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Mathematical modeling for genesis of Alzheimer disease through Markov process

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Abstract : Current indications show that 46.8 million people are living with dementia worldwide and these numbers are increasing every year. In 2015 alone, 9.9 million new cases were reported worldwide and its cost was around 818 US$. The most prominent form of dementia is Alzheimer's disease (AD). Efforts to develop a drug for AD have been ongoing and several efforts have failed in different phases of trial. We used mathematical model of Markovto test the possibility that genesis of AD might occur not in brain but at other locations but the final event of development of plaques and neuronal death occurs in brain. Ourmodel takes into account various possibilities that might leads to the development of AD. It suggests that during the genesis of AD, it is least likely that direct events are contributed by brain itself. Initial contributions are most likely made by some factor that is transported via blood to brain.
Keywords: Amyloid beta, pathogenesis, plaques, dementia, Markov process.

Introduction:

Dementia is one of the most common cause of disability in later life and Alzheimer's disease (AD) is most prevalent form of dementia. Current indications show that 46.8 million people are living with dementia worldwide. In 2015 alone, worldwide, 9.9 million new cases of dementia have been reported in annual report of Alzheimer Disease International (ADI), London[1, 2].In 2015, database information on Alzheimer's of USA suggests that 5.3 million Americans of all ages have AD [3].The projection of the people living with dementia almost doubles every 20 years. It is suggestive that maximum number of people with dementia are from Asia (22.9 million) followed by Europe (10.5 million), America (9.9 million) and then Africa (4.0 million) respectively (Prince et al.,2013, 2015)[1]. Worldwide, economically, total estimated cost for dementia have increased from 604 billion US$ in 2010 to 818 billion US$ in 2015, which will rise to 1 trillion US$ in 2018 and around 2 trillions US$ in 2030[2].Alzheimer's is becoming a more common cause of death, although deaths from other major causes have decreased significantly in USA. Official records indicate that deaths from Alzheimer's disease have increased significantly. Between 2000 and 2013, death attribute to Alzheimer's disease boosted 71%, while those attributed to the number one cause of death (heart disease) reduced 14% [4](Fig-1).

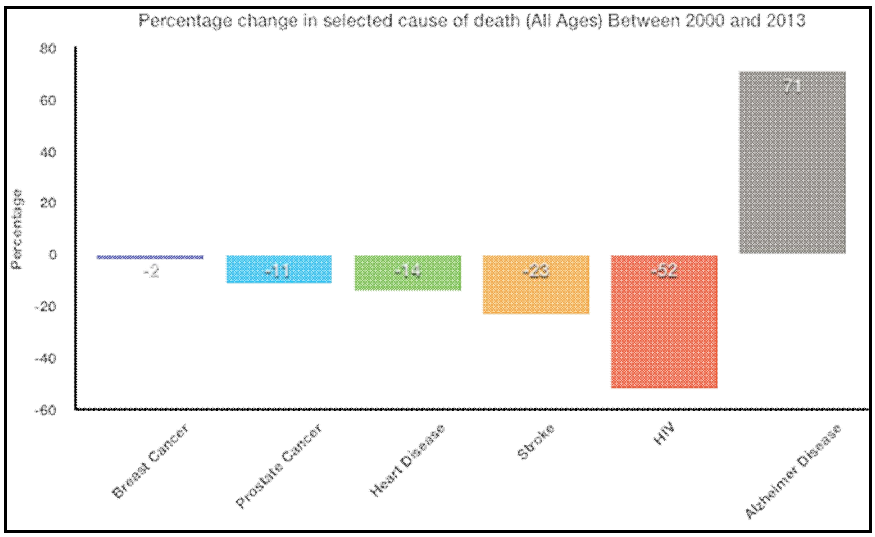

Fig-1: Percentage change in selected cause of death in USA between 2000 and 2013 (Created from data of Data of National center for health statistics).

