Autism Spectrum Disorders and Alzheimer's Disease

Israa Burhan Raoof*, Mayssaa E. Abdalah*
Department of Clinical Laboratory Science, College of Pharmacy, Mustansiriyah University,Baghdad- Iraq

Article Info:

Received 4 April 2024
Revised 20 May 2024
Accepted 6 June 2024
Published 31 Aug 2025
Corresponding Author email:
israaburhan@uomustansiriyah.edu.iq
Orcid: https://orcid.org/0000-0001-8923-0264

DOI: https://doi.org/10.32947/ajps.v25i3.1173

Abstract:

Autism and Alzheimer's disease are neurological disorders associated with defects in certain areas of the brain which share common clinical signs like language impairment, executive function, physiological and pathological abnormalities, DNA methylation, myelin change, and abnormal Peripheral blood cells like B-cell and T-cells.

A genetic factor was proposed as the main cause of disease; however, the molecular mechanisms are still not well known. S-nitrosylation (SNO) in neuropathology targets key protein of gene mutations in patients that may lead to synaptic defects which return to the pathogenesis of Autism and Alzheimer's Disease, while phosphorylation of protein tau and the amyloid-β protein precursor (APP) has been showed to play vital role in neurodevelopmental disorder.

Additionally, neurite growth plays a role in brain enlargement during the first years of human life, typically expanding the anterior cortex of the brain. White matter in the brain and cerebellum appeared in more than half of the human brain that decreased with age, it was determined by a secret of myelin, tumor growth factor, cytokine, and release of kinase enzyme. in contrast, the gray matter was determined by ventricle region, area of cortex, neural stem cell, and thickness. Neurological disorders of mRNA may be due to limited social communication, and irregular behaviors in patients with autism and Alzheimer's disease. Despite that, scientists' efforts to identify management against the progression of this pathology, have only able to decrease some symptoms of autism and Alzheimer's disease are usually available, it's important to need for additional therapeutic strategies for complications, so, the World Health Organization (WHO) has made this disease a public health priority. The time period specified for this review article lasted from 2013 to 2023.

Keywords: Autism, Alzheimer's disease, Neurology

اضطرابات طيف التوحد ومرض الزهايمر

اسراء برهان رؤوف*، ميساء عصام عبد الله*
فرع العلوم المختبرية السريرية /كلية الصيدلة/ الجامعة المستنصرية، العراق-بغداد

خلاصة

التوحد ومرض الزهايمر من الاضطرابات العصبية المرتبطة بخلل في مناطق معينة من الدماغ ولها سمات سريرية مشتركة مثل ضعف اللغة، والوظائف التنفيذية، والتغيرات المرضية والفسيولوجية، ومثيلة الحامض النووي، وتغيرات في المايلين،

وتشوهات خلايا الدم المحيطية التائية والبائية. تعتبر العوامل الوراثية سبب رئيسي للمرض ومع ذلك فإن الميكانيكية الجزيئية لا تزال غير مفهومة جيدا. إن نتروزيليشن لل (SNO) في علم الاعصاب يستهدف البروتين المسؤول عن الطفرات الجينية لدى المرضى، وقد تؤدي إلى اختلالات متشابكة تعزى الى مسببات التوحد ومرض الزهايمر، بينما فسفرة بروتينات tau و amyloid-β protein precursor (APP). لها دورا هاما في اضطرابات النمو العصبي.

