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Choroid plexus portals and a deficiency of melatonin can explain the neuropathology of Alzheimer's disease

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SUMMARY

Presently, the textbook description of cerebrospinal fluid absorption is through the arachnoid granules into the superior sagittal sinus. The theory is based on non-physiologic experiments and fails to explain multiple observations. Photographs and microphotographs of choroid plexus portals are included. Evidence is presented that cerebrospinal fluid is moved from the choroid fissure into the ventricular system. The deposition pattern of corpora amylacea demonstrates the bulk flow of cerebrospinal fluid. Melatonin is found in higher concentration in the cerebrospinal fluid than in simultaneously sampled blood. Melatonin is a potent antioxidant and the loss of its protection in the cerebrospinal fluid in Alzheimer's disease can explain the pattern of cell destruction. Challenges of the embedded dogma of the arachnoid granule absorption of cerebrospinal fluid have been ignored; however this old faulty theory must be abandoned in order to understand the pathophysiology of Alzheimer's disease.

Introduction

The presence of choroid plexus portals is not recognized as an entity and the functions of the portals are not understood. Cerebrospinal fluid (CSF) is primarily produced by the ventricular choroid plexuses and bulk absorption is said to occur through the arachnoid granule–superior sagittal sinus system, as described in textbooks of anatomy and physiology. This presently accepted theory of CSF absorption is entrenched in medical literature. However, it is based on original experiments that were not physiological [1]. Such widely accepted dogma, held for so many years, is extremely resistant to scientific challenge.

The choroid plexus portal theory of CSF circulation can offer explanations for the neuropathology of Alzheimer's disease (AD), the deposition pattern of corpora amylacea (CA) on the surface of the brain, the neuropathology of intrathecal vincristine, the cisternograms of intrathecal radioactive gold, events in normopressure (communicating) hydrocephalus, the findings in superficial siderosis of the brain, the movement of intrathecal horseradish peroxidase from cistern to choroid plexus capillaries with the lack of staining in the arachnoid granules, the movement of radioactive inulin, the high concentrations of melatonin in ventricular CSF, the distribution pattern of intrathecal carbon particles, the findings in sudden infant death syndrome, the lack of hydrocephalus in patients with complete thrombosis of the superior sagittal sinus, the cause of deafness following bacterial meningitis, and why the absence of arachnoid granules in human infants does not cause hydrocephalus [1–15]. The arachnoid granule–superior sagittal sinus theory fails to explain the mentioned observations.

Photographs and microphotographs of the anatomy and histology of the choroid plexus portals will be presented. Understanding the circulation of CSF through these portals combined with understanding the consequences of deficient CSF melatonin elicits solutions to the puzzle of AD neuropathology. Oxidative stress plays an important role in the development of AD, which most commonly is a disease of aging. However, the pathological changes in the brain are not uniform or general. They are regional with specific neural groups subject to damage. Why?

Flow of CSF and corpora formation

Most CSF is produced by the choroid plexuses of the ventricles. If the bulk flow of CSF does not pass through the arachnoid granules, where does the fluid produced by the choroid plexus go? For decades, evidence that some CSF is removed by the lymphatic system has been repeatedly observed and reported. Also, some is absorbed by penetration of tissues in contact with CSF [2]. Water can penetrate all living tissues to a varying degree. Therefore, some CSF flows diffusely into all tissues contacting the CSF compartment.

CA are small spheroid bodies which form on the surface of the brain tissue that has close contact with the CSF. CA increase in numbers as we age and are found in even larger numbers in

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neurodegenerative states, such as AD. They originate in astrocytes, of which the cellular structure disappears at a later time [16]. CA are composed of cellular debris. Numerous components of cell degeneration have been chemically identified in CA and evidence suggests neuronal and glial origin [17]. Mitochondrial constituents have been identified [18]. CA are apparent trash cans for the debris of cell degeneration. Although unknown at this time, there is probably a utilitarian reason for their development.

Because the CA normally form with aging and are usually found in brain tissue that has close contact with the CSF, it seems reasonable to assume that the CA are derived from substances in the CSF. The flow of the fluid should influence the number and pattern of deposition. Sections of apical cerebral cortex from the vicinity of the arachnoid granule system examined microscopically reveal only rare corpora, while abundant depositions are found in the choroid fissure. If the premise that CA are derived from cellular debris present in CSF is correct, then the choroid fissure and choroid plexus portals are involved in the bulk flow of CSF and the arachnoid granule system is not. Movement of fluid through the portals into the ventricular CSF would be a completed cycle of the fluid.

