Clinical Neurology and Neurosurgery 177 (2019) 47–53

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Genetic influences on white matter and metabolism abnormal change in Alzheimer's disease: Meta-analysis for neuroimaging research on presenilin 1 mutation

Xiaochun Gu[a,b,*], Tao Chu[c], Li Liu[b], Xiao Han[b]

[a] Jiangsu Key Laboratory of Molecular and Functional Imaging, Department of Radiology, Zhongda Hospital, Medical School, Southeast University, 87 Dingjiaqiao Road, Nanjing 210009, China
[b] Key Laboratory of Developmental Genes and Human Diseases, Department of Histology Embryology, Medical School, Southeast University, 87 Dingjiaqiao Road, Nanjing 210009, China
[c] Nanjing Normal University Affiliated Middle School Xincheng Junior High School, 123 Huangshan Road, Nanjing 210009, China

ARTICLE INFO

Keywords:
Presenilin1
Imaging marker
Alzheimer's disease
White matter integrity
Mean diffusivity
Metabolism change

ABSTRACT

Mutations in the presenilin1 (*PSEN1*) cause familial Alzheimer's disease (FAD), providing a special opportunity to study pre-symptomatic individuals who would be predicted to develop Alzheimer's disease (AD) in the future. However, whether presenilin1 (*PSEN1*) genotype and neuroimaging markers is a harbinger of AD remains controversial. We aimed to explore the association of PSEN1 genotype with neuroimaging markers of AD: white matter integrity, cerebral amyloid deposition and brain metabolism. We reviewed studies of diffusion tensor imaging (DTI), amyloid deposition and cerebral metabolism in patients with AD and control, in order to address the relative change of white matter microstructural associated with PSEN1 genotype. We performed a systematic meta-analysis and review of 11 cross-sectional studies identified in several database from 2008 to 2018 (n = 165). The pooled standard mean difference (SMD) value was calculated to estimate the association between PSEN1 and white matter change and brain metabolism. PSEN1 mutation carrier status was associated with mean diffusivity (MD) change (pooled SMD: 2.29; 95% CI 1.04 to 3.53; $p < 0.001$) and increased cerebral amyloid positron emission tomography tracer (pooled SMD: 3.78, 95% CI 1.04 to 6.53, $p = 0.007$). *PSEN1* was not associated with white matter metabolism change ($p = 0.069$). PSEN1 was associated with mean diffusivity (MD) increase in DTI markers and decreased brain metabolism. Theses associations may suggest the potential role of the PSEN1 gene and imaging marker in Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease in the world. So far, the molecular, genetic and biochemical properties of the disease remain unclear and remain to be studied [1]. In a family with dominant familial AD (FAD), approximately half of siblings are mutation carriers (MC), and AD usually occurs at an earlier age. Three mutations have been found: presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) [2–4]. Pathological features of FAD include neurofibrillary tangles (NFT), amyloid plaques (APs), neuronal loss, and brain atrophy, similar to sporadic AD [5]. AD is characterized by intracellular neurofibrillary tangles and amyloid plaques. Pathologically, cumulative accumulation of NFT and AP in brain tissue ultimately leads to neuronal death and gray matter (GM) atrophy [6,7], all of which can be measured by imaging techniques such as magnetic resonance imaging (MRI).

The degeneration of AD mainly affects gray matter (GM), and the evidence also indicates that early white matter (WM) also has defects [8]. In AD disease, WM abnormalities have been reported using diffusion tensor imaging (DTI) [9]. Both autopsy studies [10,11] and magnetic resonance imaging (MRI) studies [12–14] have showed evidence of defects of white matter (WM) defects in AD. In addition, there is a significant correlation between disease severity and WM indicators [15,16], which provides evidence that white matter measurements can be used as markers of AD disease progression. MRI techniques, such as diffusion tensor imaging (DTI), can study the direction and integrity of WM bundles by measuring the diffusion of water molecules in nerves and axons [17]. The mean diffusivity (MD) and fractional anisotropy (FA) are the two most common measurement methods in DTI. MD provides a marker of isotropic diffusion of water molecules and FA

* Corresponding author at: School of Medicine, Southeast University, Life Science Bldg, Rm. 505, Nanjing, 210009, PR China.
E-mail address: xiaochun.gu@seu.edu.cn (X. Gu).

https://doi.org/10.1016/j.clineuro.2018.12.016
Received 5 May 2018; Received in revised form 18 October 2018; Accepted 24 December 2018
Available online 26 December 2018

