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Is encroachment of the carotid termination into the substantia innominata associated with its atrophy and cognition in Alzheimer's disease?

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ABSTRACT

The internal carotid artery termination (CAT) ends in a T-shaped bifurcation just below the substantia innominata (SI), which contains cognitively strategic cholinergic neurons and undergoes atrophy in Alzheimer's disease (AD). This study investigated whether an elongated CAT with possible resulting encroachment into the SI would correlate with SI atrophy and with cognitive dysfunction in AD. We rated the degree of CAT encroachment upon the SI and measured SI volume on magnetic resonance imaging in 30 AD patients, 30 AD patients with subcortical small vessel disease, and 30 age-matched controls. CAT encroachment significantly correlated with SI volume after adjusting for age within the overall group and the groups with dementia. AD patients with higher CAT encroachment scores had lower SI volumes and lower attention, memory, and executive test scores. These data suggest that CAT encroachment may mechanically injure the SI, exacerbating cholinergic damage and contributing to cognitive impairment. This process may represent a possible previously underappreciated mechanism for interaction between large-vessel cerebrovascular disease and AD.

1. Introduction

The substantia innominata (SI) of the basal forebrain contains the basal nucleus of Meynert, which accounts for 70% to 80% of cholinergic innervation to most of the cerebral cortex (Mesulam and Geula, 1988; Selden et al., 1998). Cholinergic deficits contribute to memory, attention, and executive dysfunction, especially in patients with Alzheimer's disease (AD) (Behl et al., 2007; Mesulam, 2004; Sarter et al., 2003). SI atrophy has been widely demonstrated using magnetic resonance imaging (MRI) from the presymptomatic state to clinical dementia of AD in vivo (Callen et al., 2001; Hall et al., 2008; Hanyu et al., 2002; Teipel et al., 2005), and profound cholinergic neuron loss in the SI has been shown in AD post mortem (Vogels et al., 1990; Whitehouse et al., 1981).

Although mechanisms underlying cholinergic basal forebrain atrophy in AD remain to be fully elucidated, cerebrovascular disease may be implicated. Large-vessel atherosclerosis has been found to be more severe at the circle of Willis in AD patients than in normal controls (Roher et al., 2003; Yarchoan et al., 2012). As the SI is irrigated by penetrating branches from the carotid artery termination (CAT), which bifurcates into the proximal anterior and middle cerebral arteries, atherosclerosis-induced hypoperfusion could exacerbate SI atrophy in AD (Roher et al., 2003; Roman and Kalaria, 2006). Furthermore, atherosclerotic or arteriosclerotic arteries can also gradually become elongated and tortuous with aging or increased blood pressure, a phenomena called dolichoectasia (Dobrin et al., 1988; Dougherty and Varro, 2000). It is known that sclerotic elongated arteries can produce direct compression on adjacent structures, such as cranial nerves and brainstem, resulting in cranial nerve palsies, motor limb weakness, gait ataxia, and even

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obstructive hydrocephalus (Passero and Rossi, 2008; Smoker et al., 1986). The unique "T"-shaped CAT receives greater hemodynamic forces than the main artery even under normal circumstances (Foutrakis et al., 1999), and anatomically abuts the SI (Fig. 1). Thus, it is conceivable that an elongated CAT could gradually encroach upon the SI, eventually contributing to compressive SI atrophy.

In a previous MRI study of the limbic system in AD, we noticed incidentally that severe SI atrophy was often associated with encroachment by an elongated CAT (Callen et al., 2001). Our objective, therefore, was to assess possible relationships between degree of CAT encroachment and both SI volumes on MRI and cognition, in AD patients and age-matched controls. We hypothesized that increased CAT encroachment would correlate with decreased SI volumes and with lower cognitive performance, especially on attention, memory, and executive tasks, which appear to be selectively impaired with cholinergic dysfunction (Behl et al., 2007).

2. Methods

2.1. Study population

We included 60 patients with probable or possible AD, based on the National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984; their diagnoses would also be compatible with McKhann, et al., 2011). Subcortical ischemic small-vessel disease (SVD) was the only secondary contributing pathology, with half of the AD patients (n = 30) having mild white matter hyperintensities (WMH) at the most on their MRI and being defined as having "pure" AD. The other half of AD patients, showing lacunes or moderate but not severe WMH, were called AD/SVD (n = 30); these patients did not meet criteria for vascular dementia (Roman et al., 1993). Severity of WMH was assessed using the age-related white matter change (ARWMC) scale (maximum score, 30) (Wahlund et al., 2001). Mild WMH were defined as ARWMC scores <8, and moderate WMH were defined as ARWMC scores ≥ 8 (the upper tertile in this series). Thirty age-matched, healthy, community-dwelling controls were also included.

