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Epileptic seizures in autosomal dominant forms of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a heterogeneous neurodegenerative disorder and represents the most common form of dementia in the elderly. Mutations in genes encoding presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*) and amyloid precursor protein (*APP*) are responsible for early-onset familial AD (EOFAD).

Several pieces of evidence report that patients with rare autosomal dominant forms of AD carry a significant risk to develop seizures. However, the molecular mechanisms linking epilepsy and AD are needed to be clarified: the pathophysiology of seizures in AD may be related to an increased production of amyloid-β (Aβ) peptide or structural alterations in neurons probably due to cerebrovascular changes, neurotransmitter or cytoskeletal dysfunctions. Seizures have traditionally been related to neuronal loss in the late stages of AD as a consequence of neurodegeneration, however, recent studies indicated that seizures may contribute to the emergence of AD symptoms in early stages of the disease, mainly in familial AD. So, a better understanding of possible common neural mechanisms might help to improve the clinical management of both conditions.

This review aims to give a comprehensive overview and to analyze the association between epilepsy and EOFAD, focusing on possible overlapping pathological mechanisms.

1. Introduction

Alzheimer's disease (AD; MIM#104300) is the most common form of neurodegenerative disorder occurring predominantly in later life with complex etiology and a strong genetic component [1]. AD is a devastating progressive disease characterized by memory loss, confusion, thinking difficulty and changes in behavior, personality and language. The definitive diagnosis of AD is only possible by post-mortem histopathology examination of the intraneuronal presence of neurofibrillary tangles (NFTs), composed of highly phosphorylated forms of the microtubule-associated protein tau, and plaques constituted by the amyloid-β (Aβ) peptide. Both NFTs and senile plaques lead to the activation of microglia and astrocytes, found in the regions that are significantly affected by synapse loss and neuronal death. AD has a sporadic age of occurrence with an onset typically beginning at 65 years and older. The early-onset familial AD (EOFAD) shows an autosomal dominant pattern of inheritance and accounting for approximately 0.5% of all AD cases; it has an age at onset under the 65 years in individuals with a positive family history in at least three generations. About 50% of the EOFAD patients carry mutations in one of three genes, namely *PSEN1*, *PSEN2* and *APP*, encoding the presenilin 1, presenilin 2 and Aβ precursor protein, respectively [2]. All the mutations in these genes lead to an increased amyloidogenic processing of APP, resulting in the production or aggregation of Aβ peptide. Mutations in *PSEN1* gene represent the major cause of familial AD, accounting for about 50% of EOFAD cases with 480 families identified so far [3].

Several studies pointed out that AD has been associated with a high risk to develop epileptic seizures [4]. In these patients, seizures might be the result of alterations in the inhibitory-excitatory systems, even if their causes are not still entirely understood [5,6]. The relationship between AD and epilepsy is even stronger in EOFAD [7], due to the presence of genetic mutations. In a human *APP* mouse model, the transgenic mouse with high levels of Aβ in the brain develop spontaneous non-convulsive seizure activity in the cortical and hippocampal networks, even in the absence of neurodegeneration [8]. These observations suggest that seizure activity may be considered as an integral part of the damaged neuronal networks in AD brain, contributing in this fashion to the cognitive decline. Moreover, the structural alterations due to tau pathology (such as aberrant neuronal sprouting and loss of synaptic contacts) may promote to the development of recurrent hypersynchronous discharges of seizure activity. Along with Aβ

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deposition, phosphorylated tau overexpression has also been found in epileptic patients and in the animal models of epilepsy [9].

In addition to these above considerations, in the early stages of AD, intracellular NFTs, extracellular Aβ deposits and dystrophic neurites are essentially found in the hippocampus and the entorhinal cortex, which represent the key regions of memory and learning [10]. These networks are among the most epileptogenic formations of the brain and are also strongly involved in temporal lobe epilepsy (TLE), a type of epilepsy involving the temporal lobe, a region that is critical to memory and influences behavior [4].

Seizure activity in AD has been widely thought as a secondary process caused by the late stage of neurodegeneration, perhaps in combination with other age-related factors. However, recent evidences both in mouse and in humans reported that seizures may occur early in the development of AD, mainly in the familial patients. In this case, the possibility has been raised that an abnormal excitatory activity in neurons might represent a primary upstream mechanism contributing to the cognitive impairment in these mouse models [11].

2. Epileptic seizures in familial Alzheimer's disease

As mentioned above, EOFAD is linked either to point mutations or indels within *PSEN1*, *PSEN2* and *APP* or to duplications of *APP* gene. From a clinical point of view, while most of them cause typical AD phenotype, others are associated with atypical presentation, such as early myoclonic epilepsy [12].

Genetics factors strongly influenced the prevalence of seizures in AD: epilepsy in EOFAD patients occurred several times more often than in sporadic ones [7]. Moreover, a recent study performed on a large cohort of EOFAD patients reported that seizures occurred in 47.7% of individuals harboring a mutation in these responsible genes [13].

Several hypotheses have been proposed to explain why seizures are frequent in EOFAD. In transgenic mice overexpressing *APP* gene, it has been demonstrated that high levels of Aβ disrupted neuronal activity by damaging synaptic neurotransmission (Fig. 1). This could lead to increased excitability, an aberrant synchronization of neuronal network and seizures [14,15]. Other authors reported that Aβ levels modulated the postsynaptic transmission and the presynaptic efficacy, that in turn may generate the epileptiform activity [16].