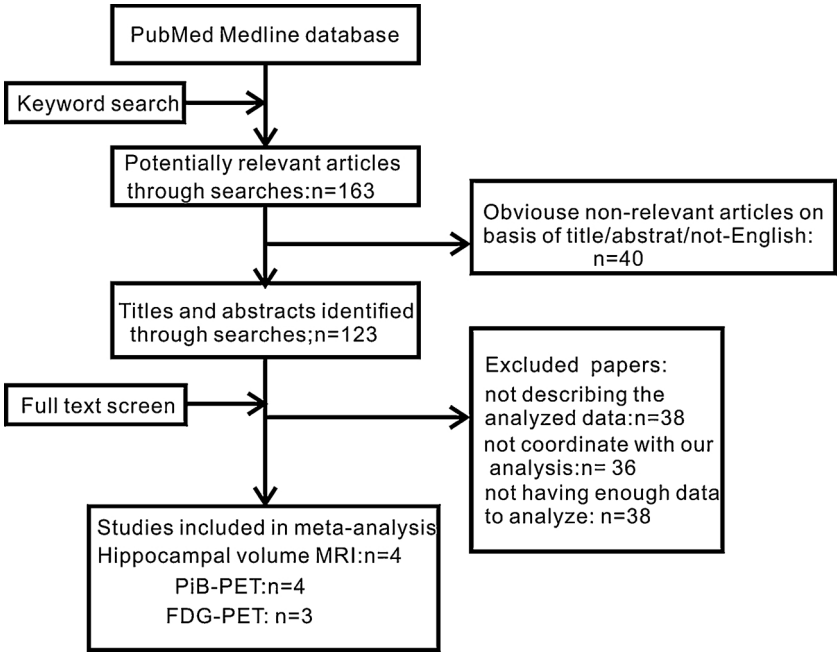

Fig. 1. Flow chart of studies through screening, inclusion and exclusion. FDG PET, flurodeoxyglucose positron emission tomography; PiB-PET, Pittsburgh compound B positron emission tomography.

measure the anisotropic water diffusion. Ringman et al found that FA decreased in the fornix of pre-MCs and early symptomatic MCs. [18]. Recently, Ryan et al found that patients with symptomatic MC had significantly increased MD and decreased FA compared with healthy controls [19]. In addition, biochemical abnormalities in the cerebrospinal fluid (CSF) [20–22] and fibrillar amyloidosis, using positron emission tomography imaging of brain amyloid [23], have also been reported in symptomatic MCs.

Overall, higher MD and lower FA values were detected in DTI studies in the AD and MCI groups compared to controls. Despite this, there is a large amount of heterogeneity in different brain regions and different studies. Although there are some DTI descriptive studies on AD and MCI [24–26]. However, to date, no studies have been conducted to quantitatively assess the relationship between *PSEN1* genotype and white matter integrity and metabolic changes. Therefore, our goal is to provide a meta-analysis and systematic review to assess the relationship between PSEN1 mutations and white matter abnormalities and metabolic changes. Here, related neuroimaging markers mainly include MD values; Aβ deposition and glucose metabolism.

2. Methods

2.1. Search strategy and selection criteria

The literature published from January 1, 1997 to May 1, 2018 was systematically screened in PubMed, MEDLINE, and EMBASE. Use the following terms in the title, abstract or descriptor according to the preferred report item of the Systematic Review and Meta-analysis (PRISMA) guide: PSEN1, presenlin1, MRI, DTI, PET, glucose metabolism, PiB, amyloid, Alzheimer disease, AD. We limit our search to human research. The detailed Boolean operators as follows("PSEN1″ OR "presenilin 1″) AND ("Magnetic Resonance Imaging " OR "MRI ") AND ("Positron emission tomography " OR "PET ") AND ("glucose metabolism " OR "PiB-PET" OR "Pittsburgh compound B-PET") AND ("Alzheimer disease " OR "AD").

Our included study tested the association of *PSEN1* with at least one neuroimaging marker of white matter changes and cortical metabolism. The following are the criteria included: (1) original research; (2) reported in English; (3) peer review; (4) AD (the clinical diagnosis of AD based on stroke - Alzheimer's disease and related disease association and national nervous and (Communication Disorders Institute Standard) or Health Control; (5) For MRI, only DTI imaging is selected; (6) For PiB-PET and FDG-PET studies, it uses statistically significant thresholds to determine uncorrected spatial range thresholds or correct multiple comparison data.

2.2. Data extraction and quality assessment

The following data were independently extracted by two authors: sample size, study population, mean age, DTI characteristics and sequences, PET characteristics and related technical details. To measure the association between PSEN1 and MRI markers, we recorded the mean, SD or SE for the continuous MD value. To measure the association between *PSEN1* genotype and PET markers, the mean and SD on standardized uptake values ratios (SUVRs) or the global [^{11}C] Pittsburgh compound B non-displaceable binding potential were extracted for the included florbetapir [^{11}C] and [^{18}F] PET studies. To measure the association between *PSEN1* genotype and FDG-PET marker, the value of SUVR is also included. If no measures are followed, qualitative results were reported. Two authors extracted the above information from each study and resolved any disagreements through discussion.

2.3. Statistical analyses

Meta-analysis was performed when at least three studies were available for the same outcome. Here, *PSEN1+* was defined as a homozygous wild type genotype, and *PSEN1-* means heterozygous dominant mutation. To compare the association between different genotypes (PSEN1+ Vs. PSEN1-) and MD values. We summarized the MD values changes of each groups separately. For MD value change, Pib-PET and FDG-PET calculation, meta-analysis of all statistics was performed using standard mean difference (SMD) methodology in Stata 12.0 software (Stata Corp, College Station, TX, USA). A random-effects model was used if the heterogeneity between studies was statistically significant and a fixed-effects meta-analysis was used in the absence of heterogeneity. Overall, heterogeneity was assessed using the Cochran Q (p value > 0.10 on the Q test, which reflects a lack of heterogeneity

Table 1
Characteristics of the included studies for the meta-analysis of MRI.

