INTRODUCTION:

What is Alzheimer's disease and what is its cause?

Alzheimer’s is a neurological disorder when memory loss takes place as a result of the death of brain cells, and also causes cognitive decrease\(^1\). It is a neurodegenerative type of dementia, which means the disease which is connected to the nerves, that is likely to gradually worsen (brain cells progressively die) as time passes\(^1\). A brain which is affected by Alzheimer’s disease slowly shrinks and the tissue has gradually less nerve cells and connections\(^1\). Plaques and tangles, which are spotted in a brain diagnosed with Alzheimer’s in the nerve tissue, have been often detected through autopsy or postmortem\(^1\). Plaques are detected in between the dying brain cells, and are produced from accumulation of a protein called beta-amyloid, also known as amyloid plaques\(^1\). Tangles are detected inside the brain neurons, from a decomposition of another protein called tau\(^1\). The plaques and tangles in a brain tissue affected by Alzheimer’s are always there, but there could be another hidden process which is the cause of the disease, but scientists aren’t sure yet\(^1\).

What are the symptoms of Alzheimer's disease?

The symptoms can be diagnosed at any stage of the disease, and the progression should be controlled after the first diagnosis. The developing symptoms indicate how its care should be performed. For doctors to first make a diagnosis of Alzheimer’s disease they have to be sure that dementia is present, which is when they notice that the cognitive or behavioral symptoms decreased in relation to the earlier levels of how the brain functions and performs, and also intervene with the manner the brain works during work or normal activities\(^1\). The cognitive decrease is included in at least two of the following symptom areas written below\(^1\): (from guidelines jointly produced by the USA National Institute on Aging and the Alzheimer’s Association\(^1\)).
1. The ability to take in and remember new knowledge gets aggravated (for e.g.):
   - "Repetitive questions or conversations"
   - "Misplacing personal belongings"
   - "Getting lost on a familiar route"
   - "Forgetting events or appointments."

2. Not being able to reason, do complex tasking or exercising judgment properly:
   - "Poor understanding of safety risks"
   - "Inability to manage finances"
   - "Poor decision-making ability"
   - "Inability to plan complex or sequential activities."

3. Impairment to visuospatial (relating to or denoting the visual perception of the spatial relationships of objects) abilities (not because of, for example, bad eyesight)
   - "Inability to recognize faces or common objects or to find objects in direct view"
   - "Inability to operate simple implements, or to orient clothing to the body."

4. The ability to read, speak or write is flawed:
   - "Difficulty thinking of common words while speaking, hesitations"
   - "Speech, spelling and writing errors."

5. Changes in behaviour and personality (for e.g.):
   - "Out-of-character mood changes, including agitation; less interest, motivation or initiative; apathy; social withdrawal"
   - "Loss of empathy"
   - "Compulsive, obsessive, or socially unacceptable behavior."

Once dementia is confirmed from those example symptoms, the certitude that it is due to Alzheimer’s disease is generally because of the development of the symptoms and its progress in months to years (rather than hours to days) and an obvious aggravation of the patient’s normal levels of understanding in certain areas. When the symptoms of memory loss are most evident, is when the confirmation of Alzheimer’s dementia is most common, notably in the field of learning and remembering new information. However, the start of the development of the symptoms can also principally be problems with language, when the strongest symptom is when a person has difficulty in finding the right words. Furthermore, if the visuospatial shortages are the most pronounced, then the person wouldn’t have the ability to recognize objects or faces, or to understand various parts of a scene at once (simultanagnosia). They would also struggle with reading text (alexia), as well as reasoning, judging, and problem-solving, which is the most noticeable loss in the “executive dysfunction” area.

The elderly are more likely to be diagnosed with Alzheimer’s disease.
How common is it?

The most recent census in the US has allowed researchers to estimate the number of people who have Alzheimer’s disease\(^1\). In 2010, about 4.7 million people at the age of 65 and older had Alzheimer’s disease in the United States. The 2013 statistical report of Alzheimer’s Association shows that just about a tenth of the population that are 65 years of age and older have the disease in the US\(^1\). Furthermore, it increases to a third of the elders of 85 years of age and older who have Alzheimer’s\(^1\). There are several different types of dementia, but Alzheimer’s is most of the time the problem (between 60% to 80% of cases of dementia\(^1\) specifically for cases of cognitive decline and memory loss\(^1\)).

What are the risk factors?

There are some factors which are usually identified with Alzheimer’s disease, that are not often detected in people without the disease. Some of them are avoidable or changeable, for example, lowering the risk of diabetes or heart disease could successively reduce the risk of dementia\(^1\). If scientists manage to earn more knowledge on these risk factors, or scientifically prove several causes connecting to Alzheimer’s, then it would help them develop treatments against it or find a way to prevent it. The risk factors linked with Alzheimer’s disease are the following\(^1\):

- **Unavoidable risk factors:**
  - Age: the disease is more likely to develop in older people, and a larger percentage of the 85-year-olds and older have it than the 65-year-olds and older\(^1\).
  - Family history (inheritance of genes): there is a greater risk of having Alzheimer’s disease if it is already in the family. It is the second greatest factor after age\(^1\).
  - Genes: having a certain gene (the apolipoprotein E or APOE gene), gives a person (depending on their specific genetics) a higher risk of getting Alzheimer’s disease than people with other types of genes. Many other genes have even recently been discovered to be related to the disease\(^1\).
  - Females have a greater risk of having Alzheimer’s disease than males\(^1\).

- **Possibly avoidable or modifiable factors:**
  - Factors increasing blood vessel (vascular) risk: diabetes, high cholesterol, and high blood pressure are examples\(^1\).
  - If a person achieved low education or the lack of an occupation\(^1\).
  - The severity of any previous traumatic head/brain injury\(^1\).
  - Sleep disorders (for example apnea, the breathing problem)\(^1\).
  - Estrogen hormone replacement therapy\(^1\).

Why is it necessary to provide early diagnosis methods?

Research is underway to provide diagnosis methods to detect the possibility of Alzheimer’s disease before its debilitating symptoms occur. This could help to start treating the patient beforehand, so that irreversible brain damage can be prevented effectively. Nuclear medicine imaging may well provide an answer to this need.

**MATERIALS AND METHODS:**

The sources employed for this study include scholarly articles, a book by the National Academies press of the USA, online resources created by the Alzheimer’s Association, resources created by the
National Institute on Aging USA, resources created by universities and websites created by doctors. Here are lists of the sources cited and the sources consulted:

Sources Cited:


Sources Consulted:

RESULTS:

What is nuclear medicine in the context of imaging and diagnosis?

Nuclear medicine is the medical specialty used to diagnose and treat diseases in way that is safe and painless to the patient. Nuclear medicine procedures often identify abnormalities at a very early stage of the disease, long before they can be detected with other diagnostic tests. This allows the disease to be treated sooner, when a successful prognosis is conducted. Nuclear medicine imaging provides functional information at a molecular and cellular level, which contributes to the determination of health status, by measuring the uptake and turnover of target-specific radiotracers in tissue. Nuclear medicine imaging offers a broad display of tools to analyze normal and disease-related states of tissue functions. These functional processes include tissue blood flow and metabolism, protein—protein interactions, expression of cell receptors in normal and abnormal cells, cell—cell interactions, neurotransmitter activity, cell trafficking and homing, tissue invasion, and programmed cell death.

The combination of anatomic imaging given by the computed tomography (CT) to the functional imaging of positron emission tomography (PET) and the single photon emission computed tomography (SPECT) has expanded the utility and accuracy of nuclear medicine imaging. By using the combined modalities, like PET/CT or SPECT/CT, the functional processes can be localized within the body to an anatomically identified, or identifiable structural alteration. These devices have increased the accuracy with which the diseases can be detected, aided depending on the determination and severity of disease, enhanced the accuracy for identifying disease-related risk, and improved the ability to monitor patient response to therapy.

How does nuclear medicine imaging technology work?

Nuclear medicine uses different technologies to diagnose the diseases. Some of the most common ones are: single photon emission computed tomography (SPECT), computed tomography (CT), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and Magnetic Resonance Imaging (MRI).

Computed Tomography (CT):

A CT scan uses a motorized x-ray source which rotates around a gantry (circular opening of a donut-shaped structure). The patient lies on a bed that moves slowly through the gantry while the x-rays rotate around the patient. The x-rays are shooting narrow beams through the body. CT scans do not use film, instead they use a special digital x-ray detectors that are located opposite from the x-ray source. Once the x-rays leave the patient the detectors picks them up and send them to a computer. Once the x-ray source finishes a full rotation, the CT computer uses sophisticated techniques to construct a 2D image slice of the patient. Once the full slice is completed, the bed is moved forwards towards the gantry. The cycle continues until the needed number of slices is collected. The slices can be displayed individually or the computer can put them together making a 3D image of the patient, showing its skeleton, organs, tissues and abnormalities that the doctor is trying to analyze.

Single Photon Emission Computed Tomography (SPECT):

The Single Photon Emission Computed Tomography combines two different technologies: computed tomography and radioactive materials (tracer). The tracer allows the doctor to see the blood...
flow to tissues and organs\(^5\). The scans are mainly used to see the flow of the blood through the arteries and veins of the brain\(^5\).

![An SPECT scan of a healthy brain (above) and a brain with a tumor (below)\(^5\).]

Before the scan the patient is injected with a chemical which is radiolabeled, so it emits gamma rays that can be detected by the scanners\(^5\). Afterwards the computer collects the information that the gamma rays sent and translates them into 2D cross-sections (slices)\(^5\). This cross-sections can be put together to form a 3D image of for example the brain\(^5\). The radioisotopes which are normally used in the SPECT scans are iodine-123, technetium-99m, xenon-133, thallium-201 and fluorine-18\(^6\). These are used to label the tracers and they are radioactive forms of natural elements so they pass safely through the patient's body and are detected by the scanner\(^5\). The type of tracer used in the scan varies on what the doctor wants to measure\(^5\). When doctors look at tumors, they normally use fluorodeoxyglucose (FDG)\(^5\).

**Positron Emission Tomography (PET):**

A positron Emission Tomography consists in using radiation in order to make a 3-dimensional, color images of the functional process in the human body\(^6\). So before a PET is carried out, a radioactive medicine is made in a cyclotron specialized machine. This radioactive medicine is tagged to a natural chemical, which could be glucose, water or ammonia\(^6\). Now the tagged natural chemical is called a radiotracer, which is then inserted in the human body\(^6\). Once the radiotracer has penetrated in the patient's body, it will go to areas in the body that use the natural chemical to which the radioactive medicine is tagged\(^6\). In the case of cancer, for example, FDG is tagged to glucose in order to create the radiotracer\(^6\). Then the radiotracer goes to the parts of the body that use glucose for energy and since cancers use glucose differently from normal tissues, the PET can detect the cancer cells\(^6\).

A PET scan can detect the energy which is emitted by positively-charge particles also known as positrons\(^6\). As the radiotracer is being broken down inside the patient, the positrons are made, and then this energy appears as a 3D image on a computer\(^6\). This image shows how the parts of the patient's body are functioning by the way they break down the radiotracer\(^6\). In the image the different levels of positrons are shown according to the brightness and color. Once the image is complete, it is studied by the radiologists who reports the results to the doctor\(^6\).
Magnetic Resonance Imaging:

The MRI machine is an expensive piece of equipment (costing between $500,000 and $2 million) that visualizes the brain using a combination of radio waves and an incredibly powerful magnetic field [source: Frost & Sullivan Research] (7). The typical research MRI scanner has a strength of three teslas -- a force about 50,000 times stronger than the Earth's magnetic field [source: University of Oxford] (7). When you lie inside the cylindrical MRI machine, it aims radio waves at protons -- electrically charged particles in the nuclei of hydrogen atoms -- in the area of your body being studied (7). As the magnetic field hits the protons, they line up (7). Then the machine releases a short burst of radio waves, which knocks the protons out of alignment (7). After the radio-wave burst has ended, the protons fall back in line, and as they do, they release signals that the MRI picks up (7). The protons in areas of oxygenated blood produce the strongest signals (7). A computer processes these signals into a three-dimensional image of the brain that doctors can examine from many different angles (7). Brain activity is mapped in squares called voxels (7). Each voxel represents thousands of nerve cells (neurons) (7). Color is added to the image to create a map of the most active areas in the brain (7).

Functional Magnetic Resonance Imaging (fMRI):

A functional magnetic resonance helps diagnose diseases of the brain, such as Alzheimer's. This scan follows the same technology of the magnetic resonance imaging (MRI), so it is a non-invasive test using a strong magnetic field and radio waves in order to create precise images of the brain (7). fMRI looks more at blood flow in the brain so that it can detect areas of activity (7). The changes in blood flow, captured by the computer, help doctors understand more about how the brain works (7). This scan is based on the idea that the blood that carries oxygen from the lungs (oxygen-rich blood) behaves differently in a magnetic field from the blood that has been released its oxygen to the cells (oxygen-poor) (7). So the two types of blood have different magnetic resonance (7). The more active areas of the brain receive more oxygen (7). The fMRI picks up this increased blood flow to pinpoint greater activity (7). The measurement of blood flow, blood volume and oxygen use is called the blood-oxygen-level-dependent (BOLD) signal (7).

How is nuclear medicine used to diagnose Alzheimer's disease in particular?

Beta-amyloid plaques, thick build-ups of protein in the brain, as well as neurofibrillary tangles, abnormal structures within brain cells, are considered the hallmarks of Alzheimer's disease. The detection of these two indicators of Alzheimer's often forms the basis of nuclear medicine imaging techniques. Pittsburgh Compound B (PIB), Amyvid, also known as florbetapir F-18, Vizamyl, also known as flutemetamol F18, Neuraceq, also known as florbetaben F18, and Florbetaben (BAY 94-9172) are radiotracers used in PET and SPECT imaging to detect amyloid plaques, since they bind to the beta-amyloid proteins (8). Carbon-11-labeled Pittsburgh compound B (PIB) and fluorine-18-labeled-2-dialkylamino-6-acylmalononitrile-substituted naphthalenes are used to detect beta amyloid as well as tau (3).

Another method of detecting Alzheimer's using nuclear medicine includes analyzing the shrinkage of certain areas of the brain, including the hippocampus, using structural imaging techniques such as MRI and CT scans (3). Functional imaging techniques, including PET scans and fMRI scans, are also capable of detecting reduced metabolism and brain activity in certain area of the brain associated with Alzheimer's (3). This includes using FDG, fluorodeoxyglucose, to detect reduced usage of glucose in the areas associated with learning, problem solving, and memory (3).
In this example image, one can see the tomographic slices of the brain at the inferior parietal/superior temporal cortex\(^3\). On the left is an image of a normal brain, while on the left is the image of a patient of Alzheimer’s disease\(^3\). The red, orange and yellow parts (in decreasing order) are the most metabolically active, while the green, blue and violet parts (in decreasing order) are less active\(^3\). Note that in the healthy brain, the whole cerebral cortex has moderately high levels of metabolic activity\(^3\). However, in the diseased brain, the parietotemporal cortex (indicated by arrows), an area associated with language processing and associating memories, has diminished metabolism\(^3\). This is a good example of how FDG- PET imaging detects indicators of Alzheimer’s disease\(^3\).

Above is another example image, showing the brain for a normal control person on the right and the brain of an Alzheimer’s patient on the left\(^3\). One can see that the patient has far more uptake of the PIB radiotracer as compared to the control person, indicating a high concentration of beta- amyloid\(^3\). This is a good example of how PIB PET is used to detect indicators of Alzheimer’s disease\(^3\).
What are the other methods apart from nuclear technology methods to diagnose Alzheimer’s?

**Biomarkers:**

Biomarkers are used for an earlier detection of the Alzheimer’s disease. Scientists believe that biomarkers (also known as biological markers) offer a promising path in order to detect the disease in an easy and accurate way (8). A biomarker is something that can be accurately measured and indicates reliably the presence of the disease (8). In the case of diabetes, the biomarker is fasting blood glucose level, it indicates the presences of diabetes if it is 126 mg/dL or higher (8). There are several biomarkers that are been studied for their capability which to diagnose early stages of Alzheimer’s (8). Some of the ones that are being investigated include beta-amyloid and tau levels in cerebrospinal fluid and brain changes detectable by imaging (8). Some research suggest that these indicators may change at the different stages of the disease process (8). Currently there are no biomarkers that are validated for Alzheimer’s disease but some of the ones that are investigated include brain imaging, proteins in cerebrospinal fluid, proteins in blood and genetic risk profiling (8).

**Cerebrospinal Fluid (CSF) Proteins:**

Cerebrospinal fluid is a clear fluid that protects the brain and spinal cord. Research suggest that Alzheimer’s disease in the early stages can cause changes of the CSF levels of tau and beta-amyloid (8). These are two types of proteins that form beta-amyloid plaques and neurofibrillary tangles, which are linked to the Alzheimer’s disease (8).

**Proteins in blood or other parts of the body:**

Researches are also investigating if presymptomatic Alzheimer’s disease causes measurable changes in urine or blood levels of tau, beta-amyloid or other types of biomarkers (8). Scientists are also exploring whether early stages of Alzheimer’s disease leads to noticeable changes anywhere else in the body (8).

**Genetic risk profiling:**

Scientists have found three genes with can have rare variations and cause Alzheimer’s and several other genes that contribute to a higher risk of getting the disease but they don’t necessarily guarantee that a person will develop the disease (8).

**Mild Cognitive Impairment Analysis**

Individuals who develop Alzheimer’s disease go through a phase called Mild Cognitive Impairment, in which they develop problems with memory or other crucial mental processes significant enough to show up on mental testing (8). Once a person is diagnosed with MCI, this could be seen as a major indicator for the future development of Alzheimer’s disease (8).
DISCUSSION:

What are the advantages and disadvantages of using Nuclear Medicine Imaging?

Nuclear imaging can have certain advantages as opposed to other methods of diagnosis of Alzheimer’s disease. MRI imaging and CT scans can be very useful to eliminate other possibilities that could be causing cognitive decline. This would include tumors, small or large strokes, severe head trauma, or fluid deposits in the brain. Alzheimer’s is very often predicted in patients of MCI (Mild Cognitive Impairment). However, this is not a very conclusive method of early diagnosis since individuals with MCI often never develop Alzheimer’s, and in some cases, even overcome MCI partially. Moreover, MCI diagnosis techniques are not standardized, and neither is the definition of MCI. Nuclear medicine can have an advantage as opposed to the MCI analysis method is early diagnosis, since it considers the brain structure and function as opposed to the rather vague diagnosis of MCI. Nuclear imaging also has the advantage over CSF (Cerebrospinal fluid) analysis that it is not an invasive procedure, while CSF analysis requires a lumbar puncture. Genetic risk profiling is also an unreliable technique that is still under development, and nuclear imaging may be more conclusive than it.

Nuclear imaging as a solution to earlier diagnosis of Alzheimer’s disease does have its drawbacks. It is often centered around the detection of beta-amyloid plaques. However, the presence of these protein deposits cannot be the sole reason for diagnosis of Alzheimer’s, since many people who have no symptoms of cognitive decline or Alzheimer’s also have such plaques in their brains. Thus, amyloid imaging cannot be prescribed as a routine and definitive test for Alzheimer’s.

Furthermore, even structural imaging that focuses on the shrinkage of the brain cannot be definitive, since scientists have not as of now decided upon standardized values of brain shrinkage that would definitely determine that a patient has Alzheimer’s disease. Functional imaging research has also not yet been able to determine patterns to translate diminished metabolism in certain areas of the brain to definitively diagnose Alzheimer’s disease. For example, FDG-PET scans have limited diagnostic accuracy since there is a high rate of glucose metabolism throughout the brain, which results in high radiotracer uptake throughout the brain. Structural and functional imaging may be able to show indicators and clues, but cannot be used for absolute diagnosis.

Another issue at the moment with nuclear imaging is that, although many radiotracers have been developed for use, not many of them are readily available. For example, fluorine-18-flouroDOPA, which is used to assess the dopamine system through PET scans, is not available readily.

Is there any radioactive risk involved?

Nuclear medicine imaging such as CT scans, PET scans, etc. also pose certain radiation risks due to the radiotracers used. The risk of developing cancer from a single scan is very small, but the imaging technology is so widely used that it does have considerable repercussions. For example, in 2007, CT scans were associated with about 29,000 future cancer cases. Getting a CT scan exposes one to as much radiation as 100 to 800 chest X-rays, and PET scans expose one to as much radiation as 10 to 2,050 chest X-Rays. To put it into perspective, an individual receives the radiation equivalent of 1 chest X-Ray from normal background radiation in about 2.5 days, while an individual receives the radiation equivalent of a CT scan in about 2.7 years. The lack of standardization makes the problem even worse. For example, in San Francisco itself, a 2009 study found that the dosage of radiotracers used for the same type of CT scan varies 13 fold between the maximum and minimum dosage given by
different hospitals\textsuperscript{(9)}. Radiation puts the patient at a risk of cancer, burns, hair loss, and cataracts in the eyes, and thus should be used with strict caution\textsuperscript{(9)}. However, one must keep in mind that a risk – benefit analysis is necessary. For many patients, especially older people, the benefit of doing a nuclear medicine scan to diagnose Alzheimer’s clearly outweighs the risks.

**CONCLUSION:**

Ultimately, nuclear medicine imaging can be considered a potent and useful tool in the early diagnosis of Alzheimer’s disease. However, the lack of conclusiveness of diagnosis means that nuclear imaging cannot be used as a routine test to predict Alzheimer’s disease, and must instead be used in partnership with other techniques such as MCI analysis, CSF analysis, genetic risk profiling, and other techniques still under research and development. Moreover, the lack of worldwide standardization of dosage of radiotracers and diagnosis parameters, and limited availability of radiotracers stand as impediments in its use. To solve these issues, the IAEA in and international organizations such as the WHO can aid the distribution of newly developed radiotracers and the standardization of radiotracers doses for CT and PET scans through their dosimetry research laboratories and their technical cooperation projects with countries around the world.

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