain sites are affected in CCHS, including the hippocampus and anterior thalamus (1), which are essential for memory processing. The areas show structural damage and impaired functional MRI signal responses to autonomic and ventilatory challenges (1-4). However, resolution and other image acquisition issues precluded detailed evaluation of other memory formation structures, including the mammillary bodies. The mammillary bodies, their afferent fornix fibers, and efferent axons of the mammillothalamic tract to the anterior thalamus are essential components of hippocampal-originated circuitry for short-term and spatial memory functions. The mammillary bodies are injured in several conditions characterized by memory deficits, including Wernicke-Korsakoff's (WKS) syndrome, Alzheimer's disease (AD), obstructive sleep apnea (OSA), and heart failure (HF). The processes triggering mammillary body damage include alcohol toxicity (WKS), suspected intermittent hypoxia, impaired perfusion, and inflammatory damage (AD, HF, OSA). An exacerbating condition in WKS, and possibly HF, is thiamine deficiency, due to nutritional malabsorption from alcoholism, or from fluid regulatory problems in HF. CCHS patients show both dietary malabsorption accompanying impaired development of visceral ganglia and fluid regulatory problems, potentially leading to thiamine deficiency and in turn reduced neuroprotection to excitotoxic or other injury from hypoxia associated with hypoventilation in the syndrome. We evaluated mammillary body volumes in CCHS using high-resolution T1-weighted MRI and region-of-interest volumetric procedures.

## Materials and methods:

Fourteen CCHS patients (mean age ± SD: 15.1 ± 2.3 years; range: 12-18 years; 8 male) and 31 control subjects (15.1 ± 2.4 years; 10-19 years; 17 male) were studied. The diagnosis of CCHS was based on American Thoracic Society criteria, and subjects were recruited through the CCHS family network. Control subjects were healthy, and were recruited through advertisements at the university campus.

Brain studies were performed with a 3.0 Tesla MRI scanner (Magnetom Trio; Siemens). Two high-resolution T1-weighted image volumes were collected using a MPRAGE pulse sequence (TR = 2200 ms; TE = 3.05 ms; inversion-time = 1100 ms; flip-angle = 10°; matrix size = 256 × 256; FOV = 220 × 220 mm; slice thickness = 1.0 mm). Proton-density (PD) and T2-weighted images were collected, using a dual-echo turbo spin-echo pulse sequence (TR = 8000 ms; TE1, 2 = 17, 133 ms; flip-angle = 150°; matrix size = 256 × 256; FOV = 240 × 240 mm; slice thickness = 5.0 mm) for anatomical evaluation. Data were analyzed with SPM5, MRIcron, and Matlab-based custom software. Both T1-weighted image volumes were realigned, and averaged to increase signal-to-noise ratio; averaged images were reoriented into a common space. The reoriented image volumes were partitioned into gray matter, white matter, and cerebrospinal fluid probability maps, and total intracranial volume of each subject was calculated (voxels classified as intracranial if probability > 0.5). Using averaged and reoriented images, subvolumes containing the mammillary bodies were oversampled at 0.2×0.2×0.2 mm. A single investigator, blinded to group assignment, delineated mammillary body structures using MRIcron. Delineated voxels in each mammillary body were counted, and volumes of the body on each side were calculated. Numerical demographic data were evaluated with independent-samples t-tests and categorical values with Chi-square test. Mammillary body volume differences were assessed using multivariate analysis of covariance, with age and total intracranial volumes included as covariates.

## Results:

Age and gender showed no significant differences between the groups. The mammillary body volumes of CCHS and controls are summarized in Table 1. No significant differences in age and gender emerged between the groups. Reduced mammillary body volumes in CCHS were visually apparent on high-resolution T1-weighted images from individual CCHS subjects (Fig. 1). Both left and right mammillary body volumes were significantly reduced in CCHS compared to control subjects after controlling for age and total intracranial volumes.

**Table 1: Mammillary body volumes of CCHS and control subjects.**

| Mammillary body | CCHS (n = 14) (Mean ± SD, $mm^3$) | Control (n = 31) (Mean ± SD, $mm^3$) | *p values |
|---|---|---|---|
| Left | 84.7 ± 15.0 | 90.5 ± 13.7 | 0.005 |
| Right | 87.1 ± 13.6 | 89.4 ± 14.2 | 0.040 |

* = p values corrected for age and total intracranial volume.

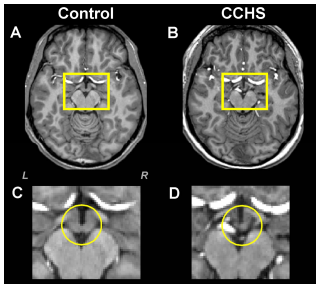


**Fig. 1:** High-resolution T1-weighted images show mammillary bodies in a control (A; *L = Left, R = Right*) and CCHS (B) subject (yellow rectangles). Images (C) and (D) show magnified areas within the rectangles of the control (A) and CCHS (B). The right mammillary body in CCHS is smaller, and the left body is much smaller, compared to the control (C vs D, yellow circles).

## Discussion:

Both left and right mammillary body volumes are reduced in CCHS compared to age- and gender-matched control subjects. The hippocampus and anterior thalamus earlier showed both structural injury and functional deficits during autonomic and ventilatory challenges in CCHS patients. The findings of additional structural injury in the mammillary bodies, which are essential components of memory circuitry, may underlie a major portion of the cognitive deficits in CCHS subjects. Hypoxic processes, along with deficiencies of micronutrients such as thiamine and magnesium resulting from malabsorption and altered fluid regulation, may contribute to the tissue injury.

## References:

1. Kumar R, Macey PM, Woo MA, et al. *J Comp Neurol* 2005; 487:361–371.
2. Kumar R, Macey PM, Woo MA, et al. *Pediatr Res* 2008; 64:275–280.
3. Harper RM, Macey PM, Woo MA, et al. *J Neurophysiol* 2005; 93:1647–1658.
4. Macey PM, Woo MA, Macey KE, et al. *J Appl Physiol* 2005; 98:958–969.

**Grants:** Supported by the National Institute of Child Health and Human Development R01 HD-22695.