MRI operating parameters							Mean age (y)		Sex, m(f)		MMSE	
Study name	year	Origin	Field (Tesla)	TR/TE (ms)	Matrix	Study used	*PSEN+*	*PSEN−*	*PSEN+*	*PSEN−*	*PSEN+*	*PSEN−*
Fortea [34]	2010	Spain	3T	2300/2.98 ms	256 × 256	AD	42.08(11.55)	47.4(8.44)	4(8)	2(3)	29.4(0.51)	22.3(7.11)
Westmen [35]	2015	Sweden	3T	8000/97 ms	96 × 96	AD	48.4(15.1)	46.5(9.3)	11(9)	8(2)	29.2(0.9)	27.3(5.8)
Parra [33]	2015	UK	1.5T	7.2 s/90ms□	256 × 256	AD	49.5 (14.3)	42.5(11.6)	11(55)	10 (77)	29(1.5)	29(0.2)
Lee [61]	2012	US	1.5T	1900/4.38ms	256 × 256	AD	38.1(8.2)	35.81(9.4)	3(7)	5(16)	28.9(0.9)	26.7(2.9)

AD, Alzheimer's disease; MMSE, mini-mental-state examination; PSEN1 + was defined as a homozygous wild type genotype, and PSEN1- means heterozygous dominant mutation.

among studies) and I^2 (considerable heterogeneity: values of more than 50%) [27,28]. The 95% CI was used to gauge the precision of the summary estimates.

3. Results

The initial literature searches identified 163 potentially relevant articles, of which 123 met the inclusion criteria. By screening the full text, 96 articles were excluded because of different reasons (Fig. 1). Fig. 1 showed the flow chart of the identification and attrition of studies, and Tables 1 and 2 show the key details of the studies included in the meta-analysis.

Finally, 11 studies that were published between 2008 and 2018 met the selection criteria, including access to information on the association between PSEN1 and the three neuroimaging biomarkers. A total of 317 *PSEN1+* subjects and 260 *PSEN1-* subjects were included. No outliers were found by the sensitivity analysis in this study. There was statistically significant change in the pooled SMD for MD change (SMD was between 1.04 and 3.53) or for the amyloid PET analysis (SMD was between 0.25 and 7.08) and no significant change for FDG-PET analysis (SMD was between -3.17 to 0.12).

3.1. *PSEN1+ and DTI marker of AD (white matter MD value)*

3.1.1. *Description of studies*

Seven studies investigated the association between *PSEN1+* and MD value change. Three studies could not be used for analysis [29–31]. Hence, a total of four studies which met criteria were included into our meta-analysis [32–35], totally including 210 *PSEN1+* carriers and 150 *PSEN1-* carriers. Of the included studies, all reported the MD value was significantly increased in *PSEN1* mutation subjects than in *PSEN1+* subjects. The pooled subjects included healthy normal subjects, and subjects diagnosed with AD in US (one study), UK (one study), Sweden (one study), Spain (one study). All the studies showed significant statistically difference in mini-mental-state examination (MMSE) between *PSEN1+* and *PSEN1-* carriers. Details of the included studies are presented in Table 1.

3.2. *White matter mean diffusivity (MD) value*

Combining the four studies using continuous mean diffusivity (MD) value and providing weighted mean differences (n = 210 *PSEN1+* population and n = 150 *PSEN1-* population), As shown in the forest plots (Fig. 2), yielded a statistically significant association between the *PSEN1* mutation and increased MD value: pooled standardized mean difference = 2.29 (95% CI 1.04–3.53) (I^2 = 90.0%, Cochran's Q = 50.21, p < 0.0001); The test for overall effect: Z = 3.61, P < 0.0001.

3.3. *PSEN1 and PET markers of AD*

3.3.1. *Description of included studies*

The search strategy identified thirteen papers met the inclusion criteria for the PET-amyloid tracer study and for the FDG-PET study [36–47]. We did not found additional articles in the reference list of the selected studies. For the PET-amyloid tracer study, data from nine studies [37,39–4244,45,47] could not be used for analysis in this meta-analysis. The clinical, demographic and technical data of participants from all recruited studies in Table 2 [38,46,48,49]. A total of 52 *PSEN1+* subjects and 62 *PSEN1-* subjects were included. For the FDG-PET study, four studies met the selection criteria, including a total of 45 *PSEN1+* subjects and 38 *PSEN1-* subjects. The detailed demographic and clinical data of participants from the five included studies are shown in the Table 2.

3.4. *PSEN1 and PET-amyloid tracers*

The *PSEN1* was significantly associated with increased amyloid deposition (test for overall effect: Z = 2.1, p = 0.035), in a sample size-weighted meta-analysis,. Combined analysis of the association between the cortical SUVR and *PSEN1* is shown in the forest plots (Fig. 3). The pooled SMD from a random-effects model was 3.66 (95% CI (0.25 to 7.08), I^2 = 95.7%; Cochran's Q = 70.55, P < 0.0001).

3.5. *PSEN1 and FDG-PET for cerebral hypometabolism*

The three included studies reported CMRgl reductions at cortex. A

Table 2
Demographic and clinical characteristics of PET studies in meta-analysis.

Study	Subjects	Number (male)		Age		MMSE	
		PSEN+	*PSEN-*	*PSEN+*	*PSEN-*	*PSEN+*	*PSEN-*
Rodriguez-Vieitez (2015) [48]	AD	10(6)	2(9)	51.1(14.2)	44.9(9.8)	28.9(1.2)	16.0(8.7)
Fleisher (2012) [38]	AD	7(13)	7(12)	33.9(8.7)	32.6(8.2)	29.8(0.5)	29.8(0.4)
Lyoo (2016) [46]	AD	4(6)	3(7)	68.8(8.2)	71.9(8.6)	29.6(0.1)	24(0.01)
Schöll (2011) [36]	AD	9(14)	3(1)	46.0(12.2)	34.2(7.4)	29.2(0.8)	29.2(1.3)
Forsberg (2008) [49]	AD	6	8(13)	NA	63.8(7.8)	29(1.2)	28.2(1.4)

AD, Alzheimer's disease; MMSE, mini mental-state examination; NA, not available. *PSEN1+* was defined as a homozygous wild type genotype, and *PSEN1-* means heterozygous dominant mutation.

