Review Article
Clinical, Biological, and Imaging Features of Monogenic Alzheimer’s Disease

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The discovery of monogenic forms of Alzheimer’s Disease (AD) associated with mutations within PSEN1, PSEN2, and APP genes is giving a big contribution in the understanding of the underpinning mechanisms of this complex disorder. Compared with sporadic form, the phenotype associated with monogenic cases is somewhat broader including behavioural disturbances, epilepsy, myoclonus, and focal presentations. Structural and functional imaging show typical early changes also in presymptomatic monogenic carriers. Amyloid imaging and CSF tau/\(\beta\) ratio may be useful in the differential diagnosis with other neurodegenerative dementias, especially, in early onset cases. However, to date any specific biomarkers of different monogenic cases have been identified. Thus, in clinical practice, the early identification is often difficult, but the copresence of different elements could help in recognition. This review will focus on the clinical and instrumental markers useful for the very early identification of AD monogenic cases, pivotal in the development, and evaluation of disease-modifying therapy.

1. Introduction

Between 1991 and 1995 different families of early onset Alzheimer’s Disease (EOAD) have been linked to mutations within Presenilin (PSEN1, PSEN2) and Amyloid Precursor Protein (APP) genes [1–3]. The discovery of monogenic forms of Alzheimer’s Disease (AD) has allowed improved knowledge of the physiopathology which, in turn, has allowed the design of new therapeutic strategies. After 20 years of basic and clinical research, understanding the early phases of monogenic AD has become pivotal in order to develop and test the efficacy of the newest target-therapeutic approaches [4].

Even though most monogenic forms of AD have been described in familial early onset AD, recent findings suggest a wider spectrum of clinical presentation, including late-onset and sporadic forms. Indeed, monogenic AD might present a wide body of clinical symptoms beyond memory deficits, and the careful characterisation is key for a proper diagnosis in unclear cases.

The present review will focus on the clinical and instrumental markers that should be considered in the identification of different forms of monogenic AD.

2. Epidemiology

The incidence and distribution of different forms of early onset (or presenile, <65 years) dementia (EOD) are still the theme of controversy [5–7]. When considering neurodegenerative conditions, most of the studies showed AD as the most common aetiology in EOD [5, 7–10], although recent findings indicate that frontotemporal lobar degeneration (FTLD) may have a similar or even higher incidence at this age [11]. Also the relative contribution of PSEN1, PSEN2, and APP mutations to early onset Alzheimer’s Disease (EOAD) is the subject of considerable controversy, and mutation frequency is highly dependent upon the studied population [12–15].

PSEN1 mutations are considered as the major cause of familial AD, accounting for 18 to 55% of families ([12–14], http://www.molgen.ua.ac.be). The second most common monogenic form of Alzheimer’s Disease involves APP mutations and duplication, accounting for 2–18% and 8% of autosomal dominant early onset cases, respectively [12, 14, 16–18]. PSEN2 mutations are rare, with only 22 families reported so far (http://www.molgen.ua.ac.be).
3. Genes and Pathophysiology of Monogenic AD

Monogenic AD shares neuropathology features with sporadic AD. Neuronal and synapse loss, extracellular plaques composed of amyloid-β(Aβ) peptides, and intraneuronal neurofibrillary tangles consisting of hyperphosphorylated tau protein [19] are the specific features of the disease [20]. All mutations in Presenilins and APP genes lead to increased amyloidogenic processing of APP, causing the deposition of Aβ peptide, the primary component of amyloid plaques deposition [19, 21]. The APP gene has 18 exons and encodes an alternatively spliced transcript that, in its longest isoform, expresses a single transmembrane spanning polypeptide of 770 amino acids that is subject to at least two independent proteolytic pathways. The bulk of APP is cleaved by a-secretase within the Aβ-domain to produce a C-terminal fragment, which can be further cleaved intramembranously by γ-secretase to produce the peptide P3 and the transcriptionally active APP intracellular domain [22]. Alternatively, APP can be sequentially cleaved to produce Aβ peptide, which requires initial cleavage of APP by β-secretase, followed by γ-secretase cleavage [23] within the single-transmembrane domain. If cleavage occurs at residue 712–713, the most common short Aβ (Aβ1-40) results; if it is after residue 714, the longer Aβ42 is generated [24]. Aβ1-42 has a higher propensity to form aggregates and has been associated with AD pathology as component of extracellular amyloid plaques [19, 25, 26]. Presenilins with nicastrin, aph1, and pen2 are required for the stability and activity of the γ-secretase complex [27].