التهاب العصب له دورفي تضخم الدماغ في السنوات الأولى من حياة الإنسان حيث يتوسع تحديدا في القشرة الأمامية. المادة البيضاء في الدماغ والمخيخ تمثل أكثر من نصف الدماغ البشري، وتتناقص مع تقدم العمر، وتتحدد بإفراز المايلين والسيتوكين وعامل نمو الورم وافراز إنزيم الكاينيز. بينما يتم تحديد المادة الرمادية من خلال سُمك ومساحة القشرة والخلايا الجذعية العصبية ومنطقة البطين. التواصل الاجتماعي المحدود والسلوك غير السوي نتيجة زيادة الالتهابات العصبية من خلال التأثير على mRNAالمرتبط التوحد ومرض الزهايمر. وعلى الرغم من الجهود العالمية لتحديد العلاجات ضد تطورالمرض، إلا أن العلاجات القادرة على تخفيف بعض أعراض التوحد ومرض الزهايمر هي الوحيدة المتاحة حاليًا، مع الاعتراف بالحاجة إلى استراتيجيات علاجية إضافية، من جهة أخرى فان منظمة الصحة العالمية جعلت هذا المرض من أولويات الصحة العامة. الحقبة الزمنية المحددة لهذا المقال استمرت من سنة 2013 إلى 2023.

الكلمات المفتاحية: متلازمة التوحد، مرض الزهايمر، علم الاعصاب

Introduction

1. Definition

Autism and Alzheimer's disease are neurodevelopmental and neurodegenerative disorders, Mutations in sensitive genes can lead to memory deficits and alterations in perception., inflammations, and demyelination (1).

2. Neuron and glial cell

The central nervous system is divided into grey matter and white matter. Grey matter comprises neuron cell bodies and their dendrites, glial cells, and capillaries (2). globally is still difficult to estimate the reasons for epigenetic and genetic risk in patients only noticing that amyloid beta protein has a role in these abnormalities (3). Many researchers approved that strong nerve protection against multiple toxicities via neurotrophic and synapse synthesis by microtubule reactions (4). Microtubules are the important constituents of the neuronal cell structure, which play a major role in axonal transport and synaptic transmissions (5). Hyperphosphorylation of the tau protein may result in the self-assembly of tangles of paired helical filaments and straight filaments, which are involved in the pathogenesis of Alzheimer's disease (6).

Many studies showed a high percentage of autism in males compared to females; the prevalence ratio is often cited as about 4 males for every 1 female diagnosed (7). Although, in some cases, autism may occur without brain enlargement, only a few cases of enlarged brain were found in autistic patients related with none neurological disorders like arteriovenous malformations, intracranial mass, skull bone structure, hydrocephalus and subdural fluid groups (8).

However other research showed an increase in the overall volume of the brain occurs gradually with increased symptoms of autism (9, 10) The increased size of the brain usually appears in a period between 2 to 6 years after that an abnormal decrease in brain growth occur in the age of 12 to 16 years. This characterizes autistic patients by a defect of the frontal lobes which are social skills, temporal lobes (language and communications), amygdala of emotional control and occipital lobes of visual-spatial abilities, on the other hand, the incomplete neurogenesis in the prefrontal and all cerebral cortex may be the cause of autism before childbirth. The cortical thickness in patients is returned to the number of cells within the cortical columns while the surface area is returned to the number of cortical columns (11). In another study magnetic resonance imaging (MRI) of autistic children with large brain found an increase in the surface area but

not in the thickness of the cortex (2) also, there were abnormal B–cells and T-cells in peripheral blood. Astrocytes in the glial cells form the blood-brain barrier Microglia cells which is the primary resident, and oligodendrocytes form a myelin sheath wrapped around the axons, creating insulation for them. Autistic children show brain enlargement in the first year after birth due to enlargement of gray and white matter, abnormal inflammation, and increased myelination. Irregular behaviors and limited social communications in some autistic patients may result from the non-amyloidogenic pathway, which could lead to brain overgrowth through genetic pathways affecting mRNA translation (11).

3. The relation between Autism and Alzheimer's Disorders

Autism spectrum disorder and Alzheimer's disease are related to defective in certain areas of the brain (12), accompanied by increased concentrations of white matter (13) and myelin levels (14). There was approved by the study the increased level of myelin and white matter till the third decade, in addition to the increase of gliogenesis and myelination, by mutation of the phosphatase and tensin homolog PTEN gene in autistic persons with brain enlargement (15).