AD is diagnosed and confirmed by the presence of extracellular deposits of β-amyloid peptide (Aβ), known as senile plaques. According to the most prevailing hypothesis, AD occurs due to the altered cleavage of Amyloid Precursor Protein (APP), bound to the cell membrane of neurons hypothalamus by secretase enzymes. Under normal conditions, α secretase enzyme cleaves APP at a site (amino acid position number 770), which yields a peptide P3 so that prevents formation of the β- amyloid peptide, and this pathway is called non-amyloidogenic (fig-2).However, activity of α secretase is dominated somehow by the activity of β and γ secretase. These enzymes cleave APP into two specific positions (amino acid position 713 and 672 respectively) that generateAβ42 peptide. Its aggregation into the brain over the time leads to the formation of senile plaques, that is the main neuropathological feature of AD. Tau is responsible for intra–neuronal neurofibrillary tangles (NFT) formation in AD brain.Tau is a microtubule binding protein found largely in axons, where it serves to stabilize microtubules and has also been reported to be one of the factors responsible for AD[5].

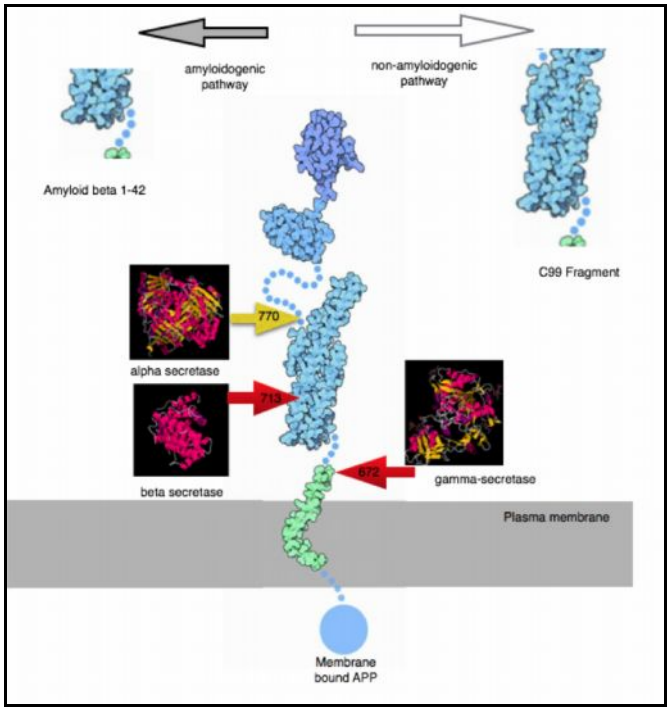

Fig. 2. Processing of APP protein (anchored in membrane) of by beta and gamma secretase. This leads to formation of Amyloid beta peptide through amyloidogenic pathway. The production of C99 fragment through cleavage by alpha and gamma secretase enzymes on position number 770 and 672 amino acid respectively leads to non-amyloidogenic pathway.

During the course of Alzheimer's disease, tau is hyper-phosphorylated, becomes detached from the microtubules, and accumulates in the somato-dendritic compartment in paired helical filaments and straight filaments [6, 7, 8]. The deposition of tangles occurs in a hierarchical fashion beginning in the entorhinal cortex and progressing through the hippocampal formation, association cortices, and only affecting primary sensory areas in late stages of the disease [9, 10] NFT deposition in human AD correlates with cognitive decline and neuronal loss [11, 12, 13, 14]. The association of NFT with neuronal loss and the presence of ghost tangles—NFT that remain in the brain after the neuron has died—strongly suggest that at least some neurons with tangles die during the course of the disease; however, the amount of neuronal loss vastly exceeds the number of neurofibrillary tangles and ghost tangles within given brain regions, supporting the idea that a tangle is not necessary for neuron death in AD [14]. Once plaque or NFT is formed, clinical symptoms of the patient are evident. Severity of AD is correlated to symptoms of patients. If this hypothesis was the only one pathway leading to AD then some break through would have been achieved keeping in view the advances in diagnostics and research developed in recent years. However this is not the case.

