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Dilated basilar arteries in patients with congenital central hypoventilation syndrome

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ABSTRACT

Congenital central hypoventilation syndrome (CCHS) patients show hypoventilation during sleep and severe autonomic impairments, including aberrant cardiovascular regulation. Abnormal sympathetic patterns, together with increased and variable CO_2 levels, lead to the potential for sustained cerebral vasculature changes. We performed high-resolution T1-weighted imaging in 13 CCHS and 31 control subjects using a 3.0-T magnetic resonance imaging scanner, and evaluated resting basilar and bilateral middle cerebral artery cross-sections. Two T1-weighted image series were acquired; images were averaged and reoriented to common space, and regions containing basilar and both middle cerebral arteries were oversampled. Cross-sections of the basilar and middle cerebral arteries were manually outlined to calculate cross-sectional areas, and differences between and within groups were evaluated. Basilar arteries in CCHS were significantly dilated over control subjects, but both middle cerebral artery cross-sections were similar between groups. No significant differences appeared between left and right middle cerebral arteries within either group. Basilar artery dilation may result from differential sensitivity to high CO_2 over other vascular beds, damage to serotonergic or other chemosensitive cells accompanying the artery, or enhanced microvascular resistance, and that dilation may impair tissue perfusion, leading to further neural injury in CCHS.

Congenital central hypoventilation syndrome (CCHS) is a genetic condition characterized by mutations in a transcription protein for cellular nervous system development, PHOX2B [2,34], which in the mouse, targets the expression of neurons in autonomic and certain brainstem respiratory ganglia [7,8,25,30]. Affected patients show multiple autonomic and physiological deficits, including impaired CO_2 and O_2 sensitivity, and reduced breathing drive during sleep [1,9,27]. Autonomic impairments in CCHS include increased and poorly-regulated sympathetic tone, with associated impaired blood pressure control, and a range of parasympathetic alterations [1,16,31,35]. Impaired sympathetic regulation, as well as increased and variable CO_2 levels from hypoventilation during sleep, and occasionally during waking, lead to the potential for cerebral vasculature constriction or dilation.

Changes in cerebral vessel diameter exert substantial blood flow and arterial pressure effects [11]. Increased CO_2 levels in blood or surrounding tissue dilate cerebral vessels [4], with hypotension accompanying the dilatation in vasculature [36]. Since CCHS subjects show increased and inconsistent CO_2 levels, as well as day-time hypotension [31], cerebral blood vessels may show long-lasting dilation after sustained exposure to hypercapnia during development.

Our aim was to assess dilation in major cerebral vessels in CCHS patients, relative to control subjects. We evaluated middle cerebral and basilar arteries, since these two arterial systems supply many of the structures affected in the syndrome [13]. We hypothesized that CCHS subjects would show dilated major arteries relative to control subjects.

We studied 13 CCHS patients (mean age ± SD: 15.1 ± 2.4 years; range: 12–18 years; mean body-mass-index ± SD: 20.8 ± 3.9 kg/m^2; 8 male) and 31 control subjects (15.0 ± 2.3 years; 10–19 years; 21.2 ± 4.3 kg/m^2; 18 male) during unsedated awake conditions. CCHS subjects were recruited from the CCHS family network (http://www.cchsnetwork.org), and were diagnosed based on standard criteria [1]. Of the 13 CCHS subjects, five showed PHOX2B mutations, tests on two were inconclusive, and the remaining six were untested. We included only those CCHS subjects who required ventilatory support during sleep, but not during waking. CCHS subjects with other conditions affecting the cerebral vasculature, e.g., cardiac disease, were also excluded.

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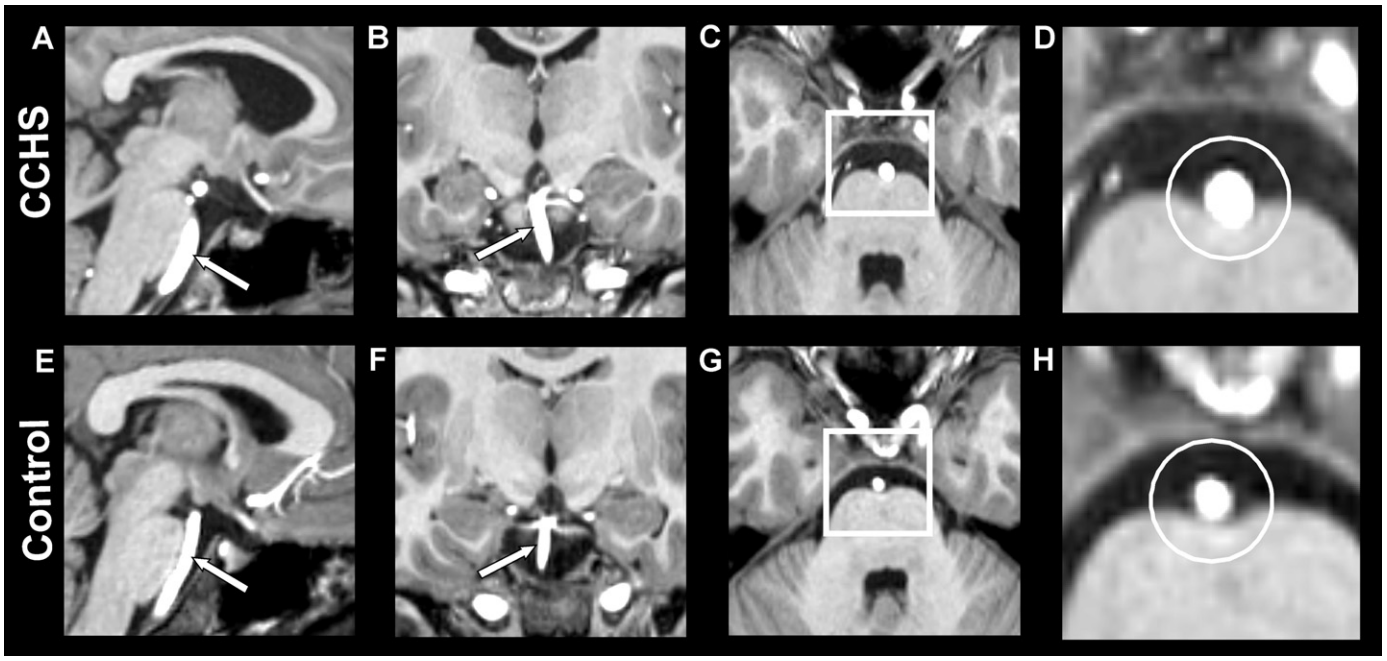

