The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH Open Access

Genetic, clinical, and biochemical aspects of patients with Alzheimer disease

Hamdy Nageeb El-Tallawy[1,3], Heba Mohamed Saadeldin[1,2], Azza Mohamed Ezzeldin[1,3], Amal Mohamed Tohamy[1,3], Sara Eltellawy[4], Ali Mabrouk Bathalath[1] and Mohamed Mostafa Shehab[1,3*]

Abstract

Background: The most common form of dementia is Alzheimer's disease (AD). The clinical manifestations of AD are loss of memory that is progressive and deterioration in cognitive function. The objective of this study is to find patterns of AD among patients regarding clinical aspects, psychological aspects, and laboratory aspects, as well as to determine the role of some genes (APOE1, APOE2, and TMEM106B) in the pathogenesis of AD. In this case–control study, 40 patients with AD were recruited from the inpatient neurology departments and outpatient neurology clinics of the university hospitals in the period of January 1 to December 31, 2017. Furthermore, 40 cross-matched control patients underwent a complete history taking, neurological examination, brain MRI or CT, psychometric tests, thyroid function, and lipid profile measurements. Extracted DNA was quantified using a nanodrop analyzer (ND-1OOO) spectrophotometer for TMEM106B (rs1990622), APOE2 (rs429358), and APOE1 (rs7412).

Results: All subtypes of lipid profiles were significantly higher in patients with AD than the controls. There was a significant difference between the two groups regarding TMEM106B. There was an insignificant difference regarding thyroid hormones T3, T4, and TSH between patients and controls. There was no significant difference between AD patients and the control group regarding APOE-1 and APOE-2. Patients were worse than controls in tests of cognition, such as The Cognitive Abilities Screening Instrument (CASI) and auditory number and letter span test. In addition, AD patients had more depression than controls.

Conclusion: There may be a significant role of a high lipid profile and TMEM106B expression in the pathogenesis of AD.

Keywords: Alzheimer's disease, Cognition, And Genetic

Background

Alzheimer's disease (AD) is a neurodegenerative disorder with progressive deterioration in cognition and behavior [1, 2].

Common genetic variants explain a large proportion of the heritability of sporadic AD dementia [3]. Pathogenesis of AD result from multiple steps that lead to deposition of amyloid plaques and neurodegeneration in important brain areas responsible for memory and cognition. AD is a neurodegenerative disease of multifactorial origin. Both neurodegeneration and chronic inflammation occur in AD [4]. Multiple genes mutations and polymorphisms (APP, PSEN1, PSEN2, and ApoE) located on 4 different chromosomes (1, 14, 19, and 21) are directly associated with AD [5]. The links between genetic and environmental factors were documented by mechanisms of epigenetics.

Human apolipoprotein E (ApoE) is a 299-amino-acid protein. Its molecular mass is 36 kDa. Astrocytes, microglia, and some neurons synthesize and secrete ApoE. The main role of ApoE is repair of brain injury via lipids redistribution among neurons, neurite outgrowth modulation and integrity of blood vessels. Human ApoE isoforms have been shown to confer differential susceptibility to

*Correspondence: Mohamed.mustafa@aun.edu.eg
[1] Present Address: Assiut University, Asyut, Egypt
Full list of author information is available at the end of the article

AD [6]. The ApoE ε4 allele is considered a risk factor in sporadic AD, while the ApoE ε2 allele is likely to be protective [7, 8].

There is still a debate about the molecular mechanism of ApoE contribution to AD pathophysiology [9]. ApoE2 is relatively rare, its incidence is only about 5%. ApoE2 may have a positive role in maintaining the brain structural integrity. This may lead to its cognition-favoring properties and increased resistance to development of AD pathology in early stages [6]. On the other hand, APOE-ε4 has well-known effects, such as compromised integrity of blood–brain barrier and increased accumulation of amyloid-β [10]. Strong association between ApoE4 and cerebrovascular deficits in the form of cerebral blood flow decline with aging [11] and a significant increase in the risk of ischemic stroke [12].

TMEM106B is a 274-residue lysosomal protein. It has a cytoplasmic domain that functions in the endosomal/autophagy pathway through dynamically and transiently interacting with different types of proteins. However, its underlying structural basis still remains unknown [13]. The risk of TMEM106B variants were associated with inflammation, loss of neurons, and deficits in cognition among older people (> 65 years), even without any brain disease. Moreover, their affection is particularly selective for the frontal cortex [14]. Satoh and colleagues [15] indicated that, in AD brains, there is reduction in TMEM106B mRNA and protein levels, but the exact TMEM106B level of expression in AD brains is still unknown.

The objective of this study is to determine the patterns of AD regarding the clinical presentation, the role of different genes (APOE1, APOE2, and TMEM106B) in the pathogenesis of AD dementia, and biochemical changes, such as lipid profile and thyroid function in AD.

Methods

In this case–control study, 40 patients with AD according to DSM-V were recruited from the inpatient neurology departments and outpatient neurology clinics of the university hospitals from January 1 to December 31, 2017. The control group consisted of 40 age and sex cross-matched healthy individuals with no past medical history of vascular dementia or other causes of dementia. Complete history taking, neurological examination (including cranial nerves, motor system, sensory system, and co-ordination), and brain MRI or CT were done for each patient. Cognitive and psychological assessment of the patients was done using the mini-mental state examination (MMSE) (includes tests of orientation, attention, memory, language and visual–spatial skills), auditory number and letter span test, sleep disturbances score (to assess sleep), geriatric depression scale (GDS) (to assess depression), Hachinsky ischemic score (HIS) (to show vascular demetia), and Cognitive Abilities Screening Instrument (CASI) (has a score range of 0 to 100 and provides quantitative assessment on attention, concentration, orientation, short-term memory, long-term memory, language abilities, visual construction, list-generating fluency, abstraction, and judgment). Serum thyroid function and lipid profiles were measured by an ELISA detection technique to study the relation between raised lipid profile and impairment in thyroid function and development of ALD.