Besides the common hypothesis of the occurrence of Aβ and tau tangles in neurons, recent evidence suggests that formation of the Aβ can occur in the non-neuronal locations also. Many factors that increase the risk of cardiovascular disease are also associated with a higher risk of developing AD and other dementias. These factors include smoking, [15, 16, 17]obesity (especially in midlife),[18, 19, 20, 21, 22, 23, 24] diabetes[17, 25, 26, 27, 28, 29]high cholesterol in midlife[20, 30]and hypertension in midlife [20, 23, 31, 32, 33]The other disease & pathways have also been linked with AD and these are: cardiovascular, diabetes, insulin deficiency, ApoE & platelets. Usually, Patients of AD also suffer from Cerebral Amyloid Angiopathy (CAA). Basic research has now recognized many of the pathway that contribute to development of AD and has provided much needed imputes to new thought process & development of new treatments [34]. Many pharma giants are also working for development of drugs for AD treatment although several trials have failed.

So far, efforts to find a cure for AD have met disappointment and the drugs currently available do not cure a patient. These drugs provide some relief in symptoms with limited effectiveness. Some side effects of current drugs have also been reported [35]. Till date, the U.S. Food and Drug Administration (FDA) approved only five drugs for AD; theapproved drugs temporarily improve detonating symptoms of Alzheimer's disease by increasing the amount of neurotransmitters in the brain. FDA approved the sixth drug in December 2014, which combines two existing FDA-approved Alzheimer's drugs and is for moderate to severe disease. Before this, the last approval of an Alzheimer's drug was in 2003 (Table-1).

Table-1: Drugs approved by FDA for AD treatment
Source: (http://www.alz.org/research/science/alzheimers_disease_treatments.asp)

S.No.	**Drug Name**	**Brand Name**	**Approved for**	**FDA approved**
	Donepezil	Aricept	All stages	1996
	Galantamine	Razadyne	Mild to moderate	2001
	Memantine	Namenda	Moderate to severe	2003
	Rivastigmine	Exelon	All stages	2000
	Donepezil and memantine	Namzaric	Moderate to severe	2014

Yet, none of the treatments available today for Alzheimer diseaseto slows stops or reverse the damage to neurons, eventually making the disease fatal. It is believed that therapeutic intervention that could delay the onset or progression of AD would dramatically reduce the number of cases in the next 50 years. This would also provide a temporary relief to the over burdened medical facilities & healthcare system. A glimpse of problems is provided by the fact that the last drug approved in 2003 was the only drug selected out of the 244 probable compounds tested and completed the clinical trials process. One of the drugs used for clinical trials targeted for γ -secretase enzyme and aimed to minimize Aβ production in brain. This clinical trial failed in phase III [36].This failure led several research groups to rethink their strategy of targeting enzymes of Aβ formation pathway [37]. Off latean alternate hypothesis has been published in few reviews that suggesting the possibility of genesis of AD much before than the appearance of symptoms. These reviews further suggest that components delivered by blood, and alternation in BBB may play a vital role in the initiation of pathogenesis[34, 1, 38].

In the present paper we have explored this alternative hypothesis using the intrinsic flexibility of mathematical modeling. Here, we evaluate the dynamic network involving multiple cross talks among distinct states and probable different ways for genesis of Alzheimer'susing Markov mathematical model.

Experimental:

Mathematical modeling details:

Model description

Markov model for AD was developed taking into account all the known & most probably implicated pathways by which AD can develop in the humans. The model assumes that cascade of events leading to AD might actually start much earlier. These early events may be un-detectable till the appearance of clinical symptoms. A state transition diagram as shown in Fig. 3was developed. This hypothesis also takes into account the possibility that AD can develop in the humans either through non-neuronal tissues or directly in brain. If non-neuronal tissues contribute to AD then further two possibilities arise- First: that cells of any organ would form $A\beta$, $A\beta$ would then be transported via blood to brain. Second: same cells in blood, like platelets etc., form $A\beta$ & these amyloid peptides then deposit in brain. In both cases the transport is via blood. We also considered the possibility of direct formation of $A\beta$ in brain and involvement of tau protein via formation of neurofibrils tangles. Finally, the $A\beta$ accumulation contributed in brain by any path, results into development of clinical symptom that became evident in patients. We have used databases (ADI and Alzheimer's Association report 2015) available for assumptions related to the rate of progressions of AD and developed a hypothetical model as represented by fig-3 (details of abbreviations in table 2). The rate of transition from one stage to another can be variable but to beep the calculation simple, we assume that all the rates will finally be depended a transformation of S3 to S4 as the final symptoms are evident only when cascades are initiated in brain. If other rates vary form person to person the progression may ultimately be slow or fast and this correlates to either early or late onset/progress of AD. According to our hypothesis the process of AD can contain total six failure rates and five stages (Fig-3).

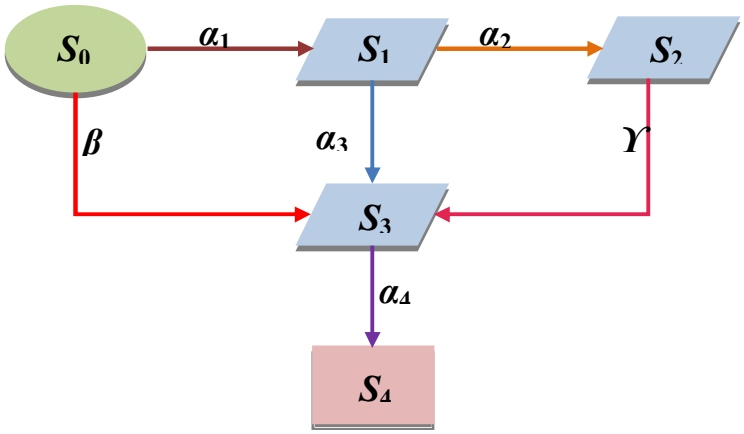

Fig-3:Hypothesis for State Transition diagram of AD. The states for the development of AD are presented as S_0: No Alzheimer's state (Healthy human being), S_1 represent the state of Amyloid beta ($A\beta$) formation in non-neuronal organs –which can be released in blood and transported to brain, S_2 state represent the $A\beta$ production by blood cells like platelets & transportation to brain by blood, S_3 state represent the $A\beta$ formation in brain and accumulation resulting in plaque formation, S_4 state represent clinical symptoms.

Table-2 Nomenclatures: All the notations used throughout the work are explained

Notation	*Explanation*
$\acute{a}_1$	Influence rate of genesis of AD from the path S_0 to S_1.
$\acute{a}_2$	Influence rate of genesis of AD from the path S_1 to S_2.
$\acute{a}_3$	Influence rate of genesis of AD from the path S_1 to S_3.
$\acute{a}_4$	Influence rate of genesis of AD from the path S_3 to S_4.
$\hat{A}$	Influence rate of genesis of AD from the path S_0 to S_3.
Υ	Influence rate of genesis of AD from the path S_2 to S_3.
$P_i(t)$	Probability of the state S_i; i=0, 1, 2, 3, 4.
$\overline{P}(s)$	Laplace transformation of $P(t)$.
$P_{up}(t)$	Probability of upstate of patient under AD at time t

Formulation of the model

We obtained the following set of difference-differential equations, which possesses the present mathematical model of AD through Markov process [39]with the consideration of probability and continuity of arguments.

$$\left[\frac{\partial}{\partial t}+\alpha_1+\beta\right]P_0(t)=0 \quad (1)$$

$$\left[\frac{\partial}{\partial t}+\alpha_2+\alpha_3\right]P_1(t)=\alpha_1 P_0(t) \quad (2)$$

$$\left[\frac{\partial}{\partial t}+\gamma\right]P_2(t)=\alpha_2 P_1(t) \quad (3)$$

$$\left[\frac{\partial}{\partial t}+\alpha_4\right]P_3(t)=\alpha_3 P_1(t)+\beta P_0(t)+\gamma P_2(t) \quad (4)$$

$$\frac{\partial}{\partial t}P_4(t)=\alpha_4 P_3(t) \quad (5)$$

Initial condition

$$P_i(0)=\begin{cases}1, & when \quad i=0\\ 0, & otherwise\end{cases} \quad (6)$$