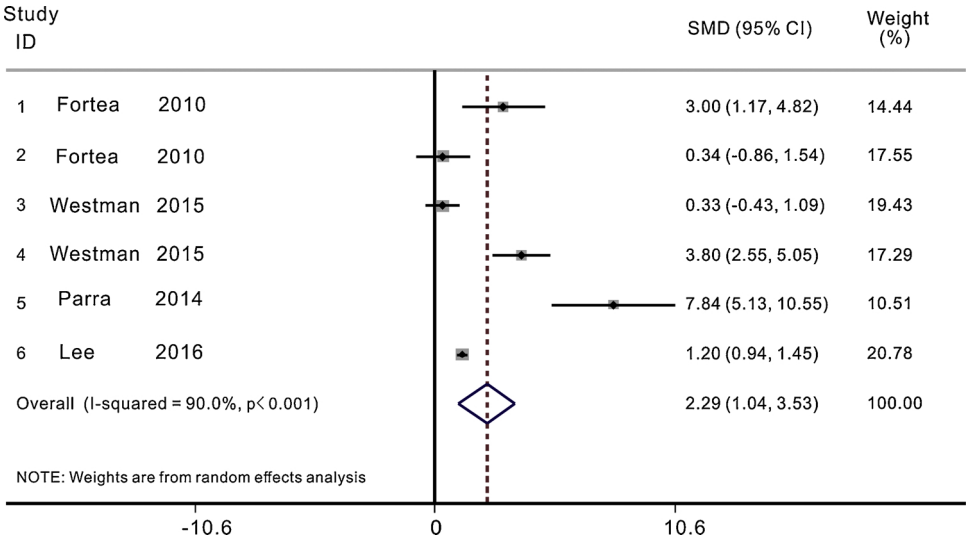

Fig. 2. Meta-analysis of studies testing the association between *PSEN1* genotype and white matter integrity (MD value). Analysis model: random effects, Statistical method: inverse variance. Data type: continuous, Effect measure: standard mean difference.

group comparison of 45 *PSEN1* + subjects and 38 *PSEN1*- subjects was carried out. In *PSEN1*- subjects, CMRgl reductions at cortex were not found. Combined analysis of the relationship between the cortex white matter SUVR and *PSEN1* is shown in the forest plots (Fig. 4). The pooled SMD from a random-effects model was -1.53 (95% CI (-3.17 to 0.12), I^2 = 87.8%; Cochran's Q = 16.43, P = 0.069).

3.6. Sensitivity analysis and publication bias

Publication bias have not been found for the association between *PSEN1* mutation and MD value change was identified by Begg's funnel plot (P = 0.272). Additionally, publication bias have not been found for the association between *PSEN1* mutation and cortical PiB-PET change was identified by Begg's funnel plot (P = 0.079). We did not use funnel plot or additional methods to do sensitivity analysis due to the limited number of studies included, since only three studies met the inclusion criteria and were included into the FDG-PET and PiB-PET meta-analysis. However, all the included studies met the criteria were studies with a relatively large cohort.

4. Discussion

The main purpose of our study was to explore published literature and to attempt to elucidate *PSEN1*-related neural markers and AD. In this meta-analysis and systematic review, the *PSEN1* gene is associated with abnormal white matter integrity and increased amyloid deposition.

Defects in brain function (such as white matter and gray matter) have provided important insights and predictions for brain changes in AD over the past two decades. Longitudinal studies have confirmed hippocampal defects in MCs before AD symptoms appear [50]. At each stage, the hippocampal volume of MC is smaller than the age- and sex-matched controls [5]. In addition to brain gray matter atrophy, DTI measurements (FA and MD value) indicating white matter damage are commonly found in AD disease. During neurodegeneration, cell death leads to an increase in the diffusion of water molecules, which can be measured by elevated MD. Similarly, a reduced FA value indicates a process leading to a WM homogeneity disorder, indicating that WM integrity in the brain was disrupted [51].

There is still confusion about the pathophysiology of white matter abnormalities in AD. Furthermore, it is unclear whether WM pathology is associated with gray matter (GM) pathology or independent of gray

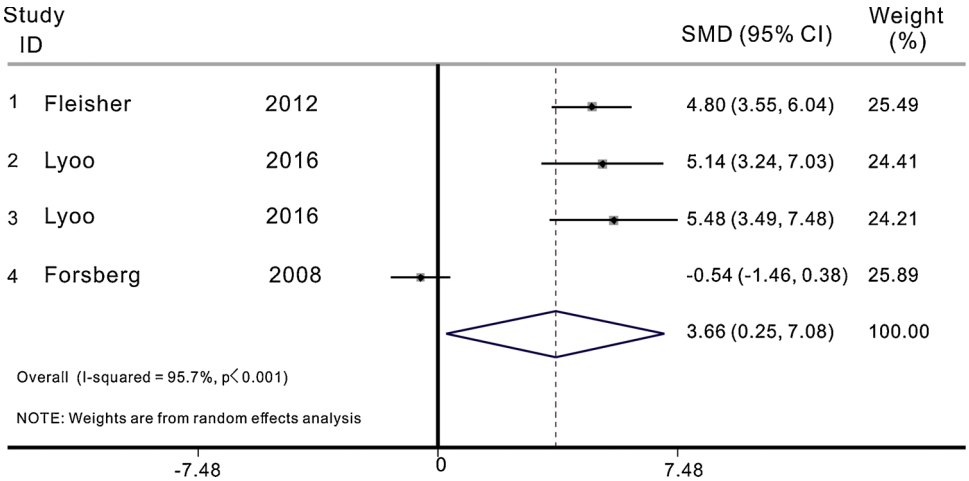

Fig. 3. Meta-analysis of studies exam the association between *PSEN1* genotype and positron emission tomography-amyloid tracers. Analysis model: random effects, Statistical method: inverse variance. Data type: continuous, Effect measure: standard mean difference.