3.1. APP Mutations. Interestingly, most of APP mutations are located at the γ-secretase cleavage sites or the APP transmembrane domain on exons 16 and 17, influencing APP processing. The substitutions near the proteolytic sites lead to an overproduction of total amyloid-β or a shift in the Aβ1-40/Aβ1-42 ratio towards formation of the more toxic Aβ1-42 peptide. The substitutions within the APP transmembrane domain result in formation of amyloid-β with increased propensity for aggregation [26]. In addition to more frequent dominant APP mutations, two recessive mutations causing disease only in the homozygous state were identified: a trinucleotide deletion E693D segregating in one Japanese family proportionally decreased Aβ40 and Aβ42 with no change in their ratio [25] and A673V in one other Italian family [28]. Additionally, the mutation spectrum extended to APP locus duplications underscoring the importance of APP gene dosage in AD, already observed in the case of Down syndrome [29]. Duplicated APP regions containing several genes [16, 30] or APP only [17] have been clinically linked to early-onset AD often with extensive cerebral amyloid angiopathy [31].

The mutation A673T within APP was found to be protective against AD and age-related cognitive decline in a study in Iceland with the evidence of a 40% reduction in the formation of amyloidogenic peptides in vitro [32]. These findings are not completely understood, given the homozygous presence of the same A673T substitution in a very early onset AD in a single Italian family [28]. On the other side, Jonnson and colleagues identified three homozygous carriers of A673T in Icelandic samples, one of whom had died at age of 88, whereas the other two were currently living at age of 67 and 83, respectively, and none had a history of dementia [32].

3.2. PSEN1 and PSEN2 Mutations. PSENs are functionally involved in the γ-secretase-mediated proteolytic cleavage of APP [21]. Thus, mutations in PSENs result in an increased Aβ42/Aβ40 ratio, by either an increase in Aβ42 as shown in plasma and fibroblast media of PSEN mutation carriers [33] or by a decrease in Aβ40, suggesting a loss-of-function mechanism rather than a gain-of-function [34, 35]. PSEN1 and PSEN2 have important sequence homology also at the protein level [2].

PSEN1 gene consists of 12 exons that encode a 467-amino acid protein that is predicted to traverse the membrane six to ten times. The amino and carboxyl terminal are both oriented toward the cytoplasm. The majority of PSEN1 mutations are single-nucleotide substitutions, but small deletions and insertions have been described as well. At present, more than 200 different AD-related mutations have been identified, scattered over the protein with some clustering within the transmembrane domains and the hydrophilic loops surrounding these domains [13, 36, 37].

PSEN2 has 12 exons and is organized into ten translated exons that encode a 448-amino acid protein. The PSEN2 protein is predicted to consist of nine transmembrane domains and a large loop structure between the sixth and seventh domain and also displays tissue-specific alternative splicing [38]. The mechanism by which PSEN2 increases Aβ generation in the brains of AD patients remains to be clarified. A recent study found that mutant PSEN2 increases β-secretase activity through reactive oxygen species-dependent activation of extracellular signal regulated kinase [39].

4. Clinical Features of Monogenic AD

In broad terms, the clinical presentation of monogenic AD is similar to that of sporadic AD. However, the phenotype associated with monogenic AD is somewhat broader than what is typically seen in sporadic AD. Moreover, neurologic signs and symptoms appear to be more common in monogenic AD as compared to sporadic forms. The copresence of different elements could help in recognition in clinical practice [37].

4.1. Age at Onset and Survival. Overall, monogenic AD usually has an earlier age at disease onset. The youngest age at onset has been described for PSEN1 mutations; symptoms typically first appear between the age of 30 and 50, but some mutations have been associated with earlier onset [40]. PSEN1 mutations show almost complete penetrance by the age of 60, with some exceptions (Table I). The causes of variability of age at onset are neither clear nor completely explained by genetic factors [41, 42] or by the biochemical abnormalities of Aβ ratio due to the mutations [34]. APP pedigrees tend to have an older age at onset, typically in the 50s and ranging
Table 1: Atypical presentation of different PSEN1, PSEN2, and APP mutations.