Taking the Laplace transformation of Equations (1) to (5) using Equation (6), we got

$$[s+\alpha_1+\beta]\overline{P}_0(s)=0 \quad (7)$$

$$[s+\alpha_2+\alpha_3]\overline{P}_1(s)=\alpha_1\overline{P}_0(s) \quad (8)$$

$$[s+\gamma]\overline{P}_2(s)=\alpha_2\overline{P}_1(s) \quad (9)$$

$$[s+\alpha_4]\overline{P}_3(s)=\alpha_3\overline{P}_1(s)+\beta\overline{P}_0(s)+\gamma\overline{P}_2(s) \quad (10)$$

$$s\overline{P}_4(s)=\alpha_4\overline{P}_3(s) \quad (11)$$

After solving the Equation [7-11], we calculated the probability of AD's patient in each state. The probability of upstate of AD's patient has been defined as the summation of probability of human with no AD genesis and the probability of all the degraded stages of AD in which genesis of AD influence in human but symptoms cannot be detected. Mathematically, it can be expressed as

$$\overline{P}_{up}(s)=\sum_{i=0}^{3}\overline{P}_i(s)$$

$$=\left[1+\frac{\beta}{s+\alpha_4}+\frac{\alpha_1}{s+\alpha_2+\alpha_3}\left\{1+\frac{\alpha_3}{s+\alpha_4}+\frac{\alpha_2}{s+\gamma}\left(1+\frac{\gamma}{s+\alpha_4}\right)\right\}\right]\overline{P}_0(s) \quad (12)$$

$$P_{up}(t)=L^{-1}\{\overline{P}_{up}(s)\}$$

$$= \frac{\alpha_1\alpha_2\alpha_4 e^{(-\gamma t)}}{(\alpha_1+\beta-\gamma)(\alpha_4-\gamma)(\alpha_2+\alpha_3-\gamma)} + \frac{\alpha_1(\alpha_3-\gamma)\alpha_4 e^{(-(\alpha_2+\alpha_3)t)}}{(\alpha_2+\alpha_3-\alpha_4)(\alpha_2+\alpha_3-\gamma)(\alpha_2+\alpha_3-\alpha_1-\beta)}$$
$$+ \frac{(\alpha_1\alpha_3\alpha_4 - \alpha_4^2\beta + \beta\alpha_3\alpha_4 - \beta\alpha_3\gamma + \beta\alpha_4\gamma - \alpha_1\alpha_2\gamma - \beta\alpha_2\gamma + \beta\alpha_2\alpha_4 - \alpha_1\alpha_3\gamma)e^{(-\alpha_4 t)}}{(\alpha_1+\beta-\alpha_4)(\alpha_4-\gamma)(\alpha_2+\alpha_3-\alpha_4)}$$
$$+ \frac{(\alpha_1\alpha_3 + \beta\gamma + \beta\alpha_2 - \beta\alpha_1 - \beta^2 - \alpha_3\gamma + \beta\alpha_3 - \alpha_2\gamma)\alpha_4 e^{(-(\alpha_1+\beta)t)}}{(\alpha_1+\beta-\alpha_4)(\alpha_1+\beta-\gamma)(\alpha_2+\alpha_3-\alpha_1-\beta)} \qquad (13)$$

Equation 13 when plotted gives a graph represented by figure 4. This graph suggests that as soon as there is onset of AD, there is a transition zone starting from 2 years to 15 years during which there can be an early or late onset.