The corpus callosum is the largest interhemispheric white matter tract, consisting of more than 200 million commissural fibers connecting the two cerebral hemispheres (16). Neurological relations of language difficulties in preschool children were found in those patients (17). Hypermetabolism was pointed in parallel with the disruption of myelination in young adult persons (18). The increase in the primed microglia is related to chronic inflammations in the gray and white matter (19). There are increased inflammations in individuals by a defect of modulator of immune functions rather than active inflammatory responses (20).

Along the progression, myelinating oligodendrocytes in the adults are manufactured in the ventricular regions by oligodendrocyte progenitor cells (OPC), then transferred and proliferate and extended to the whole area of the nervous cells, which is confirmed by a reduced ability to regenerate neural stem cells in brain tissue. (21, 22).

Chromosome changes, usually related to autism spectrum disorders (23), and mutation of activity-dependent neuroprotective proteins (ADNP) gene explain the causes of seventeen percent of individuals with autism spectrum disorders related to mental disabilities, characteristic facial signs and failure of multiple organ functions (24, 25). dependent neuroprotective proteins is one of the most dominant mutations in heterogeneous genes within Alzheimer's disease (26- 28).

The role of activity-dependent neuroprotective protein gene is very important for neuronal cell differentiations and maturations (29), it is necessary for brain functions and the regular of hundreds of major genes in vivo (30, 31) So, ADNP of mRNA is implicated not only in autistic patients (32, 33) but also in the Alzheimer disease (34) schizophrenia (35) and Parkinson disease (36). other studies showed there was a correlation between activity-dependent neuroprotective protein in old men with brain degeneration, neurodegeneration, regulated apolipoprotein E, amyloid plaque, aging, and cognitive deficit. There are eight amino acid peptides (Asn-Ala-Pro-Val-Ser-Ile-Pro-Gln) that have been shown to potent neuroprotection of the brain against decreased levels of activity-dependent neuroprotective protein (37).

The two hallmark signs that characterize patients with Alzheimer's disease are neurofibrillary tangles, representing aggregates of twisted strands of hyperphosphorylated tau protein, and amyloid plaques, consisting of accumulations of amyloid-β (Aβ) peptides. Alzheimer's

disease is a neurodegenerative disease that comprises over eighty percent of all dementias and about ten percent of the population aged sixty-five and older. Characteristic signs that severely defect the ability to perform everyday activity at the end stage of the disease include the development of loss of memory, decline of cognitive skills, and deterioration of speech (38).

The proteolytic cleavage of mature amyloid-β (Aβ) peptide protein precursors via β- and γ-secretase by the amyloidogenic mechanism generates neurotoxic amyloid-β peptides consisting of forty and forty-two amino acids. These peptides accumulate to form the main constituents of neurotic plaques, leading to brain atrophy in individuals with Alzheimer's disease. (39). Also none amyloidogenic development of amyloid-β protein precursor APP by α- secretase, produces an α-form of amyloid-β protein precursor APP that is usually distinguished as neurotrophic (40). These pathways of amyloid-β protein precursor have made a key for neurodegenerative diseases like Alzheimer's disease (41).

Impact of antenatal depressive and anxiety symptoms on adverse birth outcomes, Nutrition is an important prognostic factor for mental health including social well-being, (42). the biologically active variant of vitamin B6 serves as a co-enzyme for regular neuronal processes (43). although global studies to identify treatment against this disease, only treatments able to alleviate some signs of patients with Alzheimer's disease are currently available, meaning the need for more therapeutic steps against the development of Alzheimer's disease, therefore, the World Health Organization has made this disease a public health priority (44).

In addition to age-associated with neurodegenerative disease, tau, and the amyloid-β protein precursor APP it has been shown that the level of amyloid-β protein precursor is increased in acute cases but not in mild or moderate cases It was explained that promotion of the neurotrophic none amyloidogenic pathway lead to amyloid-β protein precursor accumulation in autistic individuals which lead to early megalocephaly and cause interneuronal misconnection that potential underlying several autism-related signs (12).