A 5-point vascular risk factor score was calculated based on the presence of hypertension, hyperlipidemia, diabetes, coronary, or peripheral arterial disease and history of transient ischemic attack (1 point for each).

All participants were part of the Sunnybrook Dementia Study (Behl et al., 2007; Bocti et al., 2005), and were recruited from the Cognitive Neurology Clinic at Sunnybrook Health Sciences Centre, an academic healthcare institution of the University of Toronto. The study was approved by the institutional Research Ethics Board, with informed consent obtained from all participants or their substitute decision makers. Of the 90 subjects, 28 (21 normal controls and 7 patients with dementia) were included in our previously mentioned study (Callen et al., 2001), in which we incidentally observed that SI atrophy was often associated with encroachment by an elongated CAT. However, these 2 studies are independent of each other.

2.2. Neuropsychological assessment

Subjects underwent standardized neuropsychological testing of major cognitive domains. Because cholinergic deficits are associated with impaired memory, attention, and executive functioning, we used both the total Mattis Dementia Rating Scale (DRS) score, (which provides subscores on attention, initiation, construction, concentration, and memory) (Mattis, 1976) and Mini-Mental State Examination (MMSE) scores to capture general cognitive function (Folstein et al., 1975). Executive functioning was additionally measured by time taken for Trail-Making Test Part B (Trail-Making B) (Reitan and Wolfson, 1993) and phonemic fluency (FAS) (Lezak, 1995). Episodic memory was measured using acquisition score on the California Verbal Learning Test (CVLT) (Delis et al., 1987).

2.3. MRI technique

Imaging was performed on a General Electric 1.5 Tesla MR magnet using a standardized protocol including proton density and T2-weighted sequences (TR = 3000 milliseconds, TE = 30–80 milliseconds, excitation = 0.5, field of view [FOV] = 20 × 20 cm, matrix = 256 × 192, slice thickness = 3 mm, acquisition time = 11.5 minutes) and an axial T1-weighted 3D volumetric spoiled gradient echo sequence (TR = 5 milliseconds, TE = 35 milliseconds, excitation = 1, flip angle = 35°, matrix = 256 × 192, in-plane resolution = 0.86 × 0.86 mm, slice thickness = 1.2 mm, and number of slices = 124). 3D-T1 MR images were resized to 0.86 × 0.86 × 0.86-mm isotropic voxels and realigned to the anterior commissure–posterior commissure (AC-PC) plane (Talairach and Tournoux, 1988).

2.4. Measuring CAT encroachment upon the SI

A rating scale was developed to quantify the severity of CAT encroachment in relation to the SI. In coronal sections perpendicular to the AC-PC plane, 3 consecutive slices (thickness = 0.86 mm) under the anterior commissure (AC) were used to score CAT encroachment from 0 to 2 on each slice (Fig. 2), and the maximum scores were 6 for each side. Two raters (J.P., F.G.), blind to clinical information and SI volumes, scored CAT encroachment.

2.5. Measuring SI atrophy

SI volume was obtained from the same 3 coronal slices used above according to our published protocol (Callen et al., 2001). SI was defined as the area under the AC. The decussation of the AC is

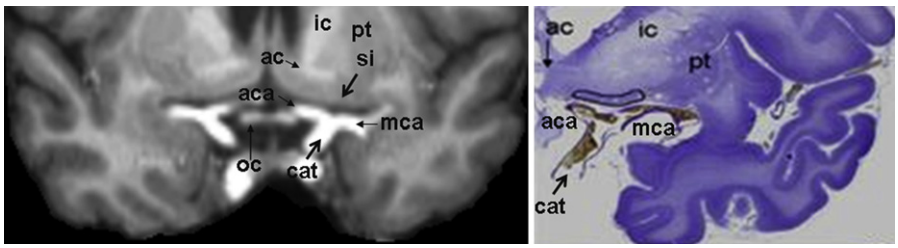

Fig. 1. MRI (left) showing the spatial relationship between the carotid artery termination (CAT) and substantia innominata (SI). Corresponding Nissl-stained coronal section (right) of the left hemisphere of a post-mortem brain (with permission from deToledo-Morrell) at the level of the anterior commissure (AC) illustrates the SI (black outline), the region containing cholinergic neurons, lies right above the CAT, which bifurcates into the proximal anterior cerebral (ACA) and middle cerebral arteries (MCA). Abbreviations: ic, internal capsule; oc, optic chiasm; pt, putamen.