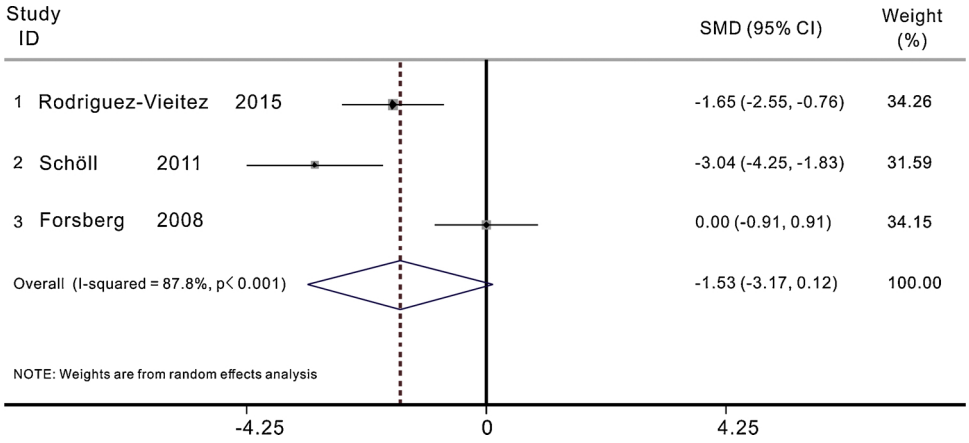

Fig. 4. Meta-analysis of studies for the association between *PSEN1* genotype and cerebral hypometabolism. Analysis model: random effects, Statistical method: inverse variance. Data type: continuous, Effect measure: standard mean difference.

matter (GM) pathology. Studies have shown that Wallerian degeneration leads to abnormal white matter integrity [52]. At the same time, studies have shown that white matter abnormalities and gray matter pathology models exist simultaneously [53]. On the other hand, the retrograde hypothesis suggests that reducing WM integrity is caused by the separate decomposition of the myelin itself [8,54]. As this theory suggests, early myelin bundles and small diameters will be affected first. Finally, local microvascular changes may also lead to WM pathology, as vascular damage also plays an important role in AD. Here, our results suggested that damage to white matter and gray matter may occur simultaneously and affect each other.

FA value change is also another important marker for abnormal WM integrity. In this study, due to our small sample size, we did not analyze the differences in FA value change. In previous study, Ringman et al reported decreased FA of the fornix in early symptomatic *PSEN1*- subjects were founded [18]. In the global brain scale, widespread decreased FA in symptomatic *PSEN1*- subjects was reported by Ryan et al [19]. Here, increased MD value in *PSEN1*- subjects was founded.

Some studies reports that gray matter defects, including brain atrophy, amyloid deposition and metabolic disruption in AD affect the left/posterior regions earlier than the right/anterior regions [55,56]. In particular, in these regions, the MD value significantly increased and became more widespread and bilateral. Furthermore, the mean values of MD from these regions showed a negative correlation with CSF levels of $A\beta_{42}$, associated with previous findings in sporadic AD [57]. The increased MD may be account for myelin loss, although the exact causes of these changes are difficult to clarify. In histological studies, a widespread decrease in myelin in WM of normal appearance, and more severe myelin loss in AD were observed [58,59]. Additionally, increased quantities of $A\beta_{40}$ and $A\beta_{42}$ accompanied by significant decreases in the amounts of myelin protein was found in biochemical analyses of WM from patients with AD [60]. Therefore, early AD brain pathology maybe detect by DTI measurements. Furthermore, MD appears to be more sensitive, compared with measures of FA and GM volume, during early pathological AD changes. [58]. Therefore, the pathological changes of gray matter and white matter were simultaneously detected. Our meta-analysis revealed that, in the case of *PSEN1* mutation, the combination of the more sensitive MD value with the amyloid deposition of gray matter metabolism is expected to detect pathological changes of AD at an earlier time.

In AD disease, studies have shown that several different brain regions have been affected, which may lead to different severity of the disease and differences in symptoms. Here, we studied the situation of the main affected brain regions of different studies. All the brain areas changed included left inferior longitudinal fasciculus and cingulum and bilateral superior longitudinal fasciculus [35]; Corpus callosum,Caudate, Accumbens, Amygdala, Hippocampus, Putamen [34];

Parr et al reported the brain area included corpus callosum and in the hippocampal part of cingulum bundle in the frontal and temporal lobes area [33]. Lee et al reported the areas included temporal and parietal lobes, the left frontal lobe and putamen [61]. All researches reported the MD and FA values changed in the similar area, the all belong to the subcortical structures.

This study has several limitations. First, longitudinal studies are needed, for changes in GM, MD were assessed at only one time-point. Second, although each acquisition parameter does not affect the quality of data, meta-analysis with different parameters is thus limited as it examines each parameter separately. For example, Firbank et al. [62] compared b values of 1000 and 4000 s/mm^2 and found that, 4000 s/mm^2 is more sensitive, additionally slice thickness is another important factor to get an improved signal-to-noise ratio. The third limitation is publication bias. For some relevant studies may not have been included in the database we searched and were missed in this study inevitably. In our meta-analyses, the number of subgroups divided by subjects was not sufficient to conduct a meta-analysis. At last, we were limited by the fact that most studies provided effect estimates for *PSEN1* mutation, with varying different mutation types, over 180 different mutations in PSEN1 are known to cause AD and all mutation carriers develop early-onset AD (http://www.molgen.ua.ac.be/AD mutations).