| Clinical phenotype | Mutations | Differential diagnosis |
|--------------------|-----------|------------------------|
| Very early onset (<30y) | PSEN1 L85P PI17L PI17S LI66P SI69L M233L M233V L235P Y256S V272A A434C P436Q G206V | GE, MD, SD, PWMD, HD |
| Late onset (>65y) | PSEN1 Uncommon, A79V M139V I43F H163R H163Y A231V K239N L271V E273A R377W C410Y | Sporadic AD, FTD, LB, Va, CJD |
| Behavioral or psychiatric symptoms | PSEN1 Possible for all mutations, especially M239I and M239V | bvFTD, LBD, HD, WE, CJD |
| “Pure” frontotemporal presentation | APP Rare at presentation D694N A713T | |
| Prominent aphasia | PSEN1 E120D H163R H163Y L166R G206V L235R A246E L250S A260V L262F P264L R278I E280A R377W L392V A431E A434C L435F | Sporadic PPA (svPPA, lvPPA, avPPA) FTD-MND, CJD |
| Epileptic seizures | PSEN1 Possible as first presentation; L113P P117Q intron4insTAC P117L E120D E120G N135S M139V I43T M146L H163P H163Y L166R S169L S169P S170F E184D G206D G206V Q222H M233T M233V P237I A246E L250V A260V P264L R269G R269H E280A E280G L282R L282V L282V A377W L392V L420R L424P A434C | GE, SD, MD, AE, CJD |
| Myoclonus | PSEN1 L113P 4insTAC P117R M139V I43T M146L M146V L153V H163P H163Y L166R S169L S169P S170F E184D G206D G206V Q222H M233T M233V P237I A246E L250V A260V P264L R269H R269G E280A L282V L392V C410Y A434C | CBS, MD, GE, CJD |
| Parkinsonism, dystonia, or apraxia | PSEN1 C92S F105L L113P P117R E120D N135D M139V M146L M146V H163P H163Y L166R S169L S169P S170F E184D I202F G206A G206V G217D M233L M233T M233V P237I L250S Y256S G266S V272A R278I E280A P284L L286V A377W L392V C410Y A431E L435F A434C | CBS, LBD, PSP, FTD, CJD |
| Spastic paraparesis | PSEN1 ΔI83/M84, L85P N135S Y154N InsFI L166P G217D P237I V261F V261L P264L P264V G266S L271V R278K R278S R278T E280G E280Q P284L P284S L286R A377W L392V A431E L435F P436Q | HSP, Va, PWMD, MND, CJD |
| Cerebellar ataxia | PSEN1 P117A N135S M139V I43T H163P L166P S169L S170F Y256S E280A L282V P436Q | CJD, SCA, MSA-C, PNS |
| Leukoencephalopathy | APP D694N A713T | VaD, PWMD, DD, V |
| CAA with or without ICH | PSEN1 Rare ΔE4 V89L 4insTAC E184D C217D L271V V272A E280G L282V S290C N405S Δ440 | Sporadic CAA, monogenic CAA (CYST C, TTR, ITM2B, PRNP mutations) |
| APP | Rare R717 N411l | |
| Open present also without cognitive impairment A692G E693Q E693G E693K D694N A713T APP duplication | |

Abbreviations: AD: Alzheimer’s Disease, AE: autoimmune encephalitis, APP: Amyloid Precursor Protein gene, avPPA: agrammatic variant of primary progressive aphasia, bvFTD: behavioural variant of frontotemporal dementia, CAA: cerebral amyloid angiopathy, CBS: corticobasal syndrome, CJD: Creutzfeldt-Jacob Disease, CYST C: Cystatin C gene, DD: demyelinating Disease, FTD: frontotemporal dementia, GE: genetic epilepsy HD: Huntington’s Disease, HSP: hereditary spastic paraplegia, ITM2B: integral membrane protein 2B gene, LB: Lewy Bodies Dementia, lvPPA: logopenic variant of primary progressive Aphasia, MD: Mitochondrial Disease, MND: Motor-neuron Disease, MSA-C: cerebellar form of multisystem atrophy, PNS: paraneoplastic syndromes, PRNP: prion protein gene, PSEN1: Presenilin 1 gene, PSEN2: Presenilin 2 gene, PSP: progressive supranuclear palsy, PWMD: progressive white matter disease, SCA: spino cerebellar ataxia, SD: storage disorders, svPPA: semantic variant of primary progressive Aphasia, TTR: Transthyretin gene, VaD: Vascular dementia, V: Vasculitis, WE: Wernicke encephalopathy.
from 45 to 60 years old. The rarer PSEN2 mutations have the widest range of onset with some late-onset cases [43], and the incomplete penetrance has been postulated.

Overall survival in monogenic AD is similar to sporadic disease with an average of 6–9 years from diagnosis, with the caveat that survival in elderly sporadic individuals tends to be lower. The different age at onset does not influence the disease duration, and, in general, PSEN1 mutation carriers may have slightly shorter survival.