Fig. 1. High-resolution T1-weighted images show the basilar artery in a CCHS and control subject. The upper panel shows longitudinal (A, sagittal section; B, coronal section) and cross-sectional views (C, axial section, white square; D, magnified area of the square in image C, white circle) of the basilar artery in a CCHS subject (age 14.3 years, male). The lower panel shows longitudinal (E, sagittal section; F, coronal section) and cross-sectional views (G, axial section, white square; H, magnified area of the square in image G, white circle) of the basilar artery in a control subject (14.4 years, male). The basilar artery cross-section in CCHS is larger than the control subject (D vs. H).

Control subjects were in good health, without neurological or cardiovascular disorders, and were recruited through advertisements at the university campus. The study was approved by the Institutional Review Board of the University of California at Los Angeles, and all subjects and their parents/guardians gave informed written consent/assent before the study.

We performed brain studies with a 3.0-T magnetic resonance imaging (MRI) scanner (Magnetom Trio; Siemens, Erlangen, Germany). During data collection, subjects lay supine; foam pads on both sides of the head reduced head-motion. The present vascular study was performed as part of other neurological evaluations; thus, angiographic procedures were not performed. Two high-resolution T1-weighted image series were collected in the axial plane (minimal oblique), using a magnetization-prepared-rapid-acquisition gradient-echo pulse sequence (repetition-time = 2200 ms; echo-time = 3.05 ms; inversion-time = 1100 ms; flip-angle = 10°; matrix size = 256 × 256; field-of-view = 220 mm × 220 mm; slice-thickness = 1.0 mm; phase-encoding = $R \gg L$; magnetization-preparation = slice-selective inversion-recovery). Proton-density (PD) and T2-weighted images were also collected in the axial plane, using a dual-echo turbo spin-echo pulse sequence (repetition-time = 8000 ms; echo-time 1, echo-time 2 = 17, 133 ms; flip-angle = 150°; matrix size = 256 × 256; field-of-view = 240 mm × 240 mm; slice-thickness = 5.0 mm), for visual examination of clinical pathology.

Both T1-weighted image series were examined for head motion-related or other image artifacts. T1-, T2-, and PD-weighted images were assessed to verify absence of major brain pathology.

The statistical parametric mapping package SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), MRIcron [28], and MATLAB-based (The MathWorks Inc., Natick, MA) custom software were used to process the high-resolution T1-weighted images, outline cerebral artery cross-sections, and calculate cross-sectional areas.

We realigned both high-resolution T1-weighted image series, and averaged the images to increase signal-to-noise ratio. The averaged images were bias-corrected for any signal inhomogeneity, reoriented into a common space, using a 6-parameter rigid-body (non-distorting) affine transformation, and sampled to a resolution of 0.9 mm × 0.9 mm × 0.9 mm.

Brain regions containing basilar and both middle cerebral arteries were oversampled to a resolution of 0.2 mm × 0.2 mm × 0.2 mm. If required, images containing the basilar artery were manually rotated such that the artery was perpendicular in sagittal and coronal views. Image contrast was visually standardized for all brain images containing basilar and both middle cerebral arteries. An investigator, blinded to subject group, outlined cross-sections of both sets of arteries. For each subject, the basilar artery was identified in sagittal views, and the cross-section was manually outlined in an axial view at the level of the mid basal-pons. Both left and right middle cerebral arteries were identified in axial views, and were traced in sagittal views at a level immediately after exit from the Circle of Willis. Pixels in each artery cross-section were counted, and cross-sectional areas were calculated.

We used the SPSS (v 15.0) statistical software for statistical assessment. Demographic data were compared with independent-samples *t*-tests and the Chi-square test. Cross-sectional areas of the basilar and left and right middle cerebral arteries between the CCHS and control groups and left and right middle cerebral arteries within CCHS and control groups were assessed using independent-samples *t*-tests. Intra- and inter-tracer reliabilities were measured with intraclass correlation coefficient (ICC) procedures.

Intra- and inter-tracer reliabilities for outlining basilar and middle cerebral artery cross-sections were established. An investigator, who outlined all cross-sections, re-outlined cross-sections of the arteries in 8 randomly-selected subjects (5 controls, 3 CCHS). A second investigator also outlined cross-sections in the same subjects. We calculated intra-tracer and inter-tracer reliabilities, which were high (intra-tracer: basilar artery, ICC = 0.99; middle cerebral artery, ICC = 0.87; inter-tracer: basilar artery, ICC = 0.98; middle cerebral artery, ICC = 0.86).