Another relation between both Alzheimer's and autistic patients has been shown in the role of S-nitrosylation (SNO) protein which is involved in multiple physiological and neuropathological pathways, in the mammalian targets of rapamycin complex 1 (mTORC1) signaling pathway as one of the shared molecular pathways which SNO-dependent mTOR activation in the Alzheimer and autistic mouse model as showed in Figure. Activation of the mammalian target of rapamycin (mTOR) in the cortex was approved by western blots and established increased phosphorylation of RPS6, a major substrate of mTORC1, which approved hyperactivation of mTORC1. Also, it was shown, that an aberrant S-nitrosylation (SNO) signaling can lead to synaptic defects that contribute to the pathogenesis of Autism and Alzheimer's disease, therefore, indicating the possibility of alteration of the mammalian target of rapamycin(mTOR) signaling as a result of aberrant S-nitrosylation (SNO) of specific protein throughout neurodevelopment and neurodegeneration (12).

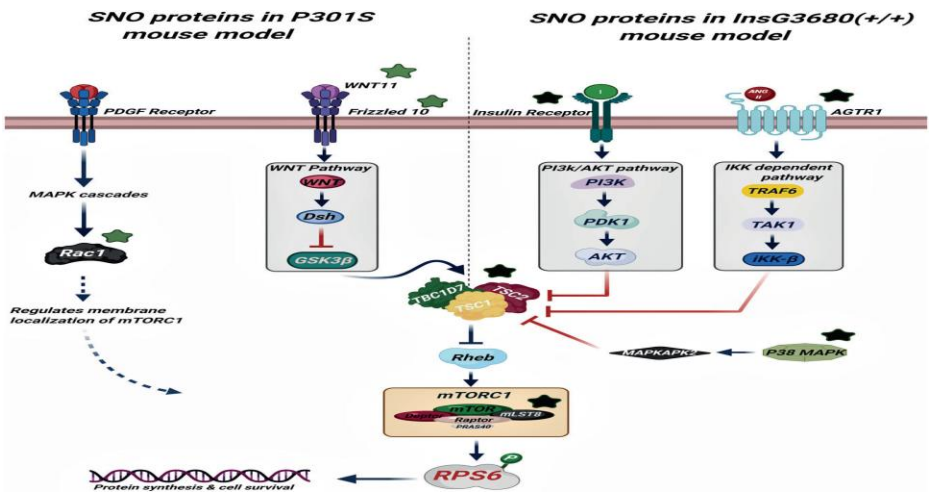

Figure: SNO-dependent mTOR activation in the mouse model (12)

-Green stars are SNO proteins in ASD.

-Black stars are SNO proteins in ASD

4. Conclusion

S-nitrosylation (SNO) protein-dependent mTOR activation led to synaptic defects which contribute to the pathogenesis in Alzheimer's and autistic patients. tau and the amyloid-β protein precursor APP playing a role in neurodevelopmental defects in autistic patients. The two hallmark signs that recognize patients with Alzheimer's disease are neurofibrillary tangle representing an aggregate of twisted strands of hyperphosphorylated tau protein, and amyloid plaque specially consisting of accumulations of amyloid-β (Aβ) peptides.

Mutation of activity-dependent neuroprotective proteins (ADNP) gene explains the causes of seventeen percent of individuals with autism spectrum disorders. The increase of gliogenesis and myelination, by mutation of the phosphatase and tensin homolog PTEN gene found in autistic persons with brain enlargement. Finally, the increase of gray and white matter in adults and the elderly, with overgrowth brain progression to develop metabolic defective, neuritis, and activated astrocytes.

5. Recommendation

The recommendation is to conduct further studies of dementia prevalence in patients with Alzheimer's disease, and also more studies for screening children at ages 18 and 24 months, along with regular developmental surveillance.

Acknowledgments

Our thanks to Mustansiriyah University for our support in completing this review.

References

1- Khan S. Khan S. Narendra A. Mushtaq G. Zahran SA. Khan S. Kamal MA. Alzheimer's Disease and Autistic Spectrum Disorder: Is there any Association? CNS Neurol Disord Drug Targets. 2016;15(4):390-402. doi: 10.2174/1871527315666160321104303.