4.3. Myoclonus and Seizures. In monogenic AD, the frequency of myoclonus increases with the duration of illness. All monogenic AD forms have been associated with the presence of myoclonus, and some PSEN1 variations have been linked to the early presentation of this sign. Several reports also suggest myoclonus as a harbinger of the more common seizures.

Seizures could represent the first presentation in many cases of monogenic AD, especially, for PSEN1 mutations. In clinical practice, in early-onset cases, it could be difficult to differentiate autosomal dominant AD from genetic epilepsy or storage disorder such as neuronal ceroidlipofuscinosis [55]. Some PSEN1 mutations have been identified in cases with prominent epilepsy at presentation (see Table 1). Seizures are very common in APP duplication and Down syndrome that have an extra copy of APP, thus reflecting a possible link between Aβ dosage and epilepsy [56]. It has been shown in experimental animals that amyloid β-peptides may induce neuronal hyperexcitability and trigger progressive epilepsy [57]. Myoclonus and seizures have not been reported in a few PSEN1, PSEN2, and APP mutations, but this absence may simply reflect restricted duration of follow-up.

4.4. Other Neurological-Associated Signs or Symptoms. PSEN1 phenotypes also include extrapyramidal, pyramidal, or cerebellar isolated presentation, rarer in PSEN2 or APP-mutated patients (Table 1). However, prominent parkinsonism associated with dementia and visual hallucinations fulfilling diagnostic criteria for Lewy Body Dementia (LBD) have been only rarely associated with PSEN1 and PSEN2 mutations [40, 58, 59].

Spastic paraparesis associated with memory complaints has been also associated with certain PSEN1 mutations [60]. The neuropathological correlate is often the presence of “cotton wool plaques”, consisting of Aβ deposits with a lack of amyloid in the core and poor neuritic and glial response [61].

Cerebellar ataxia or gaze-evoked nystagmus has been only noted occasionally in PSEN1 mutations carriers. In PSEN2 and APP cases, pyramidal or cerebellar neurological signs could be present but not representing the onset symptom.

4.5. Intracerebral Hemorrhages and Cerebral Amyloid Angiopathy. Cerebral amyloid angiopathy (CAA) is a generic morphological term describing the pathological changes occurring in cerebral blood vessels resulting from deposition of amyloid proteins of different origins. The most severe clinical consequence of CAA is cerebral haemorrhage, and according to autopsy series, 12 to 25% of all cerebral haemorrhages in the elderly are due to CAA [62, 63].

The first mutation described in the APP gene was found within the Aβ region in a family with autosomal form of CAA [64]. In this condition, cerebral haemorrhage was fatal in about two thirds of patients, whilst the one third developed multiple strokes resulting in dementia of vascular type [65]. In 2006, the duplication of APP was also associated with a clinical phenotype characterised by a progressive dementia of AD type associated with CAA [17, 30, 31]. Substitution and duplication of APP gene have been also associated with variable white matter abnormalities up to severe leukoencephalopathy.

If CAA and cerebral haemorrhage are the key features of APP monogenic AD, their presence is only rarely associated with PSEN1 or PSEN2 phenotypes (Table 1).

5. Neuroimaging Features of Monogenic AD

It is well established that in sporadic AD the brain regions early and more severely affected are the medial temporal lobes, especially, the hippocampus and entorhinal cortex, the posterior portion of the cingulate gyrus, and the precuneus [66, 67]. In monogenic AD, several reports showed a similar atrophy pattern with a slight more severe medial-temporal lobe atrophy compared with sporadic AD [68]. Gray matter regional volume loss and decreases in magnetization transfer ratio have also been reported in mildly symptomatic carriers [69]. Additionally, it has been well established that in early
onset AD, hippocampus may not always be involved as in the typical atrophy in monogenic forms compared with sporadic late onset cases [68, 70, 71]. APP mutations seem to be more associated with hippocampal atrophy, whereas PSEN1 mutation carriers have more general neocortical involvement and a prominent frontotemporal atrophy [68, 72]. However, the high heterogeneity of phenotype-genotype correlation in monogenic AD, it would be difficult to find a definitive structural biomarker specific and different for PSEN1, PSEN2, or APP.