5. Conclusion

In summary, this study indicates *PSEN1* mutation associated with white matter changes and amyloid deposition occur in AD. Increased MD is observed and shows significant increased with amyloid deposition. However, CMRgl reductions at cortex were not found. We believe that these results will be useful to clarify the progression of AD pathology and valuable in the diagnosis of AD.

Sources of funding

This research was supported in part by grant 81520108015 from National Natural Science Foundation and 2242018k30004, 3224008417, 2242018K41082 from the Fundamental Research Funds for the Central Universities of China (X. G.)

Disclosures

The authors report no conflicts of interest

Acknowledgments

We thank Yingxuan Chen and Yunqian Cai for assisting with paper search.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.clineuro.2018.12.016.

References

[1] K. Blennow, M.J. de Leon, H. Zetterberg, Alzheimer's disease, Lancet 368 (2006) 387–403.
[2] A. Goate, M.C. Chartier-Harlin, M. Mullan, J. Brown, F. Crawford, L. Fidani, et al., Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease, Nature 349 (1991) 704–706.
[3] R. Sherrington, E.I. Rogaev, Y. Liang, E.A. Rogaeva, G. Levesque, M. Ikeda, et al., Cloning of a gene bearing missense mutations in early-onset familial Alzheimer's disease, Nature 375 (1995) 754–760.
[4] E.I. Rogaev, R. Sherrington, E.A. Rogaeva, G. Levesque, M. Ikeda, Y. Liang, et al., Familial Alzheimer's disease in kindreds with missense mutations in a gene on chromosome 1 related to the Alzheimer's disease type 3 gene, Nature 376 (1995) 775–778.
[5] B.H. Ridha, J. Barnes, J.W. Bartlett, A. Godbolt, T. Pepple, M.N. Rossor, et al., Tracking atrophy progression in familial Alzheimer's disease: a serial MRI study, Lancet Neurol. 5 (2006) 828–834.
[6] J. Hardy, D.J. Selkoe, The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics, Science 297 (2002) 353–356.
[7] R. Anand, A. Kaushal, W.Y. Wani, K.D. Gill, Road to Alzheimer's disease: the pathomechanism underlying, Pathobiology 79 (2012) 55–71.
[8] G. Bartzokis, D. Sultzer, P.H. Lu, K.H. Nuechterlein, J. Mintz, J.L. Cummings, Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical "disconnection" in aging and Alzheimer's disease, Neurobiol. Aging 25 (2004) 843–851.
[9] C.E. Sexton, U.G. Kalu, N. Filippini, C.E. Mackay, K.P. Ebmeier, A meta-analysis of diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease, Neurobiol. Aging 2322 (32) (2011) e2325–2318.
[10] A. Brun, E. Englund, A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study, Ann. Neurol. 19 (1986) 253–262.
[11] E. Englund, Neuropathology of white matter changes in Alzheimer's disease and vascular dementia, Dement. Geriatr. Cogn. Disord. 9 (Suppl. 1) (1998) 6–12.
[12] G. Bartzokis, J.L. Cummings, D. Sultzer, V.W. Henderson, K.H. Nuechterlein, J. Mintz, White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study, Arch. Neurol. 60 (2003) 393–398.
[13] A.M. Brickman, J. Muraskin, M.E. Zimmerman, Structural neuroimaging in Altheimer's disease: do white matter hyperintensities matter? Dialogues Clin. Neurosci. 11 (2009) 181–190.
[14] F. Fazekas, J.B. Chawluk, A. Alavi, H.I. Hurtig, R.A. Zimmerman, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR Am. J. Roentgenol. 149 (1987) 351–356.
[15] A.M. Fjell, I.K. Amlien, L.T. Westlye, K.B. Walhovd, Mini-mental state examination is sensitive to brain atrophy in Alzheimer's disease, Dement. Geriatr. Cogn. Disord. 28 (2009) 252–258.
[16] J.H. Heo, S.T. Lee, C. Kon, H.J. Park, J.Y. Shim, M. Kim, White matter hyperintensities and cognitive dysfunction in Alzheimer disease, J. Geriatr. Psychiatry Neurol. 22 (2009) 207–212.
[17] D. Le Bihan, Looking into the functional architecture of the brain with diffusion MRI, Nat. Rev. Neurosci. 4 (2003) 469–480.
[18] J.M. Ringman, J. O'Neill, D. Geschwind, L. Medina, L.G. Apostolova, Y. Rodriguez, et al., Diffusion tensor imaging in preclinical and presymptomatic carriers of familial Alzheimer's disease mutations, Brain 130 (2007) 1767–1776.
[19] N.S. Ryan, S. Keihaninejad, T.J. Shakespeare, M. Lehmann, S.J. Crutch, I.B. Malone, et al., Magnetic resonance imaging evidence for presymptomatic change in thalamus and caudate in familial Alzheimer's disease, Brain 136 (2013) 1399–1414.
[20] J.M. Ringman, S.G. Younkin, D. Pratico, W. Seltzer, G.M. Cole, D.H. Geschwind, et al., Biochemical markers in persons with preclinical familial Alzheimer disease, Neurology 71 (2008) 85–92.
[21] M. Scholl, A. Wall, S. Thordardottir, D. Ferreira, N. Bogdanovic, B. Langstrom, et al., Low PiB PET retention in presence of pathologic CSF biomarkers in Arctic APP mutation carriers, Neurology 79 (2012) 229–236.
[22] R.J. Bateman, C. Xiong, T.L. Benzinger, A.M. Fagan, A. Goate, N.C. Fox, et al., Clinical and biomarker changes in dominantly inherited Alzheimer's disease, N. Engl. J. Med. 367 (2012) 795–804.
[23] W.E. Klunk, J.C. Price, C.A. Mathis, N.D. Tsopelas, B.J. Lopresti, S.K. Ziolko, et al., Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees, J. Neurosci. 27 (2007) 6174–6184.
[24] M. Bozzali, A. Cherubini, Diffusion tensor MRI to investigate dementias: a brief review, Magn. Reson. Imaging 25 (2007) 969–977.
[25] T.C. Chua, W. Wen, M.J. Slavin, P.S. Sachdev, Diffusion tensor imaging in mild cognitive impairment and Alzheimer's disease: a review, Curr. Opin. Neurol. 21 (2008) 83–92.
[26] D.A. Medina, M. Gaviria, Diffusion tensor imaging investigations in Alzheimer's disease: the resurgence of white matter compromise in the cortical dysfunction of the aging brain, Neuropsychiatr. Dis. Treat. 4 (2008) 737–742.