2- Ohta H. Nordahl C. Iosif A. Lee A. Rogers S, Amaral DG. Increased surface area, but not cortical thickness, in a subset of young boys with autism spectrum disorder. Autism Res. 2016; 9(2):232–48. DOI: 10.1002/aur.1520

3- Jiaxin H. Wenchi S. Shuangshuang Y. Jiarui W. Yunpeng H. Aggregation,

Transmission, and Toxicity of the Microtubule-Associated Protein Tau: A Complex Comprehension *Int. J. Mol. Sci.* 2023; *24*(19): 15023. doi.org/10.3390/ijms241915023

4- Oz S. Kapitansky O. Ivashco-Pachima Y. Malishkevich A. Giladi E. Skalka N. et al. The NAP motif of activity-dependent neuroprotective protein (ADNP) regulates dendritic spines through microtubule end binding proteins. Mol Psychiatry.2014;19(10):1115–24. DOI:10.1038/mp.2014.97

5- Ivashko-Pachima Y. Maor-Nof M. Gozes I. NAP (davunetide) preferential interaction with dynamic 3-repeat tau explains differential protection in selected tauopathies. PloS ONE. 2019;14(3):1-20. DOI: 10.1371/journal.pone.0213666

6- Gozes I. Ivashko-Pachima Y. Sayas C. ADNP, a microtubule interacting protein, provides neuroprotection through end binding proteins and tau: an amplifier effect. Front Mol Neurosci. 2018;11(151):1-4. doi: 10.3389/fnmol.2018.00151

7- Katherine N. Amy B. Catherine A. Jenny L. Kristelle H. No sex differences in core autism features, social functioning, cognition or co-occurring conditions in young autistic children: A systematic review and meta-analysis. Research in Autism Spectrum Disorders. 2023; 107:1-17. doi.org/10.1016/j.rasd.2023.102207

8- Pavone P. Pratico A. Rizzo R. Corsello G. Ruggieri M. Parano E. et al. A clinical review on megalencephaly: a large brain as a possible sign of cerebral impairment. Medicine. 2017; 96(26) :e6814. DOI: 10.1097/MD.0000000000006814

9- Vicki B. Christopher F. Neurobiological Concomitants of Autism as Informers of Clinical Practice: a Status Review. Advances in Neurodevelopmental Disorders.2023; 2023:1-13. doi.org/10.1007/s41252-023-00344-3

10- Denis P. The dopamine hypothesis of autism spectrum disorder: A comprehensive analysis of the evidence. 2023 ;173: 1-42. doi.org/10.1016/bs.irn.2023.08.009

11- Deborah K. Sokol 1. Bryan M. Cara J. et al. Novel Contribution of Secreted Amyloid-b Precursor Protein to White Matter Brain Enlargement in Autism Spectrum Disorder. Front. Psychiatry.2019;10(165):1-16. DOI: 10.3389/fpsyt.2019.00165

12- Shira M. Maryam K. Felix L. Huda S. et al. Proteomics of autism and Alzheimer's mouse models reveal common alterations in mTOR signaling pathway. Translational Psychiatry.2021;(11) 480:1-10. DOI:10.1038/s41398-021-01578-2

13- Ting M. Natalie J. Dorothea L. Flavio D. et al. Autism Is Associated With Interindividual Variations of Gray and White Matter Morphology. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2023; 8 (11) : 1084-1093. doi: 10.1016/j.bpsc.2022.08.011. Epub 2022 Sep 6.

14- Joseph F. Colin M. Debamitra D. et al. Promyelinating drugs promote functional recovery in an autism spectrum disorder mouse model of Pitt–Hopkins syndrome. *Brain*.2023;146(8): 3331–3346. doi: 10.1093/brain/awad057.

15- Frazier T. Embacher R. Tilot A. Koenig K. Mester J. Eng C. Molecular and phenotypic abnormalities in individuals with germline heterozygous PTEN mutations and autism. Mol Psychiatry. 2015; 20(9):1132– 8. doi: 10.1038/mp.2014.125. Epub 2014 Oct 7.