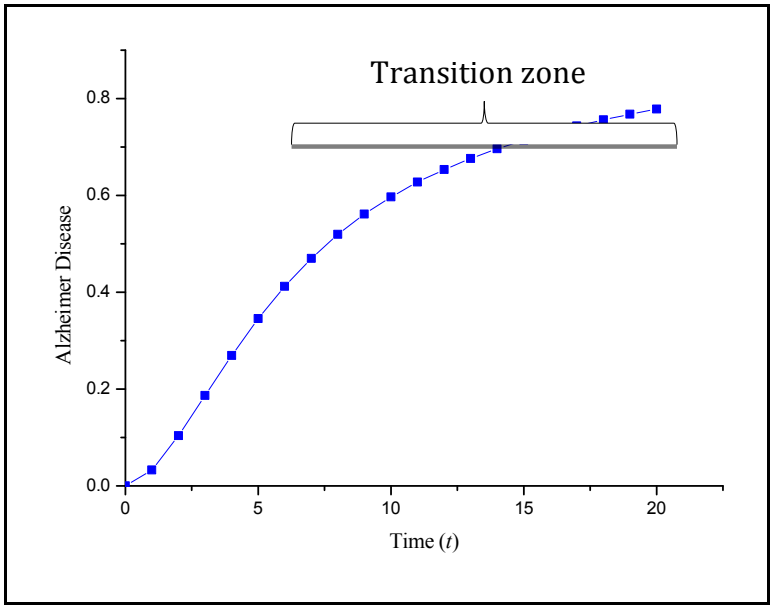

Fig-4: Growth of AD with respect to time Availability of AD in Human with respect to time. The graph showsthat AD increases with the passage of time. Progression can start with 2 years or might take next 10 year representing early or late onset.

Sensitivity of AD in human:

Sensitivity is the analysis that finds out how the uncertainty in the output or sensitive an output of a mathematical model can be assigned to different sources of uncertainty in its inputs or to change in an input while keeping other inputs as constant[40, 41] Sensitivity of AD in human being was calculated by the partial derivative of the function presented in Equation (13) with respect to their input factors as revealed in Appendix 1. Here, these input factors are the influence rates of AD genesis in human.

According to numerous theories,investigated in context of Alzheimer's Disease states thatonly

$$\alpha_4 = m\beta = m(\alpha_1+\alpha_3) = m(\alpha_1+\alpha_2+\gamma) = k \ \ (let) \qquad (14)$$

Where, k is any arbitrary constant. Rate of Amyloid beta production in blood cells especially platelets and influence rate of Amyloid beta formation in brain by blood are approximately equal. So,

$$\alpha_2 = \gamma \qquad (15)$$

Substituting the value from Equation (15) to (14), one obtain the value of influence rates of AD's Diseases as $\alpha_1 = (k/m) - k'$, $\alpha_2 = k'/2$, $\alpha_3 = k'$ (constant), $\alpha_4 = k$, $\beta = k/m$, $\alpha_2 = k'/2$. Putting all these values in the

expressions of sensitivity which were revealed in Appendix 1 and obtained the expressions of sensitivity as a function of k, k', m.

Numerical computation

Considered the values of constants as $k = 0.5$, $k' = 0.05$, $m = 3$ and getting the sensitivity of AD with respect to their influence rate of different pathways as shown in Table 3 and represented graphically in Fig.2.

Table 3: sensitivity of AD with respect to their influence rate of different pathways.

