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Alzheimer's disease: Cerebral glaucoma?

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this research study is from about 11 years ago so we will have to be considerate of whether it is the most trustworthy or if there is more recent research that can prove or disprove the study further.

SUMMARY

In a 1994 Medical Hypotheses paper, it was speculated that high intracranial pressure (ICP) might increase the probability of developing Alzheimer's disease (AD). A study of cerebrospinal fluid pressure (CSFP) in normal volunteers showed interindividual variations in CSFP. Some normals had what would normally be considered elevated CSFP. The hypothesis postulated that this subgroup with a high characteristic individual ICP level might be more susceptible to developing AD. The Medical Hypotheses paper further speculated that in more advanced stages of AD, such pressure factor could already be missing due to the disease process. The present article discusses recent research findings regarding CSFP distribution in AD patients that could be interpreted as support for this hypothesis. Exposure of central nervous system tissue to high pressure stress is not unique to the ICP space. Indeed, a similar situation occurs in the intraocular pressure (IOP) space in eyes with glaucoma. Interestingly, recent research has revealed similarities in the process leading to retinal ganglion cell death in glaucoma and neuronal cell death in AD. In the present paper, we raise the question of whether AD could be a cerebral form of glaucoma. Indeed, the linking of glaucoma to mechanisms of AD could reflect the anatomical and functional similarities between the IOP space and the ICP space. Further studies are warranted, however, especially to determine the possible role of high ICP in at least some cases of AD.

Introduction

basically introducing the readers to what AD is, what symptoms patients display, and what happens in the brain to result in AD

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive and memory deterioration, as well as changes in personality, behavioral disturbances and an impaired ability to perform activities of daily living [1]. AD is known to be the most common type of dementia [2]. There is a strong age-dependence of the disease. Its prevalence increases greatly with age [3]. With the rapidly aging population, AD represents one of the most frequent, major public health problems [4]. To date, there are no effective ways to cure or reverse the disease. In addition to synaptic degradation and extensive neuronal cell loss, neuropathological characteristics of AD include extracellular senile plaques containing β-amyloid (Aβ) derived from β-amyloid precursor protein (APP) after sequential cleavage by β-secretase and γ-secretase, and intracellular neurofibrillary tangles caused by abnormally phosphorylated tau protein [5–7]. Despite decades of intensive research, the precise etiology of AD remains elusive. The majority of AD cases are sporadic AD with late onset and seem to result from a complex interaction of multiple genetic and environmental factors [2]. Concerning the causes of AD, several hypotheses have been proposed. In an earlier Medical Hypotheses paper, it was speculated that high intracranial pressure (ICP) might increase the probability of developing AD [8]. According to recent research findings on Alzheimer's disease, normal pressure hydrocephalus (NPH) and glaucoma, there is more supportive evidence for this hypothesis nowadays.

important to keep the facts from intro in mind when reading the rest of the paper since the paper will build on the basics established here

The ICP hypothesis of AD

The present article is in follow-up to a 1994 paper, published in Medical Hypotheses, entitled "Intracranial pressure and Alzheimer's disease: a hypothesis" [8]. In this article, one of us hypothesised that, in addition to activities or diseases causing ICP elevation, a high characteristic individual ICP level might predispose a person to developing AD [8]. With regard to ICP, everyone seems to be exposed to a rather individual level of ICP. Gilland et al. [9] reported studies of cerebrospinal fluid pressure (CSFP) in 31 young normal volunteers. In half, a 22-gauge needle was used for lumbar puncture, and in the other half a 26-gauge needle [9]. The opening CSFP was monitored for 10 min in all subjects [9]. All recordings were made with the subjects in the left lateral recumbent position with the legs half flexed [9]. The head and

