

## Reduced Caudate Nuclei Volumes in Patients with Congenital Central Hypoventilation Syndrome

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### Introduction:

Congenital central hypoventilation syndrome (CCHS) patients show a range of autonomic and neuropsychological deficits, including mood and cognitive irregularities that may result from brain injury. Brain imaging studies show structural injury and functional deficits in cerebellar, brainstem, rostral brain, and limbic sites including caudate nuclei (1-5). Caudate nuclei are key structures for mood and cognition regulation. The structures interact with several brain areas, including thalamic and frontal cortices, and mediate major circuitry for higher cognitive and limbic functions, including pathways to the dorsolateral prefrontal and lateral orbito-frontal cortices. Most of these structures showed injury in CCHS, based on gross voxel-based analytic procedures. However, the magnitude of injury specific to the caudate nuclei in CCHS is unknown. Our aim was to assess caudate nuclei in CCHS and age- and gender matched control subjects using high-resolution T1-weighted imaging and volumetric assessment based on region-of-interest procedures. We hypothesized that CCHS patients would show reduced caudate nuclei volume compared to control subjects.

### Materials and methods:

We studied 14 CCHS patients (mean age  $\pm$  SD:  $15.1 \pm 2.3$  years; range: 12-18 years; 8 male) and 31 control subjects ( $15.1 \pm 2.4$  years; 10-19 years; 17 male). The diagnosis of CCHS was based on American Thoracic Society criteria, and subjects were recruited through the CCHS family network. Control subjects were healthy, without any neurological issue or other problems that could affect brain tissue, and were recruited through advertisements at the university campus.

Brain imaging studies were performed with a 3.0 Tesla MRI scanner (Magnetom Trio; Siemens, Erlangen, Germany). Two high-resolution T1-weighted image volumes were collected using a magnetization prepared rapid acquisition gradient-echo pulse sequence (TR = 2200 ms; TE = 3.05 ms; inversion-time = 1100 ms; flip-angle = 10°; matrix size =  $256 \times 256$ ; FOV =  $220 \times 220$  mm; slice thickness = 1.0 mm). Proton-density and T2-weighted images were also collected, using a dual-echo turbo spin-echo pulse sequence (TR = 8000 ms; TE1, 2 = 17, 133 ms; flip-angle = 150°; matrix size =  $256 \times 256$ ; FOV =  $240 \times 240$  mm; slice thickness = 5.0 mm) for visual examination. Data were analyzed with SPM5, MRIcron, and Matlab-based custom software. High-resolution T1-weighted image volumes were realigned to remove possible motion, and averaged to increase signal-to-noise ratio; averaged images were reoriented into a common space and sampled to  $0.9 \times 0.9 \times 0.9$  mm. The averaged and reoriented images were partitioned into gray matter, white matter, and cerebrospinal fluid probability maps, and total intracranial volume of each subject was calculated using these probability maps (voxels classified as intracranial if probability  $> 0.5$ ). Using reoriented and sampled images, a single investigator blinded to group assignment outlined left and right caudate nuclei with MRIcron software. Outlined voxels in each caudate nucleus were counted, and volumes of the structure on each side were calculated. Numerical demographic data were evaluated with independent-samples t-tests and categorical data were assessed with Chi-square test. Caudate nuclei volumes were assessed between groups using a multivariate analysis of covariance, with age and total intracranial volumes included as covariates.

### Results:

No significant differences in age and gender appeared between CCHS and control groups. Caudate nuclei volumes of CCHS and control subjects are summarized in Table 1. Both left and right caudate nuclei volumes were significantly reduced in CCHS compared to control subjects, after controlling for age and head sizes.

**Table 1: Caudate nuclei volumes of CCHS and control subjects.**

| Caudate nucleus | CCHS (n = 14)<br>(Mean $\pm$ SD, mm <sup>3</sup> ) | Control (n = 31)<br>(Mean $\pm$ SD, mm <sup>3</sup> ) | *p values |
|-----------------|--|---|-----------|
| Left            | $4293.55 \pm 549.22$                               | $4626.87 \pm 593.41$                                  | < 0.001   |
| Right           | $4376.29 \pm 565.42$                               | $4747.81 \pm 578.13$                                  | < 0.001   |

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

### Discussion:

Left and right caudate nuclei show significantly reduced volumes in CCHS over similar age- and gender-matched control subjects. Caudate nuclei interact with other cortical sites, including the thalamus, frontal, and prefrontal cortices. Cognitive deficits can be produced by injury to specific areas of prefrontal cortex, and these deficits can be reproduced with lesions to caudate nuclei; the reduced caudate nuclei volumes found here likely contribute to the cognitive and behavioral deficits found in CCHS. Tissue injury may result from hypoxic processes, together with micronutrient deficiencies, including low thiamine and magnesium levels deriving from malabsorption and impaired fluid regulation in the condition, leading to impaired cellular carbohydrate metabolism.

### References:

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