The Development of a Wearable Patch For Early Alzheimer's Disease Detection

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Background and introduction to Alzheimer's Disease:

Alzheimer's disease is a neurodegenerative disorder that has adverse effects on memory, behavior, and cognitive function [1]. Neurodegenerative disorders increase the rate of neuron degeneration in the brain. Neuron degeneration is natural with age but Alzheimer's disease and other neurodegenerative diseases significantly speed up the process. Alzheimer's disease falls under the wider category of dementia which categorizes a set of symptoms related to a decline in cognitive ability and daily function.

Alzheimer's disease is the most common disease within the scope of dementia. The World Health Organization (WHO) estimates that there are currently over 55 million people with dementia worldwide and they expect that number to triple by the year 2050 [1]. Alzheimer's disease makes up somewhere between 60% and 70% of all dementia cases globally. In the year 2018, Alzheimer's disease was the sixth most leading cause of death in the United States and it was estimated that over $230 billion went towards caring for patients with dementia [2]. Patients with Alzheimer's disease typically live 8-10 years after symptoms set in [2]. It is possible for patients to exhibit some mild and nonspecific symptoms as early as 20 years before the onset of Alzheimer's occurs. This period is called the prodromal phase.

The specific mechanisms behind the cognitive decline are still not fully understood although there have been many studies backing a claim that β-amyloid (Aβ) and the formation of intracellular aggregated phosphorylated tau in the brain have a large role in the degeneration [3]. The membrane of neurons in the brain contain a type of transmembrane proteins called Amyloid Precursor Proteins (APP) [4]. It's commonly thought that APP helps the neuron grow and repair itself after an injury. As the protein gets used, it ages and eventually gets broken down. The protein is broken down by α-secretase and γ-secretase [4]. The α-secretase cleaves the APP within the Aβ region so that Aβ can't form then γ-secretase cleaves the remaining fragment still bound in the membrane. These cleaves produce soluble fragments that can be safely dissolved. Sometimes, however, the β-secretase activates instead of the α-secretase which creates insoluble fragments. These fragments congregate outside of the neuron and form what is known as beta amyloid plaque [4]. These plaques can get in the way of neuron signaling and impair brain function. This is thought to contribute to the cognitive decline of patients with Alzheimer's disease. Beta amyloid plaques can be found in people without Alzheimer's disease but the concentration of them are significantly increased in Alzheimer's patients and they are found in more specific places like the hippocampus and the parietal and temporal lobes [4]. This causes more specific impairment than just the random presence of the plaques.

The other commonly supported mechanism behind Alzheimer's disease is the formation of neurofibrillary tangles inside the neurons [3]. The cytoskeleton of the neuron is made up of microtubules that deliver nutrients and molecules along the length of the cell. These microtubules contain a support protein called Tau [8]. It's thought that the amyloid plaque buildup outside of the neuron activates Kinase inside the neuron which transfers phosphate groups to the Tau proteins. When the Tau receives the phosphate group, it changes shape and disconnects from the microtubules [8]. This leaves the microtubules nonfunctioning. Once it's disconnected, the Tau proteins join together and form neurofibrillary tangles. Cells that contain these tangles and nonfunctioning microtubules can't signal as well as healthy cells and sometimes end up undergoing apoptosis or cell death.

The current standard for diagnosing and treating Alzheimer's Disease:

In 1984, the first set of criteria to diagnose Alzheimer's disease was introduced [1]. This set of qualifications had an 81% sensitivity and a 70% specificity. The criteria were revised 27 years later in 2011 [1]. The National Institute on Aging and the Alzheimer's Association designated a group to revise the standard criteria for Alzheimer's disease diagnosis. Both of the diagnostic guidelines utilized clinical symptoms as the main diagnostic aid while not tending to use biomarkers to make a diagnosis.

The diagnostic criteria for dementia first states that in order to consider a diagnosis of Alzheimer's disease, the symptoms the patient is exhibiting can not be explained by any other affliction [1]. After all other conditions have been ruled out, the patient then must exhibit impairment in at least two of the following fields: Memory, executive function, visuospatial abilities, language, and behavior. It must also be shown that there is evidence of cognitive decline gradually over several months to years in order to diagnose a probable Alzheimer's disease case. Memory impairment is the most commonly recognized symptom of Alzheimer's disease, but it is not always present [1]. This is especially true in younger patients. These patients might instead exhibit impairments in visuospatial abilities or language such as difficulty articulating thoughts or finding words.