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spine were strictly horizontal [9]. The average opening pressure was 145 mm of 0.15 M sodium chloride (S.D., 37) with the 22-gauge needle, and 157 mm (S.D., 36) in subjects receiving the 26-gauge needle [9]. In the individual subject, the pressure fluctuations over the 10-min period were found to vary around a characteristic individual level [9]. There was considerably more variation in the observations from subject to subject than on the same subject [9]. In five perfectly relaxed normal volunteers an average value of 200 mm was observed, with a maximal value of 240 mm [9]. The 1994 Medical Hypotheses paper postulated that this subgroup with high 'physiological' CSFP might be more susceptible to developing AD [8]. The paper further speculated that in more advanced stages of AD, such pressure factor could already be missing due to the disease process [8].

in this section, the paper is recapping the first paper in which the hypothesis was postulated to catch up readers that didn't read the initial article. talks about specific methods and results observed in that study.

Similarities between Alzheimer's disease and glaucoma

Exposure of central nervous system tissue to high pressure stress is not unique to the intracranial pressure space. Indeed, a similar situation occurs in the intraocular pressure (IOP) space in eyes with glaucoma. Glaucoma is a group of diseases that have in common a characteristic optic neuropathy and visual field defects [10]. Glaucoma is usually associated with elevated IOP, but a subset of glaucomatous patients has normal IOP and is designated normal tension glaucoma [10]. Mechanical and vascular theories for the pathogenesis of glaucomatous optic neuropathy (GON) have been presented [10,11]. According to the mechanical theory, GON may be a direct consequence of increased IOP leading to regions of high shear stress and strain in the lamina cribrosa [10,11]. The lamina cribrosa forms the bottom of the optic cup on the inner surface of the optic nerve head and allows the optic nerve to emerge from the orbit [10]. At this site, increased IOP may result in mechanical forces on retinal ganglion cell (RGC) axons with subsequent cell injury [10,11].

It is intriguing to note that AD and glaucoma have many common features [12,13]. Both are slow and chronic neurodegenerative disorders with a strong age-related incidence [14,15]. Studies consistently report decreased levels of β-amyloid (1–42) and increased levels of tau in cerebrospinal fluid (CSF) from AD patients in comparison with healthy subjects [16,17]. Recently, Yoneda et al. [17] suggested the possibility of a role for β-amyloid (1–42) and tau in the pathogenesis of glaucoma and diabetic retinopathy having found significantly decreased levels of β-amyloid (1–42) and significantly increased levels of tau in the vitreous fluid from patients with these disorders in comparison with the levels in a control group. Their findings suggested that the neurodegenerative processes in these ocular diseases might share, at least in part, a common mechanism with AD [17]. Lately, it was also demonstrated that abnormal tau AT8 is present in human glaucomas with uncontrolled elevated IOP [18]. Furthermore, evidence exists of build-up of Aβ in RGCs in experimental rat glaucoma [19]. Activation of caspases and abnormal APP processing, which includes production of Aβ, are important events in AD [19]. McKinnon et al. [19] detected a similar situation in experimental glaucoma. Indeed, in their study using a chronic ocular hypertensive rat glaucoma model, the authors found that caspase-3 is activated in RGCs, where it cleaves APP to produce neurotoxic fragments that include Aβ [19]. This suggested a new hypothesis for RGC death in glaucoma involving chronic Aβ neurotoxicity, mimicking AD at the molecular level [20]. A study published by Guo et al. [14] provided further evidence from an animal model of glaucoma that Aβ is a likely mediator of pressure-induced RGC death and that targeting multiple phases of the Aβ pathway raises the possibility of a neuroprotective approach to the treatment of glaucoma. By manipulating the Aβ pathway, the authors investigated three different

wow, very interesting. i didn't know that glaucoma and AD had similarities on such a close molecular level.

approaches to targeting Aβ in experimental glaucoma and their combination effects: (i) reduction of Aβ formation by a β-secretase inhibitor; (ii) clearance of Aβ deposition by an anti-Aβ antibody; and (iii) inhibition of Aβ aggregation and neurotoxic effects with Congo red [14]. The authors showed that combined treatment (triple therapy) was more effective than either single- or dual-agent therapy [14].

congo red = organic compound dye

Similarities between the IOP space and the ICP space

Due to similar pathogenetic mechanisms, glaucoma has been called "ocular Alzheimer's disease" [20]. Here, we raise the question of whether Alzheimer's disease could be a cerebral form of glaucoma. Indeed, the linking of glaucoma to mechanisms of AD could reflect the anatomical and functional similarities between the IOP space and the ICP space. In fact, the optic nerve and eye are embryologically derived from the third ventricle [21]. Moreover, both IOP and ICP have similar physiologic pressure ranges and similar responses to changes in intrathoracic and intraabdominal pressure [22]. The IOP is controlled by a balance between the production and outflow of the aqueous humour [23]. Aqueous humour is produced by the ciliary body epithelium in the posterior chamber and passes through the pupil to the anterior chamber to exit the eye either through the trabecular meshwork into Schlemm's canal and aqueous veins or through the ciliary muscle and other downstream tissues [23,24]. In a similar fashion as found in the IOP space, ICP is dependent on a balance between the production and reabsorption of CSF [23]. The CSF is produced largely by the choroid plexus (CP), a highly vascularized secretory neuroepithelium found in the lateral, third and fourth ventricles of the brain [25]. The CSF circulates within the brain ventricles, from the lateral ventricles to the third ventricle, through the aqueduct of Sylvius into the fourth ventricle, and finally along the spinal channel and subarachnoid space where CSF is reabsorbed into the blood or lymphatic system [25]. Given the above similarities between the IOP space and the ICP space, it can be speculated that increased pressure stress may contribute to a similar neurodegenerative mechanism in both pressure spaces.

CSFP distribution in AD patients

With regard to the previously advanced hypothesis of a causal link between high ICP and AD [8], it is interesting to note that a recent article by Silverberg et al. [26] entitled "Elevated cerebrospinal fluid pressure in patients with Alzheimer's disease" reported elevated CSFP in a small subset of AD patients. The authors performed a clinical trial to evaluate the safety and efficacy of low-flow shunting in subjects that met strict National Institutes of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [26]. The therapeutic objective guiding low-flow ventriculoperitoneal shunting as a treatment for AD was to improve safely the CSF turnover and clearance of metabolic by-products, such as β-amyloid and tau, from the brain [26]. Subjects were carefully screened to exclude those with clinical, radiographic, or CSFP signs of NPH [26]. As a final exclusion prior to shunt implantation, CSFP was measured supine under general anesthesia via the implanted ventricular catheter [26]. Normally, the CSFP ranges from 5 to 15 mm Hg (or 68–204 mmH_2O) [12,27]. In adults, age is not known to affect CSFP [27]. During the initial implantation procedure, seven of the 181 subjects (3.9%) with no clinical or radiographic signs of NPH had an opening CSFP >200 mmH_2O [26]. These subjects were withdrawn from the remainder of the study, because of probable associated early NPH [26]. For this AD-elevated CSFP group, the mean CSFP was 249 ± 20 mmH_2O [26]. AD patients with

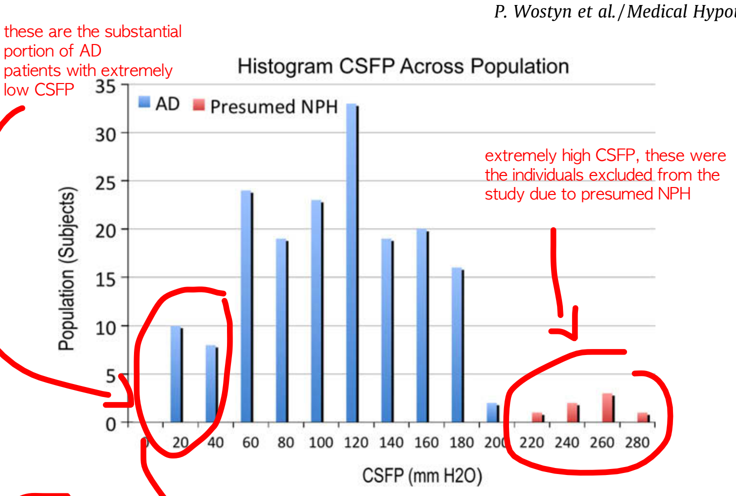

Fig. 1. Frequency histogram showing the distribution of cerebrospinal fluid pressure (CSFP) in all subjects with Alzheimer's disease (AD). Reproduced from Silverberg et al. [26] with permission.

elevated CSFP were significantly younger (67 ± 6 years vs. 74 ± 6) and significantly less demented on the Mattis Dementia Rating Scale (MDRS) (118 ± 6 vs. 106 ± 17) than those without elevated CSFP [26]. The AD group without elevated CSFP consisted of 174 subjects (the remaining 96.1%) [26]. Mean opening CSFP in this group was 103 ± 47 mmH_2O, which was statistically significantly lower when compared to the AD-elevated CSFP group and a somewhat younger non-demented control group of subjects with Parkinson's disease (140 ± 60 mmH_2O) [26,28]. The distribution of CSFP in all AD subjects is shown in Fig. 1. Remarkably, the frequency histogram of the CSFP distribution shows a substantial portion of AD patients with very low CSFP. Indeed, it could be argued that there are really two subgroups of AD patients within the group without elevated CSFP: those with nearly normal CSFP and those with much lower CSFP (Silverberg, personal communication, 2008). An unexpected finding of this study was the relatively high (>30%) proportion of subjects with moderate to severe dementia as measured by MDRS total scores below 100, despite inclusion–exclusion criteria designed to capture subjects with mild to moderate dementia (Mini-Mental State Examination score between 15 and 24, inclusive) [26,29]. Although not specifically investigated in this study, cerebral atrophy associated with moderate to severe AD could be hypothesised to be associated with lower CSFP (Silverberg, personal communication, 2008).

The article by Silverberg et al. [26] mainly discussed the AD-elevated CSFP group. As the authors hypothesised previously, in the setting of pre-existing AD, NPH could arise with an increase in CSF outflow resistance due to amyloid deposition and fibrosis in the meninges and arachnoid granulations [26,30]. In an animal model of NPH, CSFP is initially elevated but soon returned to normal after ventricular enlargement, decreased CSF production and other compensatory events [26,31]. Silverberg and colleagues [26] anticipated that the AD patients in their study with elevated CSFP were in the earliest stages of this process at the time that their elevated pressures were discovered, and that over time they would go onto develop enlarged ventricles and clinical signs of NPH.

Although admittedly speculative, we believe the earlier 1994 hypothesis of a causal link between high ICP and AD [8] may also be compatible with the above observations of Silverberg et al. [26]. Given that interindividual variations in CSFP were observed in a study of normal volunteers [9], and given that some normals had what would normally be considered elevated CSFP [9], the 1994 Medical Hypotheses paper postulated that such high characteristic individual CSFP level might predispose a person to developing AD [8]. As it follows from this hypothesis that high ICP could be causally related to AD [8], the question arises whether the elevated CSFP reported in the study by Silverberg et al. [26] is simply an effect (very early NPH) or could be a causal factor for AD. Silverberg et al. [26] noted that the AD subjects with increased CSFP in their report could not, strictly speaking, be called NPH, since they had neither the clinical syndrome nor the enlarged ventricles associated with NPH. The authors supposed that over time these subjects would go onto develop enlarged ventricles and clinical signs of NPH [26]. Interestingly, AD patients with elevated CSFP were significantly younger and significantly less demented on the MDRS than those without elevated CSFP [26]. In this context, we believe elevated CSFP as a pre-existing causal factor for AD may also be consistent with the above findings. The 1994 Medical Hypotheses paper further speculated that in more advanced stages of AD, such pressure factor could already be missing due to the disease process [8]. The study by Silverberg et al. [26] showed that a substantial proportion of AD patients had very low CSFP. Based on the characteristics (older and more demented on the MDRS) of these subjects, our group recently hypothesised that more advanced AD may be associated with a decrease in CSFP [32]. As noted above, cerebral atrophy in these AD patients could be assumed to be the cause of the lower CSFP. This is also in line with the hypothesis proposed in the 1994 paper.

