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Stroke, Dementia and Alzheimer's Disease: Vascular Disorders of the Brain

Clinical Description and Possible Breakthrough Therapies

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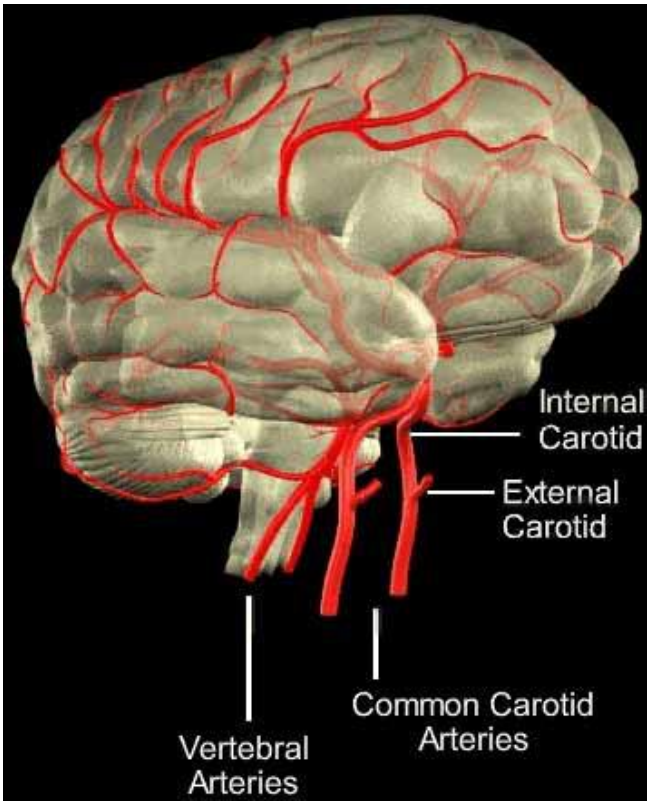
I. Introduction

A. The Brain's Vascular System

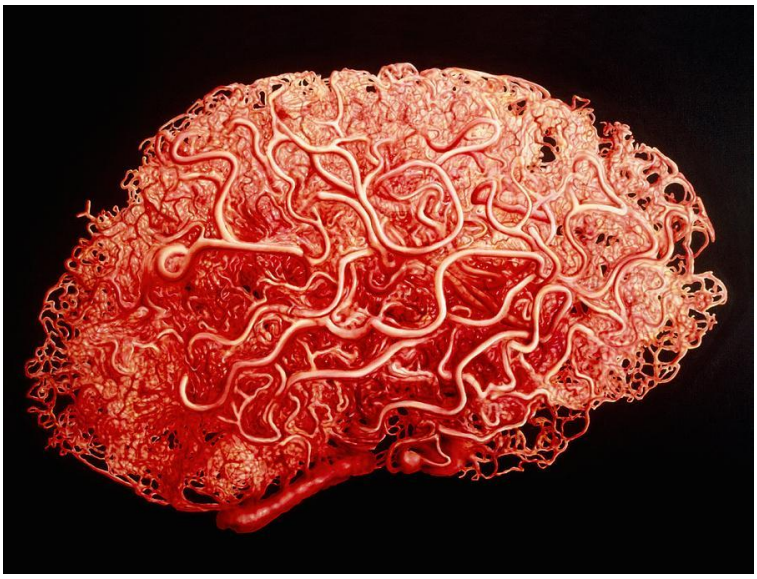
Although the brain is only about 2% of the total body weight in humans, it receives 15-20% of the body's blood supply. Because brain cells will die if the supply of blood which carries oxygen is stopped, the brain is the body's top priority for blood perfusion. Even if other organs need blood, the body first attempts to supply the brain with a constant flow of blood. Two major groups of arteries supply the brain with blood, including the left and right carotid arteries and the middle, anterior and posterior cerebral arteries (Figure 1 below). As will be discussed in greater detail below, blockage of these arteries leads to acute stroke resulting in neuronal cell death, functional impairment and death in many cases.

Figure 1: *The Major Arteries Supplying Blood to the Brain, Including the Carotid and Vertebral Arteries*



These major arteries break down into a vast array of smaller arteries, arterioles and capillaries in the brain supplying glucose and other necessary nutrients to the billions of neurons comprising the brain and removing waste products that these neurons generate as part of their intense metabolic functioning. Figure 2 is a representation of this vast array of blood vessels in the brain. As will be described below, blockage or rupture of these smaller vessels can lead to mini-strokes, which over time can give rise to a condition known as multi-infarct dementia. In addition, recent evidence has pointed to vascular dysfunction in the smaller vessels of the brain as the very earliest step in the progression of events that ultimately leads to Alzheimer's disease.

Figure 2: *The Brain's Vasculature: The supply of blood to the brain is carried out by a vast network of arteries, smaller arterioles and capillaries*



This extensive vascularization of the brain is crucial to bring the brain its primary fuel source, glucose. Glucose is virtually the sole fuel for the human brain, except during prolonged starvation. The brain lacks fuel stores and hence requires a continuous supply of glucose, which in turn is dependent on an intact and functional vascular architecture.

In humans, the brain consumes ~20% of glucose-derived energy making it the main consumer of glucose. Tight regulation of glucose metabolism is critical for brain physiology and disturbed glucose metabolism in the brain underlies several diseases affecting both the brain itself as well as the entire organism. For example, if there isn't enough glucose in the brain, neurotransmitters, the brain's chemical messengers, are not produced and communication between neurons breaks down. As will be discussed later in this paper, long-term diabetes—either type 1 or type 2—has many consequences for the brain and for its neurons, including that high blood glucose levels can lead to small-vessel disease in the brain, which restricts blood flow, and can lead to cognitive difficulties and, if severe enough, spur the development of vascular dementia.

B. Vascular Dysfunction in the Brain

A healthy and intact vascular system in the brain is critical for normal human functioning, both motor and cognitive. Any disruption in the brain's blood perfusion system can lead to dire consequences, as the brain neurons are deprived of glucose and oxygen and begin to quickly atrophy and die. A number of medical conditions are characterized by a disruption of blood flow to the brain and these will be reviewed below. Some conditions, such as stroke, have long been known to be directly tied to a breakdown in the brain's vasculature system. With others, such as Alzheimer's disease, it has only recently been appreciated that a critical early step in the

progression of this disease is a disruption in the functioning of the small arteries supplying blood to the brain.

II. Acute Stroke

Stroke (Figure 4) is the 5th leading cause of death in the US, with one person dying every 4 minutes as a result. Approximately 800,000 people have a stroke each year; about one every 40

Figure 4: *The Onset of Stroke with Destruction of Brain Tissue*

seconds. Only heart disease, cancer, chronic lower respiratory diseases and accidents are more deadly. In the US, approximately 40% of stroke deaths are in males, with 60% in females. According to the American Heart Association (AHA), compared to white people, black people have nearly twice the risk of a first-ever stroke and a much higher death rate from stroke.

Strokes are a direct result of a disruption in the brain's vascular system: either the blood supply is blocked or a blood vessel within the brain ruptures, causing brain tissue to die.

There are three main kinds of stroke: