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REVIEW ON EARLY ONSET ALZHEIMER'S DISEASE

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Abstract

Alzheimer's disease (AD) is the most common progressive neurodegenerative disease and the most common form of dementia. There are two major types of AD these are early onset Alzheimer's disease (EOAD) and late onset Alzheimer's disease (LOAD). The genetics of EOAD are largely understood with mutation in three different genes leading to the disease. Here we review the known genetics of EOAD. The most widely accepted hypothesis is the amyloid cascade hypothesis. Preliminary data suggest that CSF markers such as Aβ and Tau levels may be considered as a helpful tool in the diagnosis of early onset Alzheimer's disease (EOAD). Assessment of biomarkers in EOAD should be recommended in order to increase diagnostic accuracy in those cases with atypical presentation and /or familial aggregation of the disease. The typical presentation is more frequent in EOAD than in late onset Alzheimer's disease (LOAD). To date more than 160 highly penetrant but rare mutation have been described in three genes amyloid precursor protein(APP), presenilin 1(PSEN1) and presenilin 2(PSEN2). PSEN1 is the most frequently mutated EOAD gene with a mutation frequently of 18-50% in autosomal dominant EOAD.

Key Words: Alzheimer's disease,gene mutation, dementia, β-amyloid peptide(Aβ), Early Onset Alzheimer's Disease(EOAD), Kinase enzymes.

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INRODUCTION

Alzheimer's disease (AD) originally meant a disorder of early onset (EOAD) and did not include older patient with senile dementia[1]. Early onset Alzheimer's is an uncommon form of dementia. That strikes people younger than age 65.The disease that would upon the suggestion of his colleague Dr.Emil Kraepelin eventually bear his name was first described by Aloysius "Alois" Alzheimer in 1907, based up on his observations and treatment of a 51 years old patient August Deter (1850-1906)[2]. Her symptoms includes memory loss, confusion, language impairment and unpredictable, agitate, aggressive and paranoid behavior and an autopsy revealed that characteristic neurological markers of AD[3]. These include extra cellular plaques formed from cleaved amyloidal precursor protein(APP) and intracellular tangles of hyperphosphorylated microtubule associated protein tau (MAPT),with the observation of similar neuropathology associated with cognitive decline in all age groups, investigators subsequently broadened the diagnosis of AD ton include the much more common late onset Alzheimer's. The typical presentation is more frequent in EOAD than LOAD. The few epidemiological studies on EOAD in despite that the vast majority are familial, making up about 4-6% of all AD[4-6].Early onset Alzheimer's disease is an uncommon form of dementia. It affects memory, thinking and behavior. That strikes people younger than age 65. Of all the people who have Alzheimer's disease about 5% develop symptoms before age 65[6].

EPIDEMOLOGY

Alzheimer's disease is the most common cause of dementia[7]. The disease that would, upon the suggestion of his colleague Dr. Emil Kraepelin, eventually bear his name was first described by Aloysius "Alois" Alzheimer in 1907, based upon his observations and treatment of a 51-year-old patient, August "D"[2].Its prevalence among dementia patients increase to 80%, if AD lesions in conjunction with other pathologic brain eosin are considered[6].If 4 million Americans have Alzheimer's, at least 200,000 people have the early-onset AD (EOAD) form of the disease. Onset can be as early as age 30 years, resulting in the arbitrary age classification of early onset(age less than 65 years) and late onset(age 65 years and older)[8].AD is an age dependent disease that may be seen as early as age 40 years and increase incidence up to 9th decade. It appears to occur more frequently in woman than in men. Community surveys indicate that about 10% of population over age 65 years had mild to moderate degrees of dementia and were able to lead semi independent lives. It is the 4th/5th prevalence cause of death in late life. Dementia is not only an elderly disease as it can also affect young people, the term early onset dementia define all dementia related conditions onset before 65 years of age. This definition is based on traditional and historical cut-off but is just on artificial separation, despite the world wide renowned use[9]. The number of people with EOAD is growing the disease in becoming more recognized with a clinical significance and important social problems. The prevalence of dementia in people under age 65 years has been investigated and it is observed from 35 years and 50 years there prevalence rate is double every five years such as in senile dementia[10].

PATHOPHYSIOLOGY

Alzheimer's disease is a progressive neurodegenerative disease that represented a growing global health crisis. Two major forms of disease exits; early onset AD (familial) and late onset

AD (sporadic)[11] . The genetics of early onset Alzheimer's disease (EOAD) are longley understood with variant in three different genes leading to disease[12].EOAD is most often caused by rare, highly penetrate mutation in three genes encoding protein involved in amyloid precursor protein(APP) breakdown and Aβ generation namely, the Aβ, presenilin-1(PSEN1) and presenilin-2(PSEN2) [13] gene.In 1984, Glenner first proposed that cerebral Aβ drives all subsequent pathology. This central thesis was later reinterpreted and reported as the amyloid cascade hypothesis of AD, which maintains that the accumulation of Aβ is the primary driver of AD related pathogenesis, including neuronal cell death [14]. Amyloid precursor protein (APP): The function of APP is not completely understood[11]. APP is collated on chromosome 21(21q21.2-21q21.3) and was one of the first cause genes identified for AD[12]. The extra function of APP is not certain, but several possible functions have been suggested such as synoptic development, neuronal migration or as a receptor, although there have been arguments against this[15]. The AD linked APP mutations located near the β and γ- secretase cleavage sites serve to increase Aβ42 production. The Swedish mutation, lying immediately before the begging of the Aβ peptide sequence, affects the efficiency of β-secretase cleavage and increase the amount of Aβ peptide produced by 2-3 fold. APP mutation at the C-terminal end of Aβ after the activity of γ-secretase cleavage and shift proteolysis to produce more Aβ42, resulting in an increased Aβ42/Aβ40 ratio but not increase in the total amount of Aβ peptides formed. The arctic mutation (E693G) is located within Aβ dominent. The amyloid hypothesis is further supporting by the opposite situation, in which an APP mutation reducing the amount of amyloid formation in fact protects against AD[16].

Presenilins (PSENs): PSEN1, PSEN2 is located on chromosome 14(14q24.3) and has at least two isoforms. The PSENs are important determinant of gamma secretase activity and are responsible for proteolytic cleavage of the APP and NOTCH receptor protein[17]. Both PSEN1 and PSEN2 are part of the γ-secretase complex; therefore, they are functionally involved in the γ-secretase mediated proteolytic cleavage APP. γ-secretase containing mutation-altered presenilin still catalyzes cleavage of APP, but proteolytic site is altered; therefore, it causes either an increase in Aβ42 levels or a decrease in Aβ40 levels, reading to an increase in the Aβ42/Aβ40 ratio the relative increase in Aβ promotes the aggregation of the peptide into oligomer and ultimately amyloid fibrils[14,18].

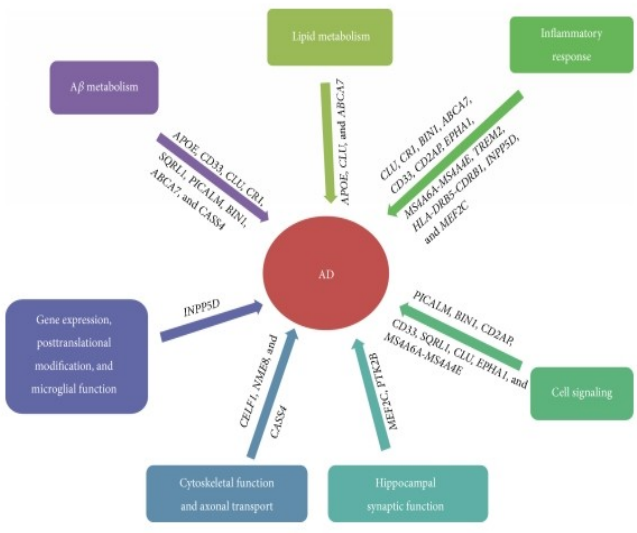

Figure 1: Potential pathways of susceptibility genes involved in the pathogenesis of AD.

CLINICAL FEATUTERS

Memory loss is the key symptom of Alzheimer's disease. An early sign of the disease is usually difficulty remembering recent events or conversations. The patient may have vague memory complaints initially or the patient significant other may report that the patient is forgetful.

Symptoms are classified as three main types as follows[19]:

COGNITIVE	NON-COGNITIVE	FUNCTINAL
Memory loss. Apraxia. Aphasia.	Depression. psychiatric Symptoms. hallucinations and delusions	Inability to care for self. (dressing, bathing, eating etc).

- Disturbances in memory are the hallmark of this disease but other cognitive areas such as language use visual spatial perception and the ability to earn, solve problems, think abstractly and make judgments are also affected.
- The loss of choline acetyltransferase begins with in the first year of the onset of symptoms in these patients.
- EOAD is recognized as a syndrome of clinical features characterized by a decline of memory and other cognitive functions in comparison with the patient's previous level of function[20].
- Patient con not recognize relatives, remember their own names. Progressive washing functions. Death is usually the result of pneumonia and other infections[19].
- An early sign of the disease is usually difficulty to remembering recent events or conversations.
- Making judgments and decisions: - Its may be more difficult to respond effectively to everyday problems such as food burning on the stove, unexpected driving situations[20].

DIAGNOSIS

- Screening is being promoted as part of the medicare annual wellness visit by the Alzheimer's Association (AA) [21].
- Until recently the only way to conform a clinical diagnosis of EOAD was through direct examination of brain tissue.
- Several criteria have been used in clinical practices and diagnosis of EOAD is given below:
- Diagnostic and statistical manual of mental disorder (DSM-5) criteria.
- The American Academy of Neurology Guidelines.
- Alzheimer's disease and Related Disorders Association (ADRDA) [22].

DIAGNOSTIC TESTS

- History from patient, relatives, close associates.
- Mental status examination
- Neurological examination
- Thyroid function tests
- Urine analysis
- Chest X-ray
- Psychiatric assessments of mood, apathy, anxiety etc [21,22].

TREATMENT

NON-PHARMACOLOGICAL TREATMENT

- Symptoms such as sleep disturbances, urinary incontinence, wandering in patients with dementia are best managed using behavioral interventions rather than medication[23].
- Care giver education and support programs have been shown to improve care giver skills, knowledge, confidence and quality of life[24].

PHARMACOLOGICAL TREATMENT[22]:

ANTI DEPRESENTS

BRAND NAME	DRUG NAME	DOSE	FREQUENCY
Pamelor	Nortriptyline	10mg	b.i.d-t.i.d
Desyrel	Trazodone	50mg	q.d-b.i.d
Nardil	Phenelzine	15mg	b.i.d

ANTI ANXIOLYTICS

BRAND NAME	DRUG NAME	DOSE	FREQUENCY
Ativan	Lorazepam	0.5mg	b.i.d
Xanax	Alprazolam	0.25mg	b.i.d-t.i.d
Serax	Oxazepam	10mg	b.i.d-t.i.d

NEUROLEPTICS

BRAND NAME	DRUG NAME	DOSE	FREQUENCY
Mellaril	Thioridazine	10mg	q.d-b.i.d
Haldol	Haloperidol	0.5mg	q.d-b.i.d
Navane	Thiothixene	1.0mg	q.d-b.i.d

HYPNOTICS

BRAND NAME	DRUG NAME	DOSE	FREQUENCY
Halcion	Triazolam	0.125mg	q.d
Restoril	Temazepam	15mg	q.d
Noctec	Chloral hydrate	250-500mg	q.d

CONCLUSION

Alzheimer's disease is an age dependent disease that may be seen as early as age 40 and increase in incidence up to the ninth decade. Dementia is not only affecting older people as it can also affect young age people. Studies involving larger numbers of individual are required in order to determine whether and which marker abnormalities are consistently detected at early stage in young onset dementia. Up to now, no clear-cut conclusions might be drawn. Preliminary data suggest that CSF markers such as Aβ and Tau levels may be considered as a helpful tool in the diagnosis of EOAD. The assessment of biomarkers in EOAD should be recommended in order to increase diagnosis accuracy in those cases with atypical presentation and/or familial aggregation of the disease.

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