Interestingly, as previously reported, certain mutations within APP genes presented leukoencephalopathy that should be evaluated on MRI in order to exclude a possible influence of white matter lesions on cognitive decline [73]. In suspected cerebral amyloid angiopathy, an MRI with gradient echo sequences should be performed to show the presence of cerebral microbleeds (or microhaemorrhages), visualized as small, rounded, dot-like lesions of low signal intensity in the T2*-weighted images [74]. Susceptibility-weighted imaging has considerably increased microbleed detection rates compared with gradient echo sequences [75] although the sensitivity to detect microbleeds is also dependent on slice thickness and magnetic field strength. Microbleeds in deep brain regions are most likely to be associated with vasculopathy owing to hypertension, whilst their distribution is mostly lobar in specific disorders such as sporadic cerebral amyloid angiopathy [76].

In atypical monogenic AD phenotypes, such as epileptic, paraparetic, or ataxic variants, MRI is also essential to distinguish AD from storage or mitochondrial disorders [77], Creutzfeldt-Jacob Disease (CJD) [78], or other specific forms [79].

Along with structural imaging, cerebral blood flow SPECT (single-photon emission computer tomography) and brain FDG-PET (fluodeoxyglucose Positron emission tomography) scans in monogenic AD patients show predominant hypoperfusion or reduced glucose metabolism in the temporoparietal regions, including the precuneus and the posterior cingulate cortex, a pattern similar of sporadic AD [80]. However, as outlined in the clinical section, many autosomal dominant cases showed an extended phenotype involving also frontal and prefrontal areas, and cases with pure frontotemporal hypoperfusion pattern have been reported [51, 52].

Only few studies compared the ability of SPECT and FDG-PET to discriminate AD from other dementia. FDG-PET revealed to have higher sensitivity and specificity if compared to SPECT [81, 82]. In atypical focal monogenic AD functional neuroimaging reflects the topographical distribution of neurodegeneration and not the underlying pathology. Thus the role of SPECT and FDG-PET is still controversial.

5.1. Amyloid Imaging. More recently, PET amyloid imaging studies with Pittsburgh Compound B (PiB) have revealed evidence of fibrillar Aβ deposition in monogenic AD, including carriers who were up to 10 years younger than the age of onset for their family [83]. Interestingly, these studies have consistently reported elevated levels of PiB retention in the striatum of presymptomatic monogenic AD individuals, which occurs more variably in late-onset sporadic AD [47].

Amyloid imaging such as 11C-PiB PET has very high (90% or greater) sensitivity for AD although the specificity decreases with aging [84]. The amyloid imaging tracers flutemetamol, florbetapir, and florbetaben labelled with 18F demonstrated good accuracy for distinguishing patients with AD from other tauopathies or TDP-43 pathologies [83, 85–87]. Amyloid tracer binding is diffuse and symmetrical, with high uptake consistently found in the prefrontal cortex, precuneus, and posterior cingulate cortex, followed by the lateral parietal, lateral temporal cortex, and striatum.

Another important role of amyloid imaging will be the differential diagnosis of intracranial haemorrhage caused by small vessel disease or cerebral amyloid angiopathy, the last showing positive scans.

6. Cerebrospinal Fluid and Blood Biomarkers

In the assessment of a presenile or atypical dementia, cerebrospinal fluid (CSF) should be performed in order to exclude other mimicking diseases. In monogenic AD, multiple groups have reported that CSF Aβ42 is reduced to approximately one-half of normal values [88], a finding remarkably similar to sporadic AD [89]. While decreased Aβ42 appears to have remarkable specificity for pathologic AD and Aβ amyloidosis in the brain [90], CSF Aβ40 is not consistently different in AD individuals compared with normal individuals. However some PSEN1 mutations have been also associated with increased Aβ42 production reflected also in CSF, thus altering the paradigm of a low Aβ42 in all AD forms [91]. CSF tau and phosphotaulevels are increased almost two-fold in monogenic AD individuals compared with controls [88], again mimicking the CSF profile in later onset sporadic AD.

In clinical practice, CSF Tau/Aβ42 ratio may reflect the underlying pathology also in focal atypical presentation such as corticobasal degeneration [92], bvFTD [53] or primary progressive aphasia [93]. As for amyloid imaging, in early-onset cases in which a copathology with AD is very rare, CSF analysis should be performed, and it has a higher specificity value.

Increased plasma Aβ42 has been consistently found in monogenic AD [47, 91], while there is little, if any, consistently reported difference in sporadic AD [94].

The use of new genetic detecting methods, such as next generation sequencing, will probably change the scenario of presenile dementia genetics. A recent screening for 16 different dementia disease genes proposed by Beck et al. [95] at UCL showed a great sensitivity (82%) and specificity (100%) in detecting pathogenic alterations compared with normal methods. Interestingly, APP duplication could be missed also with these new approaches, underlying the importance of a right clinical selection of these cases [95].