[27] F. Song, T.A. Sheldon, A.J. Sutton, K.R. Abrams, D.R. Jones, Methods for exploring heterogeneity in meta-analysis, Eval. Health Prof. 24 (2001) 126–151.
[28] M. Egger, G.D. Smith, A.N. Phillips, Meta-analysis: principles and procedures, BMJ 315 (1997) 1533–1537.
[29] S. O'Riordan, P. McMonagle, J.C. Janssen, N.C. Fox, M. Farrell, J. Collinge, et al., Presenilin-1 mutation (E280G), spastic paraparesis, and cranial MRI white-matter abnormalities, Neurology 59 (2002) 1108–1110.
[30] N.S. Ryan, G.J. Biessels, L. Kim, J.M. Nicholas, P.A. Barber, P. Walsh, et al., Genetic determinants of white matter hyperintensities and amyloid angiopathy in familial Alzheimer's disease, Neurobiol. Aging 36 (2015) 3140–3151.
[31] R. Sanchez-Valle, G.C. Monte, R. Sala-Llonch, B. Bosch, J. Fortea, A. Llado, et al., White matter abnormalities track disease progression in PSEN1 autosomal dominant alzheimer's disease, J. Alzheimers Dis. 51 (2016) 827–835.
[32] S. Lee, F. Viqar, M.E. Zimmerman, A. Narkhede, G. Tosto, T.L. Benzinger, et al., White matter hyperintensities are a core feature of Alzheimer's disease: evidence from the dominantly inherited Alzheimer network, Ann. Neurol. 79 (2016) 929–939.
[33] M.A. Parra, H. Saarimaki, M.E. Bastin, A.C. Londono, L. Pettit, F. Lopera, et al., Memory binding and white matter integrity in familial Alzheimer's disease, Brain 138 (2015) 1355–1369.
[34] J. Fortea, R. Sala-Llonch, D. Bartres-Faz, B. Bosch, A. Llado, N. Bargallo, et al., Increased cortical thickness and caudate volume precede atrophy in PSEN1 mutation carriers, J. Alzheimers Dis. 22 (2010) 909–922.
[35] X. Li, E. Westman, A.K. Stahlbom, S. Thordardottir, O. Almkvist, K. Blennow, et al., White matter changes in familial Alzheimer's disease, J. Intern. Med. 278 (2015) 211–218.
[36] M. Scholl, O. Almkvist, K. Axelman, E. Stefanova, A. Wall, E. Westman, et al., Glucose metabolism and PIB binding in carriers of a His163Tyr presenilin 1 mutation, Neurobiol. Aging 32 (2011) 1388–1399.
[37] M. Scholl, O. Almkvist, N. Bogdanovic, A. Wall, B. Langstrom, M. Viitanen, et al., Time course of glucose metabolism in relation to cognitive performance and postmortem neuropathology in Met146Val PSEN1 mutation carriers, J. Alzheimers Dis. 24 (2011) 495–506.
[38] A.S. Fleisher, K. Chen, Y.T. Quiroz, L.J. Jakimovich, M.G. Gomez, C.M. Langois, et al., Florbetapir PET analysis of amyloid-beta deposition in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional study, Lancet Neurol. 11 (2012) 1057–1065.
[39] L. Saint-Aubert, P. Payoux, D. Hannequin, E.J. Barbeau, D. Campion, M.B. Delisle, et al., MR, (18)F-FDG, and (18)F-AV45 PET correlate with AD PSEN1 original phenotype, Alzheimer Dis. Assoc. Disord. 27 (2013) 91–94.
[40] H. Shimada, [The DIAN study], Brain Nerve 65 (2013) 1179–1184.
[41] L. Hausner, J.A. Tschape, H.P. Schmitt, F. Hentschel, T. Hartmann, L. Frolich, Clinical characterization of a presenilin 1 mutation (F177S) in a family with very early-onset Alzheimer's disease in the third decade of life, Alzheimers Dement. 10 (2014) e27–39.
[42] S.K. Ting, T. Benzinger, V. Kepe, A. Fagan, G. Coppola, V. Porter, et al., A novel PSEN1 mutation (I238M) associated with early-onset Alzheimer's disease in an African-American woman, J. Alzheimers Dis. 40 (2014) 271–275.
[43] A.S. Fleisher, K. Chen, Y.T. Quiroz, L.J. Jakimovich, M. Gutierrez Gomez, C.M. Langois, et al., Associations between biomarkers and age in the presenilin 1 E280A autosomal dominant Alzheimer disease kindred: a cross-sectional study, JAMA Neurol. 72 (2015) 316–324.
[44] Z. Shi, Y. Wang, S. Liu, M. Liu, S. Liu, Y. Zhou, et al., Clinical and neuroimaging characterization of Chinese dementia patients with PSEN1 and PSEN2 mutations, Dement. Geriatr. Cogn. Disord. 39 (2015) 32–40.
[45] W.Y. Yau, D.L. Tudorascu, E.M. McDade, S. Ikonomovic, J.A. James, D. Minhas, et al., Longitudinal assessment of neuroimaging and clinical markers in autosomal dominant Alzheimer's disease: a prospective cohort study, Lancet Neurol. 14 (2015) 804–813.
[46] C.H. Lyoo, H. Cho, J.Y. Choi, M.S. Hwang, S.K. Hong, Y.J. Kim, et al., Tau accumulation in primary motor cortex of variant alzheimer's disease with spastic paraparesis, J. Alzheimers Dis. 51 (2016) 671–675.
[47] R. Smith, M. Wibom, T. Olsson, D. Hagerstrom, J. Jogi, G.D. Rabinovici, et al., Posterior accumulation of tau and concordant hypometabolism in an early-onset alzheimer's disease patient with Presenilin-1 mutation, J. Alzheimers Dis. 51 (2016) 339–343.
[48] E. Rodriguez-Vieitez, L. Saint-Aubert, S.F. Carter, O. Almkvist, K. Farid, M. Scholl, et al., Diverging longitudinal changes in astrocytosis and amyloid PET in autosomal dominant Alzheimer's disease, Brain 139 (2016) 922–936.
[49] A. Forsberg, H. Engler, O. Almkvist, G. Blomquist, G. Hagman, A. Wall, et al., PET imaging of amyloid deposition in patients with mild cognitive impairment, Neurobiol. Aging 29 (2008) 1456–1465.
[50] N.C. Fox, E.K. Warrington, P.A. Freeborough, P. Hartikainen, A.M. Kennedy, J.M. Stevens, et al., Presymptomatic hippocampal atrophy in Alzheimer's disease. A longitudinal MRI study, Brain 119 (Pt 6) (1996) 2001–2007.
[51] A. Fellgiebel, P. Wille, M.J. Muller, G. Winterer, A. Scheurich, G. Vucurevic, et al., Ultrastructural hippocampal and white matter alterations in mild cognitive impairment: a diffusion tensor imaging study, Dement. Geriatr. Cogn. Disord. 18 (2004) 101–108.
[52] M. Coleman, Axon degeneration mechanisms: commonality amid diversity, Nat. Rev. Neurosci. 6 (2005) 889–898.
[53] H. Braak, E. Braak, Diagnostic criteria for neuropathologic assessment of