16- Sophie M. Patric K. Kathrin K. Larger corpus callosum volume is favorable for theory of mind development in healthy children. *Cerebral Cortex*.2023; 33(23)

:11197–11205. doi.org/10.1093/cercor/bhad353

17- Mikhail K. Ariane S. Laurent M. Language acquisition can be truly atypical in autism: Beyond joint attention.. Neuroscience & Biobehavioral Reviews.2023; 153(1):105384. DOI: 10.1016/j.neubiorev.2023.105384.

18- Mitelman S. Buchsbaum M. Young D. Haznedar M. Hollander E. Shihabuddin L. et al. Increased white matter metabolic rates in autism spectrum disorder and schizophrenia. Brain Imaging Behav. 2017; 12(5):1290– 305. DOI: 10.1007/s11682-017-9785-9

19- Yue X. Yue X. Yingbo L. Microglia and astrocytes underlie neuroinflammation and synaptic susceptibility in autism spectrum disorder. Front. Neurosci.2023 ;17 :1-10. DOI : 10.3389/fnins.2023.1125428

20- Ramu S. Anglina K. Haripriya K. Autism Spectrum Disorders: A Recent Update on Targeting Inflammatory Pathways with Natural Anti-Inflammatory Agents. *Biomedicines.* 2023; *11*(1): 115. DOI: 10.3390/biomedicines11010115

21- Horgusluoglu E. Nudelman K. Nho K. Saykin A. Adult neurogenesis and neurodegenerative diseases: a systems biology perspective. Am J Med Genet Part B, Neuropsychiatr Genet: Off Publ Int Soc Psychiatr Genet. 2017 ;174(1):93–112. DOI : 10.1002/ajmg.b.32429

22- Moreno-Jimenez E. Flor-Garcia M. Terreros-Roncal J. Rabano A, Cafini F. Pallas- Bazarra N. et al. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med. 2019; 25(4):554–60. DOI:10.1038/s41591-019-0375-9

23- Éva K. Diversity and Classification of Genetic Variations in Autism Spectrum Disorder. *Int. J. Mol. Sci.* 2023; *24*(23): 16768. doi: 10.3390/ijms242316768

24- Helsmoortel C. Vulto-van Silfhout A. Coe B. Vandeweyer G. Rooms L. van den Ende J. et al. A SWI/SNF-related autism syndrome caused by de novo mutations in ADNP. Nat Genet. 2014;46(4):380–4. doi: 10.1038/ng.2899. Epub 2014 Feb 16.

25- Van Dijck A. Vulto-van Silfhout A. Cappuyns E. van der Werf I.Mancini G. Tzschach A. et al. Clinical presentation of a complex neurodevelopmental disorder caused by mutations in ADNP. Biol Psychiatry. 2019;85(4):287–97. doi: 10.1016/j.biopsych.2018.02.1173.

26- Vijay G. Afif Ben-M. Bonsu K. Dinesh V. Zainab J. Ahmad K. Identification of two novel autism genes, TRPC4 and SCFD2, in Qatar simplex families through exome sequencing. Front Psychiatry. 2023; 14: 1251884. doi.org/10.3389/fpsyt.2023.1251884.

27- Soudeh G. et al. A Review on the Role of Genetic Mutations in the autism spectrum disorder. Molecular Neurobiology.2023; 60(9):1-17. DOI:10.1007/s12035-023-03405-9

28- Stessman H. Xiong B. Coe B. Wang T. Hoekzema K. Fenckova M. et al. Targeted sequencing identifies 91 neurodevelopmental-disorder risk genes with autism and developmental-disability biases. Nat Genet. 2017;49(4):515–26. doi: 10.1038/ng.3792. Epub 2017 Feb 13.

29- Claudio P. Kirsten E. Kevin D. et al Chromatin remodeler Activity-Dependent Neuroprotective Protein (ADNP) contributes to syndromic autism. Clin Epigenetics. 2023; 15: 45. doi: 10.1186/s13148-023-01450-8.