Gene expression analysis in monogenic forms may also help in the identification of early serum biomarkers [96], as already demonstrated for other forms of dementia [97].
7. Presymptomatic at-Risk Subjects

Several series of presymptomatic mutation carriers have been studied in order to elucidate the very early phases of monogenic AD. Owing to the geographically dispersed nature of monogenic AD families and the relative rarity of the disease, an international network of research centres has been established, formally known as the Dominantly Inherited Alzheimer’s Network [DIAN]. In 2012, the first DIAN report confirmed that changes begin in the brain about 25 years before expected symptom onset with the decline in Aβ42 concentrations in the CSF in mutation carriers, as compared with noncarriers [47]. Aβ42 deposition as measured by PIB-PET was detected at least 15 years before expected symptom onset [98]. Increases in levels of tau in the CSF and in brain atrophy were detected approximately 15 years before expected symptom onset, followed by cerebral hypometabolism and impaired episodic memory approximately 10 years before expected symptom onset and global cognitive impairment starting at 5 years before expected symptom onset.

Longitudinal structural imaging studies have demonstrated alterations in white matter structure in presymptomatic and early symptomatic carriers, with decreased fractional anisotropy in the fornix and widespread areas of brain visualized with diffusion tensor imaging [99]. Several neuroimaging studies showed that even before the bilateral hippocampal atrophy, presymptomatic mutation carriers have an increase caudate size [100] and early thalamus involvement [101]. The grey matter atrophy may be not restricted to hippocampus but also to other cortical areas, especially, precuneus, parietal, or frontal brain regions [71,102]. A recent DIAN study on more than 100 presymptomatic and symptomatic carriers confirmed the early thalamus involvement and showed white matter atrophy in the cingulum and fornix [103]. Functional connectivity has also recently showed the early disruption of the default mode network in monogenic AD even before the symptoms presentations [104].

8. Conclusions

The wide spectrum of presentation of monogenic AD leads often to late diagnosis or misidentification of cases. The memory impairment, still essential for the new revised research criteria in association with CSF or imaging biomarkers for the diagnosis of AD [105], is not always the prominent early deficit. Behavioural disturbances, epilepsy, myoclonus, or CAA (specific for APP mutations) may help in addressing diagnosis. However, structural or functional neuroimaging is more consistent with focal phenotypes than the AD pathology. Thus, CSF or amyloid imaging may be useful in the differential diagnosis with other neurodegenerative dementias, especially in early onset cases, but these biomarkers cannot be considered specific for the different involved genes.

In cases suggestive for autosomal dominant AD, we suggested a screening of PSEN1 mutation first, followed by APP and PSEN2 mutations on the basis of epidemiological data, but new specific biomarkers driving genetic screening are warranted. Since more than 20 years, the study of familial forms is giving a big contribution in the understanding of the underpinning mechanisms of AD and possible target approaches. Thus, a very early identification of monogenic cases is pivotal in the development and evaluation of disease-modifying therapy needed also in the most common sporadic form.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