important to note that the researchers of this paper are just speculating

Comments on the ICP hypothesis of AD

Interestingly, the ICP hypothesis of AD might explain several data described in AD. AD is characterized by innumerable senile plaques and neurofibrillary tangles in the brain. These changes also occur to some extent in the brains of non-demented elderly people [33]. The population distribution of cognitive impairment also shows a continuum of severity, with dementia at one extreme of the distribution [34]. Thus, from these observations it appears that AD is on a continuum with normal aging. This may result from a single underlying process that varies in magnitude. With regard to ICP, there is considerable variation in the CSFP amongst healthy human subjects [9]. Thus, everyone seems to be exposed to a rather individual level of ICP. This might explain why the histological features of AD also occur to varying degrees in normal aging. This interindividual variability in ICP may also account for the distribution of cognitive impairment in the population. Indeed, on the one extreme, high ICP may facilitate the formation of neuropathological changes that lead to AD. On the other extreme, people with low ICP may escape development of AD because too little damage occurs to exhibit memory impairment or dementia before death. Further, the proposed hypothesis may also explain the age-specific pattern of prevalence of AD. Advanced age is the strongest risk factor for AD [3]. Exposure to ICP occurs during the entire lifetime of the individual. Simply on the basis of increasing age, pathological changes may accumulate to some threshold above which dementia appears. This might explain the high prevalence of AD in older age groups. From this point of view, it is not the aging process per se which leads to AD but the pressure factor, predominantly giving rise to AD over time.

It should be stressed that high ICP as a causal factor for AD eventually accounts only for a subgroup of AD patients. Indeed, several other factors may also contribute to AD. In the vast majority of cases, the disease likely results from a complex interaction of multiple genetic and environmental factors [2].