Genomic DNA was extracted from venous blood using a pure linked kit and the procedure recommended by the manufacturer (Vivantis). Extracted DNA was quantified using a nanodrop analyzer (ND-1OOO) spectrophotometer (Nanodrop Technologies Inc., Ortenberg, Germany) for TMEM106B (rs1990622), APOE2 (rs429358), and APOE1 (rs 7412). Polymorphisms were analyzed by an Taqman allelic discrimination assay according to manufacturer's protocol (Applied Biosystems, Stepone Plus). Genotyping was performed using real-time PCR with a thermal profile of 60 ℃ for 30 s, 95 °C for 10 min, 95 °C for 15 s, and 60 °C for 90 s.

This study had been reviewed and approved by "The Committee of Medical Ethics" of the Faculty of Medicine, Assiut University on 15/1l2017 with IRB no: 17200505 and all the patients or their first degree relatives had assigned a written consent to participate in the study.

Continuous data are expressed as the mean ± standard deviation, and categorical data are expressed as numbers (percentages). Comparisons of differences in the categorical data were performed using the chi-squared test while the comparisons of continuous variables were analyzed by independent sample *T* test, and a binary logistic regression model was performed to detect the predictors of AD. All tests were two-tailed, and a *p* value of less than 0.05 ($p < 0.05$) was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20 (SPSS Inc., Chicago, IL, USA, 2011).

Results

The demographic data of the studied groups are shown in Table 1 and Fig. 1. Table 2 shows the characteristics of the AD patients regarding residence, occupation, type of previous work, and education level. Table 3 shows their clinical manifestations.

In neuro-imaging, brain atrophy was found in 28 patients (70%), and brain atrophy with infarction was found in 6 patients (15%). The MMSE indicated that 35%, 47.5%, and 17.5% of the patients had mild, moderate, and severe conditions, respectively. Table 4 shows the results of the CASI for patients and controls. The test showed

Table 1 Demographic data of studied groups

	Alzheimer's disease ($n=40$)	Control group ($n=40$)	*P* value
Age group (years)			0.08
51–60	7 (17.5%)	7 (17.5%)	
61–70	18 (45%)	21 (52.5%)	
71–80	10 (25%)	12 (30%)	
≥ 81	5 (12.5%)	0	
Sex			0.58
Male	23 (57.5%)	23 (57.5%)	
Female	17 (42.5%)	17 (42.5%)	

Data expressed as frequency (percentage), *P* value was significant if < 0.05 (*n*: number)

significantly worse performance among patients than controls in all items except reading, comprehension, and writing.

Regarding the auditory number and letter span test, all AD patients had mild conditions in terms of the memory of numbers and letters with the exception of three patients, who had moderate letter memory and two patients who had moderate number memory impairment. Figure 2 shows the sleep disturbance among AD patients based on the total sleep disturbance score. The HIS showed that none of the patients had multi-infarct dementia. Figure 3 shows the results of Geriatric Depression Scale among the AD patients, and Table 5 shows the results of thyroid hormones (T3, T4, and TSH) and different subtypes of lipids in both the patient and control groups.

Regarding the genetic analysis, all subjects in both groups had homogenous (TT, mutant) APOE-2. The majority of the AD group (90%) and control group (85%) had homogenous (CC, wild) APOE-1, while 4 patients (10%) and 6 patients (15%) in the AD group and control group had heterogeneous (CT, carrier) APOE-1, respectively. This means that there was no significant difference between the AD patients and control group regarding both APOE-1 and APOE-2 (Table 6 and Fig. 4).

The majority of the AD group (80%) and control group (85%) had homogenous (TT, wild) TMEM106B. Three patients (7.5%) with AD and 6 (15%) of the control group had homogenous (CC, mutant) TMEM106B. Only five AD patients had heterogeneous (CT, carrier) TMEM106B, which means that there is a significant difference between the two groups regarding TMEM106B, as shown in Table 6 and Fig. 4.

A logistic regression was performed to study different lipid profile parameters as predictors for AD. The logistic regression model was statistically significant, this model explained 70.3% (Nagelkerke R Square = 0.703) of the variance in AD. Increasing triglycerides was associated with an increased the likelihood of AD (p value = 0.026, Odds ratio = 1.102)), However, increasing the VLDL was associated with a reduction in likelihood of AD (p value = 0.029, Odds ratio = 0.694) (Table 7).

Discussion

The mean of ages of AD patients in this study was 69.37 ± 8.20 years, and the largest proportion (45%) was between the ages of 60 and 70 years, followed by the ages of 70–80 years (25%). The distribution of ages in the group is consistent with many studies. El-Tallawy and colleagues [16] found that there is increase in the risk of AD development with increasing age. The occurrence

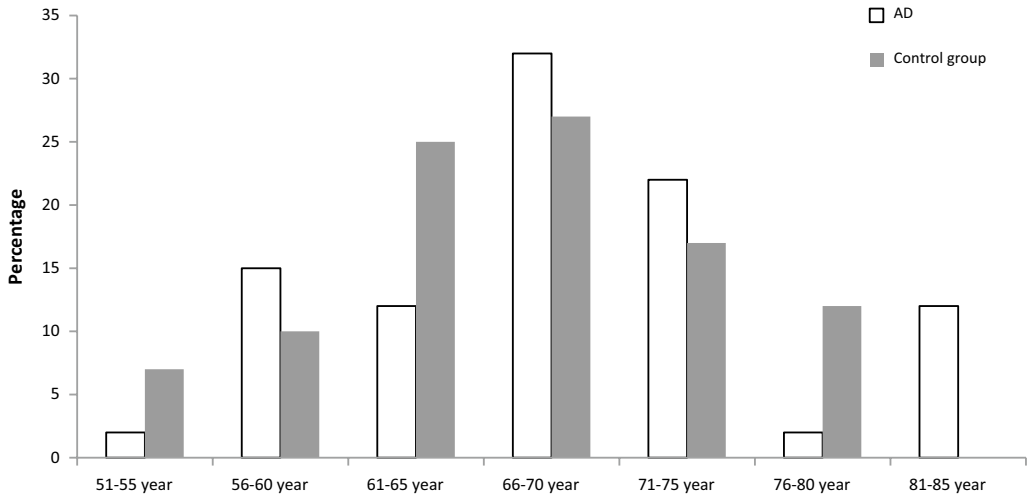

Fig. 1 Age of patients and control group

Table 2 Characteristics of studied patients with Alzheimer's disease

	n **= 40**
Residence	
Rural	34 (85%)
Urban	6 (15%)
Occupation	
Working	20 (50%)
Not working	20 (50%)
Type of work	
Mental work	7 (17.5%)
Hand work	33 (82.5%)
Education level	
Illiterate	25 (62.5%)
Low education	8 (20%)
Middle education	5 (12.5%)
High education	2 (5%)
Comorbidities	
Diabetes mellitus	7 (17.5%)
Hypertension	14 (35%)
Nothing	19 (47.5%)
Smoking	15 (37.5%)
Positive family history	6 (15%)
First-degree relative	5 (12.5%)
Second-degree relative	1 (2.5%)

Data expressed as frequency (percentage), mean (SD)

(*n*: number)

Table 3 Clinical manifestations of patients with AD

Clinical manifestation	***n*** **= 40**
Emotional changes	28 (70%)
Behavioral changes	
Normal	15 (37.5%)
Apathy	18 (45%)
Agitation	1 (2.5%)
Uncooperative	6 (15%)
Frontal release signs	15 (37.5%)
Sleep disturbance	12 (30%)
Visuospatial deficits	10 (25%)
Psychosis	
Visual hallucination	6 (15%)
Auditory hallucination	1 (2.5%)
Delusion	1 (2.5%)
Speech affection	7 (17.5%)
Impaired gait	5 (12.5%)
Urinary incontinence	2 (5%)
Pyramidal signs	3 (7.5%)

Data expressed as frequency (percentage), mean (SD)

(*n*: number)

was 0.34% for people aged 60–70 years, 2.9% for those aged 70–80 years and 9.74% for the people aged 80 years and more [16]. According to the *Alzheimer's Association,* AD occurs in 3% of people aging 65–74 years, 17% of those aging 75–84 years, and 32% in people ≥ 85 years [17, 18].

In this study, the majority of patients were illiterate (62.5%), 20% of them had low education, and 12.5% had a middle level of education. High education was recorded in only 5% of the patients. This is in agreement with many previous studies, which showed that the prevalence of AD is more in illiterate people than educated ones [19–22]. However, this is not in agreement with the results of Ghuloum and colleagues [23], who reported that there in no significant association between education level and dementia in a Qatari population. This disagreement could be explained by differences in the sample number or type of patients.

In this study, behavioral changes and emotional changes were the most frequent symptoms presented in AD patients (75% and 70% of patients, respectively), followed by frontal release signs (37.5%), sleep disturbances (30%), and visuospatial deficits (25%). In a previous study, the second most common symptom of AD was depression preceded by apathy [24]. This is consistent with the findings of this study, as most of the patients (75%) had depression with different degrees of severity (52.5% had severe depression, while 22.5% had mild depression).

Three main hypotheses may explain the relationship between depression and dementia: depression may be a risk factor or a prodrome of dementia or depression and dementia may be two independent pathologies [25]. Singh-Manoux and colleagues [26] showed that depression may be a consequence of the dementia preclinical phase. He showed that the symptoms of depression appeared in the decade preceding the dementia diagnosis without the depressive characteristics (chronic, recurrent, etc.) [26]. This hypothesis agrees with other investigators who showed that temporal proximity between the onset of depression and dementia is needed if depression is a prodrome of AD, instead of depressive symptoms remitting and reappearing later. Based on this, late depression has to be a prodrome of AD [27].

Tanaka and colleagues [28] showed that depression and anxiety are not just comorbidities or results of dementia, but they are also risk factors for dementia. Kim and his colleagues [29] used resting-state functional MRI (fMRI) to address neural systems that contribute to clinical symptoms and functional changes across late life depression and AD showing the link between the two disorders. In addition, significant association between depression and AD was found in a total of 6 meta-analyses that represented 28 studies [30].

Table 4 Results of CASI

CASI	Patient and control	*n*	Mean	STD	*T*	*P* value	CI 95%
Registration and repetition	Patient	40	2.100	1.5492	*−20.177*	0.000	{−6.0702−:−4.9798−}
	Control	40	7.625	0.7742			
Short-term memory	Patient	40	3.317	2.6817	*−7.914*	0.000	{−6.5144−:−3.8956−}
	Control	40	8.522	3.1800			
Long-term memory	Patient	40	4.278	2.8299	*−4.522*	0.000	{−3.7410−:−1.4540−}
	Control	40	6.875	2.2780			
Attention and concentration	Patient	40	3.175	2.3412	*−3.681*	0.000	{−2.6964−:−8036−}
	Control	40	4.925	1.8864			
Orientation to time	Patient	40	4.500	3.4269	*−4.072*	0.000	{−4.5785−:−1.1324}
	Control	40	7.575	3.3273			
Orientation to place	Patient	40	3.275	1.7095	*−6.146*	0.000	{−2.2176:−1.1324}
	Control	40	4.950	.2207			
Abstract thinking and judgment	Patient	40	2.725	2.5317	*−9.583*	0.000	{−6.7634:–4.4366}
	Control	40	8.325	2.6927			
Fluency 4-legged animals	Patient	40	2.200	1.6045	*−11.517*	0.000	{−6.0989:−4.3011}
	Control	40	7.400	2.3621			
Reading and comprehension	Patient	40	0.313	0.5024	0.413	0.681	{−0.1909:0.2909}
	Control	40	0.263	0.5772			
Writing	Patient	40	0.238	0.5429	−0.825	0.412	{−0.4694:0.1944}
	Control	40	0.375	0.9041			
Drawing	Patient	40	2.610	3.7471	*−4.988*	0.000	{−5.2678:−2.2622}
	Control	40	6.375	2.9586			
Naming	Patient	40	0.823	0.7277	*−18.926*	0.000	{−2.4066:−1.9484}
	Patient	40	0.823	0.7277			

n, number; STD, Slandered deviation; CI, Confidence Interval; CASI, Cognitive Abilities Screening Instruments

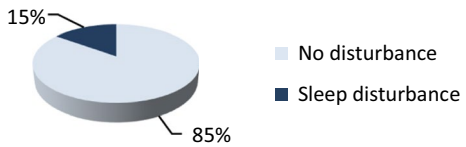

Fig. 2 Sleep disturbance in patients with AD

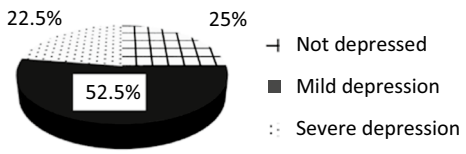

Fig. 3 Results of Geriatric depression scale in patients with AD

The total sleep disturbance score indicated that six patients (15%) had sleep disturbance. This is in agreement with Webster and colleagues [31], who made a meta-analysis on 55 studies including 22,780 participants. The pooled prevalence of clinically significant sleep disturbances was 20% (95% confidence interval (CI) 16% to 24%), and that of any symptom of sleep disturbance was 38% (95% CI 33% to 44%).

Both the patient and control groups had insignificant differences regarding thyroid hormones T3, T4, and TSH. This is inconsistent with many studies that have reported an association between AD and thyroid hormones. A total of 14 out of 23 studies showed a correlation between cognitive function and subclinical hypothyroidism (SCH) [32]. In the majority of these studies, the more high the thyroid function (indicated by low or low-normal TSH levels or high-normal FT4 levels) the more the risk of dementia and AD [33–35]. The controversial results between studies may be due differences in sample sizes.

The mean levels of cholesterol, triglyceride (TG), low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL), and the cholesterol/high-density lipoprotein (HDL) ratio were significantly higher among AD patients than the control group ($p < 0.001$). The mechanisms associating AD and lipid dysregulation is consisted of changes in intestinal microbiota, and the gut–brain axis, pathway of neuronal signaling, disruption of BBB, dysfunction of

Table 5 Laboratory data of both studied groups

	AD group ($n=40$)	Control group ($n=40$)	*P* value
Cholesterol (mg/dl)	203.45 ± 41.19	136.20 ± 27.82	< 0.001
Risk level			< 0.001
No	19 (47.5%)	40 (100%)	
Borderline	16 (40%)	0	
High risk	5 (12.5%)	0	
Triglycerides (mg/dl)	163.17 ± 80.15	101.25 ± 26.10	< 0.001
Risk level			< 0.001
No	23 (57.5%)	36 (90%)	
Borderline	4 (10%)	4 (10%)	
High risk	13 (32.5%)	0	
HDL (mg/dl)	47.77 ± 14.60	42.05 ± 4.74	0.02
Risk level			0.03
No	5 (12.5%)	0	
Borderline	8 (20%)	4 (10%)	
High risk	27 (67.5%)	36 (90%)	
Non-HDL (mg/dl)	151.57 ± 37.45	94.15 ± 27.45	< 0.001
Risk level			< 0.001
No	9 (22.5%)	35 (87.5%)	
Near optimal	19 (47.5%)	5 (12.5%)	
Borderline	7 (17.5%)	0	
High	3 (7.5%)	0	
Very high	2 (5%)	0	
LDL (mg/dl)	122.36 ± 33.83	73.76 ± 25.86	< 0.001
Risk level			< 0.001
No	9 (22.5%)	30 (75%)	
Near optimal	15 (37.5%)	10 (25%)	
Borderline	13 (32.5%)	0	
High	1 (2.5%)	0	
Very high	2 (5%)	0	
VLDL (mg/dl)	32.37 ± 16.02	22.94 ± 6.57	< 0.001
Risk level			< 0.001
No	26 (65%)	37 (92.5%)	
High risk	14 (35%)	3 (7.5%)	
Cholesterol/HDL ratio	4.49 ± 1.27	3.31 ± 0.77	< 0.001
Risk level			< 0.001
Low risk	19 (47.5%)	36 (90%)	
Average risk	18 (45%)	4 (10%)	
Moderate risk	3 (7.5%)	0	
Thyroid function			
T3	131.61 ± 52.58	129.47 ± 27.62	0.821
T4	9.35 ± 5.43	7.83 ± 1.54	0.09
TSH	2.67 ± 2.16	1.86 ± 0.81	0.06

n, number; HDL, high density lipoprotein; LDL, low density lipoprotein; VLDL, very low density lipoprotein

Table 6 Genetic results in both studied groups

	AD group ($n=40$)	Control group ($n=40$)	*P* value
APOE-1			0.36
Homogenous (CC, wild)	36 (90%)	34 (85%)	
Heterogeneous (CT, carrier)	4 (10%)	6 (15%)	
APOE-2			
Homogenous (TT, mutant)	40 (100%)	40 (100%)	
TMEM-106 B			0.04
Homogenous (CC, mutant)	3 (7.5%)	6 (15%)	
Homogenous (TT, wild)	32 (80%)	34 (85%)	
Heterogeneous (CT, carrier)	5 (12.5%)	0	

Data expressed as frequency (percentage)

mitochondria, oxidative stress, and inflammation leading to loss of synapses and impairment of memory [36].

No consistent conclusion is present regarding the relationship between cognitive function and lipid levels. Some showed a positive correlation between levels of cholesterol and risk of developing AD [37], whereas other studies have shown no correlation [38] or a negative association [39]. One study showed that TG levels in older people may increase the risk of AD [40], and another study showed that higher TG levels in elderly subjects were associated with better memory functioning [41]. Chen and colleagues [42] showed an independent association between increased LDL levels and AD, and Leritz and colleagues [43] showed an association between higher LDL levels and better memory performance.

These incongruous findings may be due to study design differences, age of participants (mid-life in comparison with later life), the time of measuring lipid in terms of age and onset of dementia, and the follow-up duration. The mean level of HDL was also significantly higher among AD patients than the control group. One Japanese study showed a negative association between high HDL-C and dementia [44], which disagrees with the results of this study. This disagreement may be explained by the difference in sample size.

In this study, there was no significant difference between AD patients and the control group regarding APOE-1, as shown in Table 6 and Fig. 4. Regarding APOE2 as well, there was no significant difference between groups (Table 6 and Fig. 4). Reiman and colleagues [45] studied more than 5000 clinically and neuropathologically characterized AD patients and controls. They found an association between the

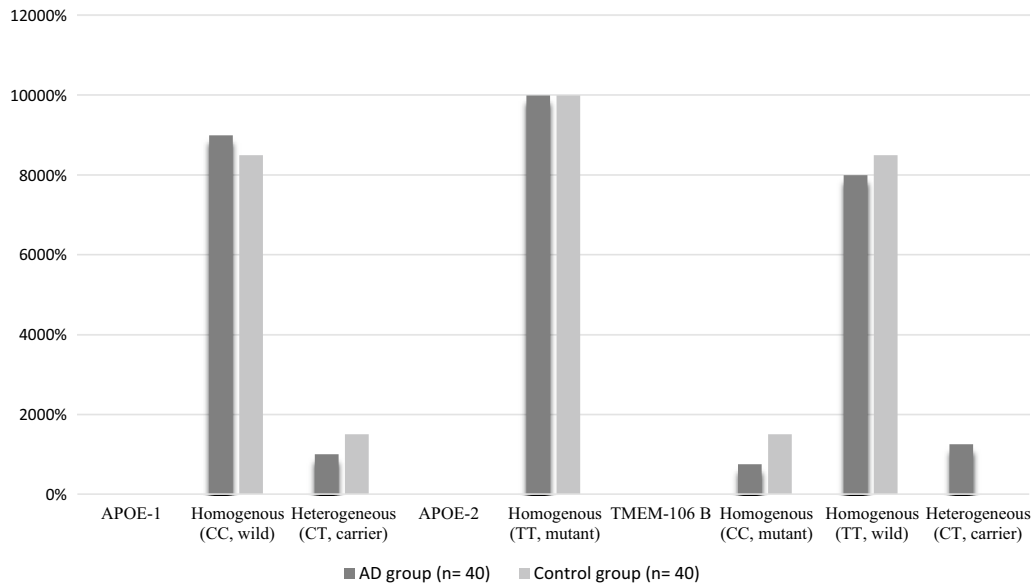

Fig. 4 Genetic studies in both studied groups

Table 7 Logistic regression analysis of predictors of AD among study participants

Variables:	*P* value	Adjusted OR	95% CI	
			Lower limit	Upper limit
Cholesterol (mg/dl)	0.292	0.912	0.767	1.083
Triglycerides (mg/dl)	0.026	1.102	1.012	1.200
HDLC (mg/dl)	0.173	1.224	0.915	1.637
NonHDLC (mg/dl)	0.118	1.057	0.986	1.133
LDLC (mg/dl)	0.328	1.078	0.927	1.254
VLDL (mg/dl)	0.029	0.694	0.500	0.963
CHOLHDLRatio	0.743	1.560	0.109	22.254

Nagelkerke *R* Square = 0.703

APOE2 allele and lower risk of AD. An association was found between APOE2/2 and low odds ratios of AD compared to APOE2/3 and 3/3, with an exceptionally low odds ratio compared to APOE4/4 [45].

Keeney and colleagues [46] showed that ApoE2 brains showed the most bioenergetically robust profiles. This may be a possible neuroprotective mechanism promoted by ApoE2 in comparison to ApoE3 and ApoE4 brains [46]. Wu and colleagues [9] showed that ApoE2 brains express higher levels of the beta subunit of V-type H+-ATPase (Atp6v) than both ApoE3 and ApoE4 brains. In this study, we found a significant difference between the two groups regarding TMEM106B, as the majority of the AD group (80%) had homogenous (TT, wild) TMEM106B, 7.5% had homogenous (CC, mutant) TMEM106B, and 12.5% had heterogeneous (CT, carrier) TMEM106B. Furthermore, 85% and 15% of the controls had homogenous (TT, wild) and homogenous (CC, mutant) TMEM106B, respectively, which may suggest a protective effect in AD patients.

These findings agree with those of Li and colleagues [47], who showed a protective variant in the TMEM106B gene that may play a neuroprotective role against aging, regardless of disease status. This could help to show the relationship between aging and survival of neurons with or without neurodegenerative disorders [47]. Satoh and colleagues [15] found that expression of TMEM106B levels is downregulated in AD, suggesting an important role of TMEM106B in AD pathological processes. In brains of AD patients, TMEM106B immunoreactivity was intense in surviving neurons, while TMEM106B was very deficient in neurofibrillary tangles, senile plaques, and the perivascular neuropil [15].

Simons and colleagues [48] demonstrated that, across multiple regions of the brain, the TMEM106B haplotypes had significant and partly conserved effects on the transcriptome. The function of TMEM106B has mostly been linked to functions of lysosome and trafficking and to myelination [48]. However, Ren and colleagues [49] suggested that TMEM106B role is broader in the response of CNS to insults that is either pathological or age-related.

Conclusions

AD has many clinical, psychological, biochemical, and genetic aspects. Changes in behavior and emotion are the main clinical manifestations in AD. Depression was common among the AD patients. Lipid profile changes were one of the important types of changes among AD patients, while changes in thyroid levels were insignificant, although there is a need for more assessment. There was no significant difference between AD patients and the control group regarding APOE-1, and APOE-2 while there was significant difference between the two groups regarding TMEM106B.

The weak point in our study is the small sample size as larger sample size was in need for strong financial support for genetic analysis and laboratory studies.

AD is a multifactorial disease which is one of the main obstacles in studying its risk factors. Interaction between genetic factors, environmental factors, and comorbidities has strong impact on incidence and prognosis of the disease. Moreover, multiple genes have a role in the pathogenesis of the disease which makes identification of one or more genes is very difficult. Further studies with good financial support need to be performed on a larger number of patients and more genes with to assess the genetic profile of AD.

Abbreviations

AD: Alzheimer's disease; APOE1: Apolipoprotein E1; APOE2: Apolipoprotein E2; Aβ: β-Amyloid; BBB: Blood–brain barrier; BIDS: Beck Inventory Depression Score; bvFTD: Behavioral variant fronto-temporal dementia; CASI: Cognitive abilities screening instrument; CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CI: Confidence interval; CNS: Central nervous system; DLB: Dementia with Lewy bodies; ELISA: Enzyme linked immunosorbent assay; EOAD: Early onset Alzheimer's disease; FTD: Fronto-temporal dementia; FTLD: Frontotemporal lobar degeneration; GDS: Geriatric depression scale; HDL: High-density lipoprotein; HIS: Hachinsky ischemic score; IBM-SPSS: Statistical Package for the Social Sciences; LDL: Low-density lipoprotein; LFA-3: Lymphocyte function-associated antigen-3; LOAD: Late-onset Alzheimer's disease; MMSE: Mini-mental state examination; MRI: Magnetic resonance imaging; T3: Triiodothyronine; T4: Thyroxine; TG: Triglyceride; TMEM106B: Transmembrane protein 106B; TSH: Thyroid stimulating hormone.

Acknowledgements

Not applicable. No acknowledgement to specific sources.

Authors' contributions

HNET: made significant contributions to the conception, design, and execution of the study and he had revised the manuscript critically for important intellectual content. HMSE: made significant contributions in genetic analysis of patients and controls and collection of data. AME: made significant contributions in laboratory tests of patients and controls and collection of data. AMT: made significant contributions in study design and collection of data. SE: made significant contributions in psychometric assessment of patients and controls, statistical analysis, and collection of data. AMB: made significant contributions in study execution, statistical analysis, and collection of data. MMS: made significant contributions to the design and execution of the study and collection of data. He also had role in statistical analysis, revision of the manuscript (corresponding author). All authors have read and approved the manuscript.

Funding

Not applicable. I declare that there is no funding received for this study.

Availability of data and materials

I declare that all data and materials are available upon reasonable request.

Declarations

Ethics approval and consent to participate

This study had been reviewed and approved by "The Committee of Medical Ethics" of the Faculty of Medicine Assiut University with IRB No: 17200505 and all the patients or their first degree relatives had assigned a written consent to participate in the study.

Consent for publication

All participants had assigned a consent for participation in the study and publication of the study.

Competing interests

Not applicable. I declare that the is no competing interests regarding this study.

Author details

[1]Present Address: Assiut University, Asyut, Egypt. [2]Anatomy Department College of Medicine, Jouf University, Sakakah, Saudi Arabia. [3]College of Medicine Assiut University, Asyut, Egypt. [4]Present Address: Faculty of Arts, Assiut University, Asyut, Egypt.

Received: 2 May 2021 Accepted: 25 January 2022
Published online: 17 February 2022

References

1. Masters CL, Bateman R, Blennow K, Rowe CC, Sperling RA, Cummings JL. Alzheimer's disease. Nat Rev Dis Primers. 2015;1:15056.
2. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, et al. Alzheimer's disease. Lancet. 2016;388:505–17.
3. Escott- PV, Myers AJ, Huentelman M, Hardy J. Polygenic risk score analysis of pathologically confirmed Alzheimer disease. Ann Neurol. 2017;82(2):311–4. https://doi.org/10.1002/ana.24999.
4. Tanaka M, Toldi J, Vécsei L. Exploring the etiological links behind neurodegenerative diseases: inflammatory cytokines and bioactive kynurenines. Int J Mol Sci. 2020;21:2431. https://doi.org/10.3390/ijms21072431.
5. Ridge PG, Mukherjee S, Crane PK, Kauwe JS. Alzheimer's disease: analyzing the missing heritability. PLoS ONE. 2013;8:e79771.
6. Wu L, Zhao L. ApoE2 and Alzheimer's disease: time to take a closer look. Neural Regen Res. 2016;11(3):412–3. https://doi.org/10.4103/1673-5374.179044.
7. Giau VV, Bagyinszky E, An SSA, Kim S. Role of apolipoprotein E in neurodegenerative diseases. Neuropsychiatr Dis Treat. 2015;11:1723–37.
8. Raichlen DA, Alexander GE. Exercise, APOE genotype, and the evolution of the human lifespan. Trends Neurosci. 2014;37:247–55.
9. Wu L, Zhang X, Zhao L. Human ApoE isoforms differentially modulate brain glucose and ketone body metabolism: implications for Alzheimer's disease risk reduction and early intervention. J Neurosci. 2018;38(30):6665–81. https://doi.org/10.1523/JNEUROSCI.2262-17.2018.
10. Lim YY, Mormino EC, Alzheimer's Disease Neuroimaging, I. APOE genotype and early β-amyloid accumulation in older adults without dementia. Neurology. 2017;89(10):1028–34.
11. Tai LM, Thomas R, Marottoli FM, Koster KP, Kanekiyo T, Morris AWJ, et al. The role of APOE in cerebrovascular dysfunction. Acta Neuropathol. 2016;131(5):709–23.
12. Belloy ME, Napolioni V, Greicius MD. A quarter century of APOE and Alzheimer's disease: progress to date and the path forward. Neuron. 2019;101(5):820–38.
13. Kang J, Lim L, Song J. TMEM106B, a risk factor for FTLD and aging, has an intrinsically disordered cytoplasmic domain. PLoS ONE. 2018;13(10):e0205856.

14. Rhinn H, Abeliovich A. Differential aging analysis in human cerebral cortex identifies variants in TMEM106B and GRN that regulate aging phenotypes. Cell Syst. 2017;4:404-415.e5.
15. Satoh J, Kino Y, Kawana N, Yamamoto Y. TMEM106B expression is reduced in Alzheimer's disease brains. Alzheimers Res Ther. 2014;6(2):17. https://doi.org/10.1186/alzrt247.
16. El Tallawy HN, Farghaly WM, El Hamed AM, Badry R, Usama K, Shehata GA, Tohamy AM, Abdulghani KO, Ghanem MK, Sayed MA, Yousef AH, Hashem HS, Rageh TA. Prevalence of Alzheimer dementia in upper Egypt (desert areas). Egypt J Neurol Psychiatry Neurosurg. 2019;55:29. https://doi.org/10.1186/s41983-019-0074-y.
17. Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimer's Dement. 2016;12:459–509.
18. Alzheimer's Association. Alzheimer's disease facts and figures. Alzheimer's Dement. 2018;14:367–429.
19. El Tallawy HN, Farghly WM, Badry R, Rageh TA, Shehata GA, Hakeem MNA, et al. Prevalence of dementia in Al-Quseir city, Red Sea Governorate, Egypt. Clin Interv Aging. 2014;9:9–14.
20. Al-khateeb E, Al-zayadneh E, Al-dalahmah O, Alawadi Z, Khatib F, Naffa R, et al. Relation between copper, lipid profile, and cognition in elderly Jordanians. J Alzheimer's Dis. 2014;41(1):203–11.
21. Khedr E, Fawi G, Abbas MA, Mohamed TA, Abo El-Fetoh N, Al Attar G, et al. Prevalence of mild cognitive impairment and dementia among the elderly population of Qena Governorate, Upper Egypt: a community-based study. J Alzheimer's Dis. 2015;45(1):117–26.
22. Chaaya M, Phung K, Atweh S, El Asmar K, Karam G, Khoury R, et al. Socio-demographic and cardiovascular disease risk factors associated with dementia: results of a cross-sectional study from Lebanon. Prev Med Rep. 2018;9:1–5.
23. Ghuloum S, Bener A, Abou-Saleh MT. Prevalence of mental disorders in adult population attending primary health care setting in Qatari population. J Pakistan Med Assoc. 2011;61(3):216.
24. Burke AD, Goldfarb D, Bollam P, Khokher S. Diagnosing and treating depression in patients with Alzheimer's disease. Neurol Ther. 2019;8:325–50.
25. Rodríguez RM, Martínez-Santos A, González RR. Depression as a risk factor for Alzheimer's disease: evidence and role of Nursing. Enfermería Global. 2019;55:628. https://doi.org/10.6018/eglobal.18.3.346711.
26. Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, et al. Trajectories of depressive symptoms before diagnosis of dementia: a 28- year follow-up study. JAMA Psychiat. 2017;74(7):712–8.
27. Heser K, Tebarth F, Wiese B, Eisele M, Bickel H, Köhler M, et al. Age of major depression onset, depressive symptoms, and risk for subsequent dementia: results of the German study on Ageing, Cognition, and Dementia in Primary Care Patients (AgeCoDe). Psychol Med. 2013;43(8):1597–610.
28. Tanaka M, Vecsei L. Editorial of special issue "crosstalk between depression, anxiety, and dementia: comorbidity in behavioral neurology and neuropsychiatry." Biomedicines. 2021;9(5):517. https://doi.org/10.3390/biomedicines9050517.
29. Kim J, Ki Y. Crosstalk between depression and dementia with resting-state fMRI studies and its relationship with cognitive functioning. Biomedicines. 2021;9:82. https://doi.org/10.3390/biomedicines9010082.
30. Sáiz-Vázquez O, Gracia-García P, Ubillos-Landa S, Puente-Martínez A, Casado-Yusta S, Olaya B, Santabárbara J. Depression as a risk factor for Alzheimer's disease: a systematic review of longitudinal meta-analyses. J Clin Med. 1809;2021:10. https://doi.org/10.3390/jcm10091809.
31. Webster L, Gonzalez SG, Stringer A, Lineham A, Budgett J, Kyle S, Barber J, Livingston G. Measuring the prevalence of sleep disturbances in people with dementia living in care homes: a systematic review and meta-analysis. Sleep. 2020;43(4):zsz251. https://doi.org/10.1093/sleep/zsz251.
32. Gan EH, Pearce SH. Clinical review: the thyroid in mind: cognitive function and low thyrotropin in older people. J Clin Endocrinol Metab. 2012;97(10):3438–49.
33. Chaker L, Wolters FJ, Bos D, Korevaar TI, Hofman A, van der Lugt A, et al. Thyroid function and the risk of dementia: the Rotterdam Study. Neurology. 2016;87(16):1688–95.
34. Rieben C, Segna D, da Costa BR, Collet TH, Chaker L, Aubert CE, et al. Subclinical thyroid dysfunction and the risk of cognitive decline: a meta-analysis of prospective cohort studies. J Clin Endocrinol Metab. 2016;101:4945–54.
35. Yeap BB, Alfonso H, Chubb SA, Puri G, Hankey GJ, Flicker L, et al. Higher free thyroxine levels predict increased incidence of dementia in older men: the Health in Men Study. J Clin Endocrinol Metab. 2012;97:E2230-2237.
36. Kao Y, Ho P, Tu Y, Jou I, Tsai K. Lipids and Alzheimer's disease. Int J Mol Sci. 2020;21:1505.
37. Solomon A, Kareholt I, Ngandu T, Wolozin B, Macdonald SW, Winblad B, et al. Serum total cholesterol, statins and cognition in non-demented elderly. Neurobiol Aging. 2009;30:1006–9.
38. Mielke MM, Zandi PP, Shao H, Waem M, Ostling S, Guo X, et al. The 32-year relationship between cholesterol and dementia from midlife to late life. Neurology. 2010;75:1888–95.
39. Mielke MM, Zandi PP, Sjogren M, Gustafson D, Ostling S, Steen B, Skoog I. High total cholesterol levels in late life associated with a reduced risk of dementia. Neurology. 2005;64:1689–95.
40. Anstey KJ, Ashby-Mitchell K, Peters R. Updating the evidence on the association between serum cholesterol and risk of late-life dementia: review and meta-analysis. J Alzheimers Dis. 2017;56:215–28.
41. West R, Beeri MS, Schmeidler J, Hannigan CM, Angelo G, Grossman HT, et al. Better memory functioning associated with higher total and low-density lipoprotein cholesterol levels in very elderly subjects without the apolipoprotein e4 allele. Am J Geriatr Psychiatry. 2008;16:781–5. https://doi.org/10.1097/jgp.0b013e3181812790.
42. Chen H, Du Y, Liu S, Ge B, Ji Y, Huang G. Association between serum cholesterol levels and Alzheimer's disease in China: a case-control study. Int J Food Sci Nutr. 2019;70:405–11.
43. Leritz EC, McGlinchey RE, Salat DH, Milberg WP. Elevated levels of serum cholesterol are associated with better performance on tasks of episodic memory. Metab Brain Dis. 2016;31:465–73.
44. Svensson T, Sawada N, Mimura M, Nozaki S, Shikimoto R, Tsugane S. The association between midlife serum high-densitylipoproteinandmild-cognitive impairment and dementia after 19 years of follow-up. Transl Psychiatry. 2019;9:26.
45. Reiman EM, Arboleda-Velasquez JF, Quiroz YT, Huentelman MJ, Beach TG, Caselli RJ, et al. The Alzheimer's disease genetics consortium. Exceptionally low likelihood of Alzheimer's dementia in APOE2 homozygotes from a 5,000-person neuropathological study. Nat Commun. 2020;11:667.
46. Keeney JT, Ibrahimi S, Zhao L. Human ApoE isoforms differentially modulate glucose and amyloid metabolic pathways in female brain: evidence of the mechanism of neuroprotection by ApoE2 and implications for Alzheimer's disease prevention and early intervention. J Alzheimers Dis. 2015;48:411–24.
47. Li Z, Farias FHG, Dube U, Del-Aguila JL, Mihindukulasuriya KA, Fernandez MV, et al. The TMEM106B FTLD-protective variant, rs1990621, is also associated with increased neuronal proportion. Acta Neuropathol. 2020;139(1):45–61.
48. Simons C, Dyment D, Bent SJ, Crawford J, D'Hooghe M, Kohlschütter A, et al. A recurrent de novo mutation in TMEM106B causes hypomyelinating leukodystrophy. Brain. 2017;140:3105–11.
49. Ren Y, Blitterswijk M, Allen M, Carrasquillo MM, Reddy JS, Wang X, et al. TMEM106B haplotypes have distinct gene expression patterns in aged brain. Mol Neurodegener. 2018;13:35.

Publisher's Note