[1] A. Goate, M.-C. Chartier-Harlin, M. Mullan et al., “Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer’s disease,” Nature, vol. 349, no. 6311, pp. 704–706, 1991.
[2] E. I. Rogaev, R. Sherrington, E. A. Rogaeva 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, vol. 376, no. 6543, pp. 775–778, 1995.
[3] R. Sherrington, E. I. Rogaev, Y. Liang et al., “Cloning of a gene bearing missense mutations in early-onset familial Alzheimer’s disease,” Nature, vol. 375, no. 6543, pp. 754–760, 1995.
[4] R. J. Bateman, P. S. Aisen, B. De Strooper et al., “Autosomal-dominant Alzheimer’s disease: a review and proposal for the prevention of Alzheimer’s disease,” Alzheimer’s Research and Therapy, vol. 3, no. 1, article 1, 2011.
[5] R. J. Harvey, M. Skelton-Robinson, and M. N. Rossor, “The prevalence and causes of dementia in people under the age of 65 years,” Journal of Neurology, Neurosurgery and Psychiatry, vol. 74, no. 9, pp. 1206–1209, 2003.
[6] C. Ikejima, F. Yasuno, K. Mizukami, M. Sasaki, S. Tanimukai, and T. Asada, “Prevalence and causes of early-onset dementia in Japan: a population-based study,” Stroke, vol. 40, no. 8, pp. 2709–2714, 2009.
[7] J. Garre-Olmo, D. Genis Batlle, M. Del Mar Fernández et al., “Incidence and subtypes of early-onset dementia in a geographically defined general population,” Neurology, vol. 75, no. 14, pp. 1249–1255, 2010.
[8] O. Yokota, K. Sasaki, Y. Fujisawa et al., “Frequency of early and late-onset dementias in a Japanese memory disorders clinic,” European Journal of Neurology, vol. 12, no. 10, pp. 782–790, 2005.
[9] L. Mercy, J. R. Hodges, K. Dawson, R. A. Barker, and C. Brayne, “Incidence of early-onset dementias in Cambridgeshire, United Kingdom,” Neurology, vol. 71, no. 19, pp. 1496–1499, 2008.
[10] S. G. Papageorgiou, T. Kontaxis, A. Bonakis, N. Kalfakis, and D. Vassilopoulos, “Frequency and causes of early-onset dementia in a tertiary referral center in Athens,” Alzheimer Disease and Associated Disorders, vol. 23, no. 4, pp. 347–351, 2009.
[11] B. Borroni, A. Alberici, M. Grassi et al., “Prevalence and demographic features of early-onset neurodegenerative dementia in Brescia County, Italy,” Alzheimer Disease and Associated Disorders, vol. 25, no. 4, pp. 341–344, 2011.
[12] D. Campion, C. Dumanchin, D. Hannequin et al., “Early-onset autosomal dominant Alzheimer disease: prevalence, genetic heterogeneity, and mutation spectrum,” American Journal of Human Genetics, vol. 65, no. 3, pp. 664–670, 1999.
[13] M. Cruts, C. M. Van Duijn, H. Backhovens et al., “Estimation of the genetic contribution of presenilin-1 and -2 mutations
in a population-based study of presenile Alzheimer disease,” *Human Molecular Genetics*, vol. 7, no. 1, pp. 43–51, 1998.

[14] J. C. Janssen, J. A. Beck, T. A. Campbell et al., “Early onset familial Alzheimer’s disease: mutation frequency in 31 families,” *Neurology*, vol. 60, no. 2, pp. 235–239, 2003.

[15] G. Raux, L. Guyant-Maréchal, C. Martin et al., “Molecular diagnosis of autosomal dominant early onset Alzheimer’s disease: an update,” *Journal of Medical Genetics*, vol. 42, no. 10, pp. 793–795, 2005.

[16] K. Kasuga, T. Shimohata, A. Nishimura et al., “Identification of independent APP locus duplication in Japanese patients with early-onset Alzheimer disease,” *Journal of Neurology, Neurosurgery and Psychiatry*, vol. 80, no. 9, pp. 1050–1052, 2009.

[17] K. Sleegers, N. Brouwers, I. Gijselinck et al., “A new amyloid-β-protein similar to that in the senile plaques of Alzheimer’s disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer’s disease,” *Nature Medicine*, vol. 2, no. 8, pp. 864–870, 1996.

[18] S. Kumar-Singh, J. Theuns, B. Van Broeck et al., “Mean age-of-onset of familial Alzheimer disease caused by presenilin mutations correlates with both increased Ap42 and decreased Ap40,” *Human Mutation*, vol. 27, no. 7, pp. 686–695, 2006.

[19] M. Bentahir, O. Nyabi, J. Verhamme et al., “Presenilin clinical mutations can affect γ-secretase activity by different mechanisms,” *Journal of Neurochemistry*, vol. 96, no. 3, pp. 732–742, 2006.

[20] A. J. Larner and M. Doran, “Clinical phenotypic heterogeneity of Alzheimer’s disease associated with mutations of the presenilin-1 gene,” *Journal of Neurology*, vol. 253, no. 2, pp. 139–158, 2006.

[21] A. J. Larner, “Presenilin-1 mutations in Alzheimer’s disease: an update on genotype-phenotype relationships,” *Journal of Alzheimer’s Disease*, vol. 37, no. 4, pp. 653–659, 2013.

[22] W. T. Kimberly, M. J. LaVoie, B. L. Ostaszewski, W. Y. E. S. Wolfe, and D. J. Selkoe, “γ-Secretase is a membrane protein complex comprised of presenilin, nicastrin, aph-1, and pen-2,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 11, pp. 6382–6387, 2003.

[23] M. H. Park, D. Y. Choi, H. W. Jin et al., “Mutant presenilin 2 increases β-secretase activity through reactive oxygen species-dependent activation of extracellular signal-regulated kinase,” *Journal of Neuropathology and Experimental Neurology*, vol. 71, no. 2, pp. 130–139, 2012.