30- Amram N. Hacohen-Kleiman G. Sragovich S. Malishkevich A. Katz J. Touloumi O. et al. Sexual divergence in

microtubule function: the novel intranasal microtubule targeting SKIP normalizes axonal transport and enhances memory. Mol Psychiatry. 2016;21(10):1467–76. doi: 10.1038/mp.2015.208. Epub 2016 Jan 19.

31- Gozes I. van Dijck A. Hacohen-Kleiman G. Grigg I. Karmon G, Giladi E. et al. Premature primary tooth eruption in cognitive/motor-delayed ADNP-mutated children. Transl Psychiatry. 2017;7(2):1-9. DOI:10.1038/tp.2017.27

32- Gozes I. Helsmoortel C. Vandeweyer G. Van der Aa N. Kooy F. Sermone S. The compassionate side of neuroscience: Tony Sermone's undiagnosed genetic journey- ADNP mutation. J Mol Neurosci : MN. 2015;56(4):751–7. doi: 10.1007/s12031-015-0586-6.

33- Ling W. Binquan W. Chunyan W. Autism Spectrum Disorder: Neurodevelopmental Risk Factors, Biological Mechanism, and Precision Therapy. *Int. J. Mol. Sci.*2023; *24*(3): 1819. doi: 10.3390/ijms24031819.

34- Walter J. MicroRNA (miRNA) Complexity in Alzheimer's Disease (AD). Biology (Basel). 2023;12(6): 788. doi: 10.3390/biology12060788

35- Fumito S. Kenji K. Seico B. et al. Associations between prefrontal PI (16:0/20:4) lipid, TNC mRNA, and APOA1 protein in schizophrenia: A trans-omics analysis in post-mortem brain. frontiers in psychiatry.2023;14:1-9. doi.org/10.3389/fpsyt.2023.1145437.

36- Ching-H. Kun-L. Cheng-Y. Chien-W. The Neuroprotective Effect of Isotetrandrine on Parkinson's Disease via Anti-Inflammation and Antiapoptosis. In Vitro and in vivo. Parkinson's Disease. 2023:1-12. doi: 10.1155/2023/8444153. eCollection 2023.

37- Ivashko-Pachima Y. Sayas C. Malishkevich A. Gozes I. ADNP/NAP dramatically increase microtubule end-binding protein–tau interaction: a novel avenue for protection against tauopathy. Mol psychiatry. 2017; 22(9):1335–44. DOI:10.1038/mp.2016.255

38- Association, A. S. 2020 Alzheimer's disease facts and figures. Alzheimers Dement. 2020; 16:391–460. doi: 10.1002/alz.12068.

39- Thinakaran G. Koo EH. Amyloid precursor protein trafficking, processing, and function. J Biol Chem. 2008;283: 29615–9. doi: 10.1074/jbc. R800019200.

40- Turner PR. O'Connor K. Tate WP. Abraham WC. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. Prog Neurobiol. 2003; 70:1–32. DOI: 10.1016/s0301-0082(03)00089-3

41- Bandyopadhyay S. Goldstein LE. Lahiri DK. Rogers JT. Role of the APP non-amyloidogenic signaling pathway and targeting alpha-secretase as an alternative drug target for treatment of Alzheimer's disease. Curr Med Chem. 2007; 14:2848–64. DOI: 10.2174/092986707782360060

42- Moatamad H. Manal K. Hayder S. Impact of Pyridoxine Supplement on Oxidative Stress in Type 2 Diabetic Patients,2023; AJPS;24(1):89-104. DOI:10.32947/ajps. v24i1.1030.

43- Ola A. Mohammed M. Hind A. Impact of antenatal depressive and anxiety symptoms on adverse birth outcomes in Baghdad, Iraq: a prospective cohort study. AJPS ;2023; 23(1):68-80. DOI: https://doi.org/10.32947/ajps.v23i1.988

44- Lane CA, Hardy J, Schott JM. Alzheimer's disease. Eur J Neurol. 2018 ;25(1) :59–70. doi.org/10.1111/ene.13439