While the deposition of CA on the external surface of the brain seems to reflect the local volume of CSF flow, within the ventricular system that is not always the case. Tissue immediately surrounding the cerebral aqueduct does not develop CA even though most of the ventricular CSF output passes through the aqueduct. Neural tissue lining the aqueduct must either resist penetration of CA generating trash or have a mechanism for transporting the

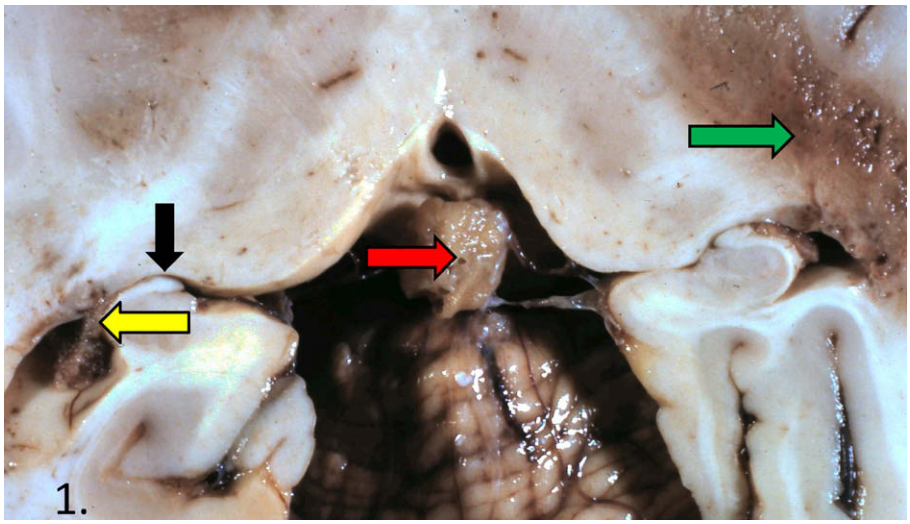

Fig. 1. Horizontal brain section of formalin-fixed brain. Red arrow – the pineal gland with surrounding basal cistern. White arrow – the third ventricle. Black arrow – the choroid fissure. Yellow arrow – the choroid plexus of the inferior horn of the lateral ventricle. Green arrow – pathological lesion.

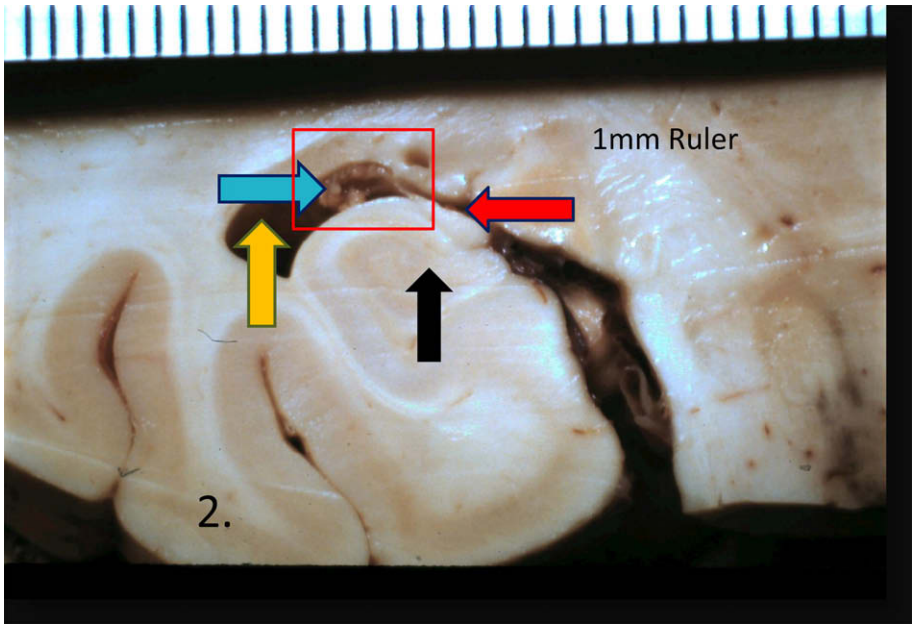

Fig. 2. Coronal section of formalin-fixed brain from the base of the temporal lobe demonstrating the hippocampal area. Red arrow – the choroid fissure. Black arrow – the hippocampal formation. Blue arrow – the choroid plexus. Yellow arrow – inferior horn of the lateral ventricle. Red rectangle – an example of sampling of tissue for histologic examination of a portal area.