Time (*t*)	Sensitivity					
	$\frac{\partial P_{up}(t)}{\partial \alpha_1}$	$\frac{\partial P_{up}(t)}{\partial \alpha_2}$	$\frac{\partial P_{up}(t)}{\partial \alpha_3}$	$\frac{\partial P_{up}(t)}{\partial \alpha_4}$	$\frac{\partial P_{up}(t)}{\partial \beta}$	$\frac{\partial P_{up}(t)}{\partial \gamma}$
0	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
1	0.00738	0.00005	-0.00777	-0.05510	-0.18279	-0.00005
2	0.04509	0.00067	-0.05004	-0.14646	-0.53858	-0.00068
3	0.11681	0.00283	-0.13675	-0.22022	-0.89949	-0.00292
4	0.21366	0.00752	-0.26408	-0.26326	-1.19652	-0.00785
5	0.32376	0.01549	-0.42266	-0.27853	-1.41061	-0.01637
6	0.43641	0.02721	-0.60187	-0.27366	-1.54588	-0.02911
7	0.54353	0.04289	-0.79187	-0.25633	-1.61557	-0.04645
8	0.63981	0.06247	-0.98444	-0.23258	-1.63495	-0.06854
9	0.72232	0.08577	-1.17314	-0.20662	-1.61809	-0.09533
10	0.78995	0.11243	-1.35325	-0.18111	-1.57669	-0.12664
11	0.84281	0.14204	-1.52149	-0.15753	-1.51983	-0.16217
12	0.88187	0.17414	-1.67578	-0.13656	-1.45425	-0.20158
13	0.90852	0.20825	-1.81496	-0.11839	-1.38475	-0.24445
14	0.92437	0.24391	-1.93858	-0.10292	-1.31462	-0.29037
15	0.93107	0.28064	-2.04670	-0.08989	-1.24598	-0.33891
16	0.93018	0.31804	-2.13975	-0.07899	-1.18015	-0.38965
17	0.92316	0.35570	-2.21841	-0.06990	-1.11785	-0.44219
18	0.91127	0.39328	-2.28352	-0.06232	-1.05941	-0.49613
19	0.89562	0.43045	-2.33603	-0.05598	-1.00490	-0.55111
20	0.87713	0.46695	-2.37690	-0.05065	-0.95422	-0.60679

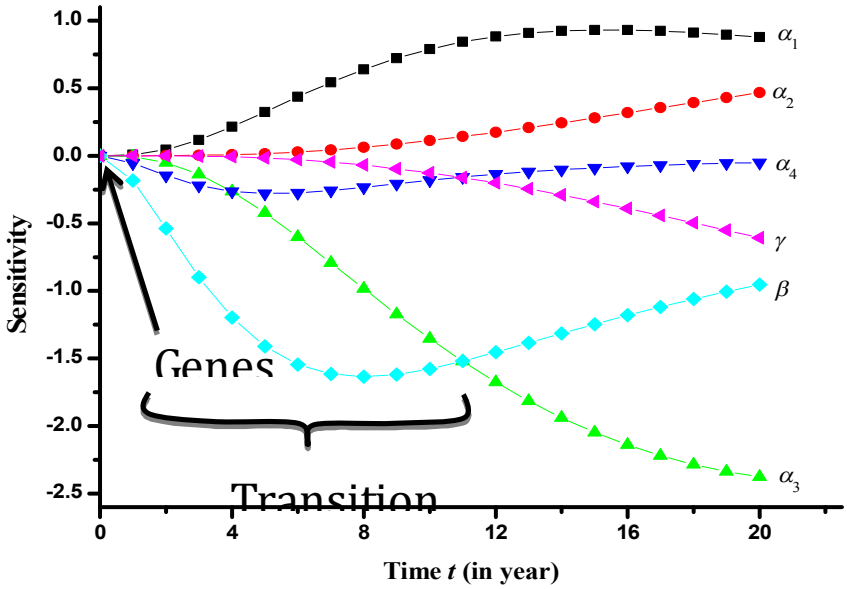

Fig-5: Graphical representation of sensitivity based on the rate of new emerging cases worldwide & the increasing number of AD patients as per ADI database, Alzheimer's association 2015. The sensitivity of AD after its genesis in 0 time scale increases with different influence rates as notated in table-2. The analysis point out to the fact that α_1 sensitivity is highest for the genesis followed by the α_2 (both these influence rates go slightly high after the first decade of genesis and then get saturate after influence of different pathways). The genesis of AD directly in brain is less probable till the first decade after genesis (as evident from data series β in fig-). β shown a increase only after the transition zone period (about a decade). It suggests that during the genesis of AD, it is least likely that direct events are contributed by brain itself. Initial contributions are most likely made by some factor that is transported via blood to brain.