Alzheimer's disease, Neurobiol. Aging 18 (1997) S85–88.
[54] B. Reisberg, E.H. Franssen, L.E. Souren, S.R. Auer, I. Akram, S. Kenowsky, Evidence and mechanisms of retrogenesis in Alzheimer's and other dementias: management and treatment import, Am. J. Alzheimers Dis. Other Demen. 17 (2002) 202–212.
[55] D.A. Loewenstein, W.W. Barker, J.Y. Chang, A. Apicella, F. Yoshii, P. Kothari, et al., Predominant left hemisphere metabolic dysfunction in dementia, Arch. Neurol. 46 (1989) 146–152.
[56] R.L. Buckner, A.Z. Snyder, B.J. Shannon, G. LaRossa, R. Sachs, A.F. Fotenos, et al., Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory, J. Neurosci. 25 (2005) 7709–7717.
[57] X. Li, T.Q. Li, N. Andreasen, M.K. Wiberg, E. Westman, L.O. Wahlund, The association between biomarkers in cerebrospinal fluid and structural changes in the brain in patients with Alzheimer's disease, J. Intern. Med. 275 (2014) 418–427.
[58] M. Sjobeck, E. Englund, Glial levels determine severity of white matter disease in Alzheimer's disease: a neuropathological study of glial changes, Neuropathol. Appl. Neurobiol. 29 (2003) 159–169.
[59] M.S. Fernando, J.T. O'Brien, R.H. Perry, P. English, G. Forster, W. McMeekin, et al., Comparison of the pathology of cerebral white matter with post-mortem magnetic resonance imaging (MRI) in the elderly brain, Neuropathol. Appl. Neurobiol. 30 (2004) 385–395.
[60] C.E. Sexton, C.E. Mackay, J.A. Lonie, M.E. Bastin, E. Terriere, R.E. O'Carroll, et al., MRI correlates of episodic memory in Alzheimer's disease, mild cognitive impairment, and healthy aging, Psychiatry Res. 184 (2010) 57–62.
[61] G.J. Lee, P.H. Lu, L.D. Medina, Y. Rodriguez-Agudelo, S. Melchor, G. Coppola, et al., Regional brain volume differences in symptomatic and presymptomatic carriers of familial Alzheimer's disease mutations, J. Neurol. Neurosurg. Psychiatry 84 (2013) 154–162.
[62] M.J. Firbank, A.M. Blamire, M.S. Krishnan, A. Teodorczuk, P. English, A. Gholkar, et al., Diffusion tensor imaging in dementia with Lewy bodies and Alzheimer's disease, Psychiatry Res. 155 (2007) 135–145.