[24] B. J. Snider, J. Norton, M. A. Coats et al., “Novel presenilin 1 mutation (S170F) causing Alzheimer disease with lewy bodies in the third decade of life,” *Archives of Neurology*, vol. 62, no. 12, pp. 1821–1830, 2005.

[25] P. Pastor, C. M. Roe, A. Villegas et al., “Apolipoprotein E4 modifies Alzheimer’s disease onset in an E280A PS1 kindred,” *Annals of Neurology*, vol. 54, no. 2, pp. 163–169, 2003.

[26] L. Bernardi, M. Gallo, M. Anfossi et al., “Role of TOMM40 rs10524523 polymorphism in onset of Alzheimer’s disease caused by the PSEN1 M146L mutation,” *Journal of Alzheimer’s Disease*, vol. 37, pp. 285–289, 2013.

[27] T. D. Bird, E. Levy-Lahad, P. Poorakaj et al., “Wide range in age of onset for chromosome 1-related familial Alzheimer’s disease,” *Annals of Neurology*, vol. 40, no. 6, pp. 933–936, 1996.

[28] E. K. Warrington, S. K. Agnew, A. M. Kennedy, and M. N. Rossor, “Neuropsychological profiles of familial Alzheimer’s disease associated with mutations in the presenilin 1 and amyloid precursor protein genes,” *Journal of Neurology*, vol. 248, no. 1, pp. 45–50, 2001.

[29] A. K. Godbolt, L. Cipolotti, H. Watt, N. C. Fox, J. C. Janssen, and M. N. Rossor, “The natural history of Alzheimer disease:
a longitudinal presymptomatic and symptomatic study of a familial cohort,” *Archives of Neurology*, vol. 61, no. 11, pp. 1743–1748, 2004.

[46] N. C. Fox, E. K. Warrington, A. L. Seiffer, S. K. Agnew, and M. N. Rossor, “Presymptomatic cognitive deficits in individuals at risk of familial Alzheimer’s disease. A longitudinal prospective study,” *Brain*, vol. 121, no. 9, pp. 1631–1639, 1998.

[47] R. J. Bateman, C. Xiong, T. L. Benzinger et al., “Clinical and biomarker changes in dominantly inherited Alzheimer’s disease,” *The New England Journal of Medicine*, vol. 367, pp. 795–804, 2012.

[48] A. Ardila, F. Lopera, M. Rosselli et al., “Neuropsychological profile of a large kindred with familial Alzheimer’s disease caused by the E280A single presenilin-1 mutation,” *Archives of Clinical Neuropsychology*, vol. 15, no. 6, pp. 515–528, 2000.

[49] A. Jimenez-Escrig, A. Rabano, C. Guerrero et al., “New V272A presenilin 1 mutation with very early onset subcortical dementia and parkinsonism,” *European Journal of Neurology*, vol. 11, no. 10, pp. 663–669, 2004.

[50] E. J. Sitek, E. Narozanska, B. Peplonska et al., “A patient with posterior cortical atrophy possesses a novel mutation in the presenilin 1 gene,” *PloS ONE*, vol. 8, Article ID e61074, 2013.

[51] R. J. Ellis, J. M. Olichney, L. J. Thal et al., “Cerebral amyloid angiopathy with susceptibility-weighted imaging,” *The Lancet*, vol. 358, no. 9277, pp. 925–932, 2009.

[52] F. Fazekas, R. Kleinert, G. Roob et al., “Histopathological analysis of foci of signal loss on gradient-echo T2-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds,” *American Journal of Neuroradiology*, vol. 20, no. 4, pp. 637–642, 1999.

[53] E. M. Haacke, Z. S. DelProposto, S. Chaturvedi et al., “Imaging cerebral amyloid angiopathy with susceptibility-weighted imaging,” *American Journal of Neuroradiology*, vol. 28, no. 2, pp. 316–317, 2007.

[54] R. I. Scahill, G. R. Ridgway, J. W. Bartlett et al., “Genetic influences on atrophy patterns in familial Alzheimer’s disease: a comparison of APP and PSEN1 mutations,” *Journal of Alzheimer’s Disease*, vol. 35, pp. 199–212, 2013.

[55] P. B. Gorelick, A. Scuteri, S. E. Black et al., “Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association,” *Stroke*, vol. 42, no. 9, pp. 2672–2713, 2011.

[56] F. Fazekas, R. Kleinert, G. Roob et al., “Histopathologic analysis of foci of signal loss on gradient-echo T2-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds,” *American Journal of Neuroradiology*, vol. 20, no. 4, pp. 637–642, 1999.