After the previously laid out steps have been taken and the process has led the physician to believe Alzheimer's disease to be the cause of the patient's symptoms, more screening and criteria are implemented to further support this [1]. This includes laboratory studies, neuropsychological assessments, and the use of biomarkers. One biomarker used for Alzheimer's disease is the levels of amyloid-beta and tau proteins in the cerebrospinal fluid (CSF) [5]. Elevated protein concentration in the CSF indicates that Alzheimer's disease may be the cause of neurodegeneration. Another common biomarker used is positron emission tomography (PET) imaging to show amyloid plaques or tau tangles in the brain that could be contributing to decreased cognitive function [5]. These tools are not yet routine in most clinical settings because of their high cost and low availability, but they do help to improve diagnostic confidence of Alzheimer's, especially in cases with atypical symptoms [5].

Neurological examinations play a crucial role in the assessment of the progression of Alzheimer's disease. Standard neurological examinations evaluate reflexes, coordination, eye movement, and motor strength [6]. These functions typically present as normal in patients affected by early stage Alzheimer's disease, but they will begin to decline as the disease progresses. The severity in which the functions are affected indicates to the physician both how far the disease has progressed and also the severity that the disease in that particular patient [6]. This is helpful in figuring out a treatment plan and the best course of action for the physician to take with the patient's medical care.

Currently, the treatments for Alzheimer's disease primarily treat the symptoms of the disease, not the underlying neurodegeneration [7]. Cholinesterase inhibitors like donepezil and rivastigmine as well as Memantine, an NMDA receptor antagonist, provide improvements in cognition and daily functioning but fail to significantly affect the progression of the disease [7]. There are recently approved monoclonal antibodies that show promising results in slowing the cognitive decline associated with Alzheimer's disease, but their benefits are limited to early stage patients and are associated with major risks such as brain bleeding or swelling [7]. The shortcomings of these treatments highlight the need for earlier diagnosis because initiating treatments before extensive neurodegeneration occurs could potentially enhance the efficiency and preserve cognitive function for longer.

Innovation for the diagnosis of Alzheimer's disease:

Current Alzheimer's disease diagnostic methods are applied only after significant cognitive decline of the patient which limits opportunities for early intervention. Treatment can not reverse any damage that has already been done and can only treat the symptoms that the disease presents [1]. The limitations of early and non-invasive diagnosis can be addressed by a wearable biosensor patch that detects Alzheimer's disease specific biomarkers using micro needle based electrochemical sensing [9].

The patch would consist of three layers: the outer layer, the diagnostic layer, and the hydrogel interface. The outer layer is a protective barrier against the environment. It would need to be biocompatible, flexible, water resistant, and durable. The diagnostic layer would contain flexible biosensor arrays, microfluidic channels, and a bluetooth chip that would transmit data. The hydrogel interface would be a skin-safe adhesive layer that contains microneedles that collect deep interstitial fluid (ISF) which is similar to blood plasma in composition [9].

The patch would have biorecognition elements that bind specifically to biomarkers specific to Alzheimer's disease like phosphorylated tau (p-tau) and the ratio of amyloid-beta 42 (Aβ42) to amyloid-beta 40 (Aβ40). It would also contain electrochemical sensors that convert the binding event into a measurable signal that can be sent through the bluetooth chip to a receiver device like a cellphone or a clinician's computer [9]. The device would receive the biomarker ISF data that indicates the onset of Alzheimer's disease and then the device would utilize this data to determine if Alzheimer's disease is either present or progressing. If the patch detects a decrease in Aβ42 and a decrease in the ratio between Aβ42 and Aβ40, an accumulation of amyloid-beta plaques in the brain is indicated and therefore it's likely that Alzheimer's disease is contributing. If the patch detects increased levels of p-tau, it indicates the formation of neurofibrillary tangles in the brain neurons which is also indicative of Alzheimer's disease [10].

The data from the detection patch would update about every hour. This gives the device enough time for the binding events to take place and stabilize before a reading is recorded. It would also significantly decrease the amount of power the device would consume. Given routine mechanical stress and skin contact, the patch would be designed to be replaced weekly. It would function very similarly to a dexcom glucose monitor that is replaced every ten days and updates every five minutes. Since the levels of biomarkers fluctuate slowly and not rapidly like glucose levels, a five minute update period is not necessary for the patch [9].

The patch design addresses many of the current shortcomings of the diagnostic standard for Alzheimer's disease and improves upon them. This includes being cost-effective, widely available, and able to detect Alzheimer's disease indicators earlier. The biggest problem with the current standard of care is that it is implemented too late. By the time symptoms are detected and a physician is confident enough to call it Alzheimer's disease, neurodegeneration has already begun and there's no way right now to undo that damage [1]. This device would allow for the early detection of Alzheimer's disease which would lead to a longer life expectancy and higher quality of life for the patient. The device would also be more widely available because it would allow for lower cost outpatient testing. The device would especially benefit patients in rural or underfunded areas where advanced imaging technology is not readily available [1].

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