In the context of the present article, the question arises as to whether there is a correlation between pseudotumor cerebri (PTC) and AD. Pseudotumor cerebri, also known as idiopathic or benign intracranial hypertension, is a condition of increased ICP in the absence of intracranial infection, space-occupying lesion, or hydrocephalus [35]. The pathophysiology of this disorder is unclear. Potential mechanisms underlying PTC include increased CSF production, decreased CSF absorption, idiopathic brain swelling, and idiopathic intracranial venous hypertension [36]. However, unrelated to the pathophysiological mechanism, this condition is associated with an elevation of ICP. Seemingly inconsistent with the idea that elevated ICP can contribute to AD, there is no evidence in literature of a correlation between dementia and PTC [37]. Although a possible link between PTC and AD was suggested by a recent study by Peng et al. [38], this link was only based on increased ALZ-50 immunoreactivity in the CSF of PTC patients. The lack of clear evidence of an association between PTC and AD, however, is not inconsistent with the proposed hypothesis. There is evidence that production and turnover of CSF help to clear toxic molecules such as Aβ from the interstitial fluid space of the brain to the bloodstream [30]. In PTC, a diagnostic criterium is the normal or low level of CSF protein and normal cell count [39]. Such a low CSF protein level suggests a fast circulation of CSF [39]. On the contrary, in NPH, there is evidence for CSF stagnation with decreased clearance of various macromolecules [40]. Although the primary change in NPH is an increase in CSF outflow resistance, decreased CSF production also has been reported [28,30,40]. Both conditions lead to a decrease in CSF turnover and, in turn, a decreased clearance of macromolecules [40]. In NPH, a decrease in clearance of Aβ and tau is suggested by the higher than expected coincidence of AD pathology in cortical biopsy samples obtained at shunt implantation [40]. From 30% to 50% of NPH patients will exhibit plaques and tangles consistent with AD, and, in the severely demented NPH patients, 75% will be AD positive [40]. Reduced CSF production and turnover have also been demonstrated in AD [41]. It has been suggested that both AD and NPH are physiologically related to CSF circulatory failure, resulting in reduced CSF clearance and accumulation of neurotoxins, such as β-amyloid peptides, that play a role in the pathogenesis of AD [30]. Higher concentrations of Aβ increase the probability of aggregation and fibril formation [30,42]. Hence, reduced CSF clearance of Aβ should facilitate amyloid burden in the brain [30]. In contrast to the 40-amino acid form of Aβ, the longer 42-residue form is more prone to aggregate and form plaques [30]. According to the observed decrease in the secretion rate of CSF in patients suffering from NPH, Silverberg et al. [28] postulated that chronic increased ICP causes downregulation of CSF production. As noted earlier, CSF is produced mainly by the choroid plexus which is located in the ventricles of the brain [25]. Studies in animals have shown that chronically elevated CSF pressure decreases CSF production and that chronic hydrocephalus damages the choroid plexus secretory epithelium [43]. CSF production also decreases in association with age [44]. Aging of the CP is associated with flattening of epithelial cells and basement membrane thickening [45,46]. In AD, choroid plexuses present similar, although much more pronounced, abnormalities than those observed in aging [45,46]. With regard to hydrocephalus, Knuckey et al. [47] studied the function of the CP in rats exposed to increased ICP. Results demonstrated a decrease in the ability of the CP to release chloride following hydrocephalus. This decrease in chloride efflux might reflect a decrease in the water movement by the epithelial cells and hence a decrease in CSF formation [47]. In a recent paper, Johanson et al. [48] proposed that ventriculomegaly and transient elevations in ICP in NPH might elicit a compensatory response in CP to downregulate CSF formation by promoting ion reabsorption via the Na-K-2Cl cotransporter isoform 1 (NKCC1). This ion-translocating protein coupled to CSF formation is highly expressed in the apical membrane of choroid plexus epithelial cells, thereby being strategically positioned to sense physical changes in CSF [48]. Changes in pressure or volume represent potential stimuli for inducing NKCC1 in CP [48,49]. The above findings raise the possibility that chronic ICP elevation resulting from a high characteristic individual ICP level also might lead to downregulation of CSF formation. Indeed, it is hypothesised here that such chronic high ICP might result in histological and/or functional changes of the choroid plexus leading to decreased CSF production, and hence to diminished CSF clearance of neurotoxins such as Aβ. However, unlike in NPH, a stagnation of CSF circulation may be missing in pseudotumor cerebri due to different mechanisms underlying the two diseases.

Testing the ICP hypothesis of AD

Although there is evidence that at least in some cases of AD, ICP is increased, there is no proven causal association. As hypothesised by Silverberg et al. [26], relative CSFP elevations resulting from increasing outflow resistance might lead to manifestations of NPH superimposed on AD. Definite proof of a causal relationship, however, would require a prospective study examining the association between high characteristic individual ICP and the subsequent development of AD. Therefore, it could be useful to develop animal models of high 'physiological' ICP for assessing if such models induce Alzheimer's disease-like pathology. If the hypothesis could be confirmed, then a randomized clinical trial could be recommended to test whether one could alter the risk of developing AD by manipulating CSFP.

Conclusions

here they are wrapping up the paper by taking note of how there is no causation proven yet btw elevated ICP and AD developmentt. they are also stating a call to action as well as potential for future studies

In conclusion, the data described above could be interpreted as support for the hypothesis that high ICP may increase the probability of developing AD and that more advanced AD may be associated with a decrease in ICP. Given the anatomical and functional similarities between the IOP space and the ICP space, and given that recent research has revealed similarities in the process leading to RGC death in glaucoma and neuronal cell death in AD, we raise the question of whether AD could be a cerebral form of glaucoma. At this stage, the present hypothesis remains highly speculative. Further study will be necessary to determine the possible role of high 'physiological' ICP in at least some cases of AD.

Conflicts of interest statement

None declared.

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