2.1. PSEN1 and PSEN2 mutations

As reported in Table 1, about sixty mutations in *PSEN1* and three in *PSEN2* have been found to be associated with epilepsy [13,17–21]. Regarding *PSEN1*, epilepsy-associated mutations are spread throughout the gene. Among them, some authors reported that patients harboring mutations within the domains of the protein hydrophilic I (HL-I), transmembrane II (TM-II), TM-III, TM-IV and TM-V showed a higher risk in seizure frequency, as compared to other domains, indicating a strong correlation between causative mutations and seizure [13]. A possible explanation could be the fact that these critical regions affect the conformational structure of the protein and are implicated in its endoproteolysis or PSEN1-substrate activity [22]. Mutations or deletions of *PSEN1* were found to decrease the threshold of seizure and thus increase excitability [19].

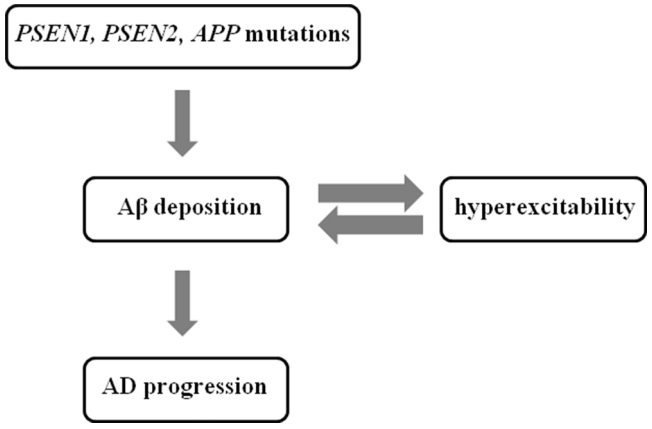

Fig. 1. Potential self-amplifying neurodegenerative cascade leading to AD progression and hyperexcitability.

Table 1
PSEN1, *PSEN2*, *APP* mutations associated with epileptic seizures by exon, domain and, mutation type.

Gene	Exon	Mutation type	Domain	Mutation
PSEN1	4	missense	HL-I	p.Leu113Pro, p.Leu113Gln
	intron 4	deletion	HL-I	g.2304delG (intron4insTAC)
	5	missense	HL-I	p.Tyr115Cys, p.Tyr115His
	5	missense	HL-I	p.Thr116Ile
	5	missense	HL-I	p.Pro117Leu, p.Pro117Ala
	5	missense	HL-I	p.Glu120Gly, p.Glu120Asp
	5	missense	TM-II	p.Asn135Ser
	5	missense	TM-II	p.Met139Ile, p.Met139Val, p.Met139Thr, p.Met139Lys
	5	missense	TM-II	p.Ile143Thr
	5	missense	TM-II	p.Met146Ile, p.Met146Leu
	5	missense	TM-II	p.Leu153Val
	6	missense	HL-II	p.His163Pro, p.His163Arg, p.His163Tyr
	6	missense	TM-III	p.Leu166Arg
	6	missense	TM-III	p.Ser169Leu, p.Ser169Pro
	6	missense	TM-III	p.Ser170Phe
	6	missense	TM-III	p.Leu173Trp
	6	missense	TM-III	p.Phe177Leu
	7	missense	HL-III	p.Glu184Asp, p.Glu184Gly
	7	missense	TM-IV	p.Gly206Asp, p.Gly206Val
	7	missense	TM-IV	p.Gly209Val
	7	missense	TM-IV	p.Ile213Thr
	7	missense	TM-V	p.Gln222His
	7	missense	TM-V	p.Met233Thr, p.Met233Val
	7	missense	TM-V	p.Leu235Pro
	7	missense	TM-V	p.Phe237Ile
	7	missense	TM-VI	p.Ala246Glu
	7	missense	TM-VI	p.Leu250Val
	8	missense	TM-VI	p.Ala260Val
	8	missense	HL-VI	p.Pro264Leu
	8	missense	HL-VI	p.Pro267Ser
	8	missense	HL-VI	p.Arg269Gly, p.Arg269His
	8	missense	HL-VI	p.Glu280Ala, p.Glu280Gly
	8	missense	HL-VI	p.Leu282Arg, p.Leu282Val
	8	missense	HL-VI	p.Leu286Val
	9	deletion	HL-VI	g.56305_62162del (Δ9)
	9	deletion	HL-VI	g.56681_61235del (Δ9Finn)
	10	missense	TM-VII	p.Arg377Trp
	11	missense	TM-VII	p.Phe386Ser
	11	missense	TM-VII	p.Leu392Pro, p.Leu392Val
	11	missense	TM-VIII	p.Cys410Tyr
	12	missense	TM-VIII	p.Leu420Arg
	12	missense	TM-VIII	p.Leu424Pro
	12	missense	TM-IX	p.Ala434Cys
PSEN2	5	missense	TM-II	p.Asn141Ile
	7	missense	TM-V	p.Met239Val
	12	missense	TM-IX	p.Thr430Met
APP	17	missense	N-term	p.Ala692Gly
	17	missense	TM-I	p.Thr714Ala, p.Thr714Ile
	17	missense	TM-I	p.Val717Gly, p.Val717Ile, p.Val717Leu

Concerning *PSEN2*, only three mutations have been reported as associated with epilepsy in EOFAD patients, namely p.Asn141Ile, p.Met239Val and p.Thr430Met [13,17,18]. Interestingly, about 30% of patients harboring the same mutation p.Asn141Ile showed epilepsy [23]. In a study performed on a large Italian AD family carrying the p.Met239Val, the authors hypothesized that the presence of white matter ectopic neurons may represent the neuropathological substrate of seizure, as shown in cases of generalized epilepsy [18]. Regarding the