Results and Discussion

Our mathematical modeling suggests that the formation of Aβ and tau might not be the only responsible factor for the genesis of AD. There can be several reasons/factors, which might modulate or trigger genesis and formation of Aβ in several other organs, responsible for AD pathogenesis. Our theory of mathematical modeling describes the following points about sensitivity of AD with respect to its influence rates for different path-

From the critical examination of Fig.4 and Fig 5, one can see that the sensitivity of AD increases with respect to the influence rate of AD in non-neuronal tissues as time passes but after a long time period it decreases slightly. If AD gene is develop in non-neuronal tissues of human then after some time it transport in brain either directly or via blood-brain-barrier (i.e. develop in platelets before brain).

The sensitivity of AD also increases with the increment in time with respect to the influence rate of AD in blood while it was lower as compared to non-neuronal organs.

In this model, the sensitivity of AD has three possibilities. One, if AD's gene is directly develop in brain then its sensitivity is decreases smoothly in the starting period of life but after a fixed period, it increases in a similar discipline as age increases. Secondly, if gene of AD contributes in brain only through non-neuronal organs then its sensitivity decreases greatly under a smooth curve with the leading time. Lastly, the sensitivity of AD decreases as time increases if it contributes in brain via blood-brain-barrier. While the vital study of Fig.2 suggested that it is approximately zero in the beginning. The comparative study of all three possibility

shows that AD most likely in human being via blood-brain-barrier. After the formation Aβ in brain and accumulation resulting in plaque formation, the sensitivity of AD's disease increases with the increasing age.

The well-known criterion of AD is usually associated with the old age people but the brain changes associated with this disease may begin 20 years or more years [42, 43, 44]. As per the criteria for the progression of AD (Alzheimer's Association USA), it is divided into three main stages named Earliest, Moderate and Severe Alzheimer's respectively. The earliest stage may begin 20 years before diagnosis and moderate generally detected 2-10 years after AD genesis. The severe may last form 1-5 years. Generally the AD is detected at the age of 60 in patients but as per the evidences it may arise decades before its symptoms. Franco and Cedazo- Minguez described the difficulties of successful preclinical research on AD mouse models translate into clinical practices. The predictive effect of new drugs tested on mouse model may not always effective for humans. This is also a fact that most of the AD-mouse models do not present the extensive neuronal loss observed in the brain of AD patients [45]. Keeping all the above facts and observations our models calculations correlate to general observation about AD. Our model predicts that once cascade of AD is initiated, transition to clinical symptoms happens within 2 years or clinical symptom development can take upto 15 years. Our sensitivity plots suggests that after the initiation of AD cascade, initially the body tries to act as a sink and tries to buffer the events via blood (higher or positive rates of alpha 1 and alpha 2 and lower rate of alpha 4, beta and nearly constant gamma). However when this buffering is compromised (region marked as transition zone), it leads to development of AD. What factors are involved and how the buffering is compromised is a matter of further investigations.

Conclusion

AD is most likely in human being through non-neuronal organs and minimum likely through direct contribution in brain or contributed in brain via non-neuronal organs only. In the beginning period, it is least likely with respect to the direct contribution in brain but after some time period its chance increases and AD becomes minimum likely when it contributes in brain via non-neuronal organs only. The most famous model for AD research is a Tg2576 mouse. (Tg2576, PDAPP, TgAPP23) models used for pre- clinical studies could be more accurate than using early plaque models. A clinical study conducted on Tg2576 late-plaque model showed the deposition of Aβ fibrils in the brain but no denaturation of neurons till the age of 16 months. The soluble Aβ starts the memory deficits at the age of 6 months, which is equivalent to the 18 years of human age (rats). The age of 18 months is equivalent to 45 years of human in rats. This can easily tell us about the fact ofdeposition and genesis of AD in humans.

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