

알츠하이머 질환의 신경생물학

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Neurobiology of Alzheimer's Disease

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ABSTRACT

Alzheimer's disease(AD) is associated with a characteristic neuropathology. The major hallmarks of AD are senile plaques (SPs) and neurofibrillary tangles(NFTs). β -amyloid protein(A β) is derived from the proteolysis of amyloid precursor protein(APP) and then converted to SPs. Mature SPs produce cytotoxicity through direct toxic effects and activation of microglia and complement. NFTs are composed of paired helical filaments(PHF) including abnormally phosphorylated form of the microtubule-associated protein(MAP) tau and increased tau level in cerebrospinal fluid may be observed in most AD. The aggregation of A β and tau formation are thought to be a final common pathway of AD. Acetylcholine, dopamine, serotonin, GABA and their receptors are associated with AD. Especially, decreased nicotinic acetylcholine receptors(nAChRs) in AD are reported. Genetic lesions associated with AD are mutations in the structural genes for the APP located on chromosome 21, presenilin(PSN)1 located on chromosome 14 and PSN2 located on chromosome 1. Also, trisomy 21, Apo-E gene located on chromosome 19, PMF locus, low density lipoprotein receptor-related protein and α_2 -macroglobulin increase risk of AD. In this article, we will review about the neurobiology of AD and some newly developed research areas.

KEY WORDS : Alzheimer's disease · β -amyloid protein · MAP tau · Genetics.

서 론

1980년 65세 이상 노인 인구는 약 1억 2천만 명으로, 2010년에는 2억 2천만 명으로 증가할 것으로 예상되며, 2020년에는 3억 2천만 명으로 증가할 것으로 예상된다(1996).

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Wisniewski 1984). PHF (microtubule-associated protein) tau

(1998, 2). 가

(Halper 1986). (age-specific densities)

(acetylcholine esterase inhibitor) 가

가

가

(microvasculature) (meningeal vessels)

(cerebral amyloid angiopathy) (Mountjoy 1982).

(amyloid)

10

가 가

(pyramidal cells)

(granulovacuolar degeneration)

(cell death)

(Ball 1977).

hironobodies가

(Gibson Tomlinson

1977)

(senile plaques : SPs)

(neurofibrillary tangle : NFTs)

(cerebral neocortex) (hippocampus)

(Small 1996).

(A)

(Masters 1985)

dystrophic neurites

(microglia)

(1).

20nm paired

helical filaments(PHF)

(Wischik 1985 ;

1. Amyloid precursor protein

(amyloid precursor protein : APP)

21 가 18 exon

16, 17 exon A 가 (Van Br-

oeckhoven 1995). APP presenilin 1(PSN1),

presenilin 2(PSN2) . APP가 A

신경병리

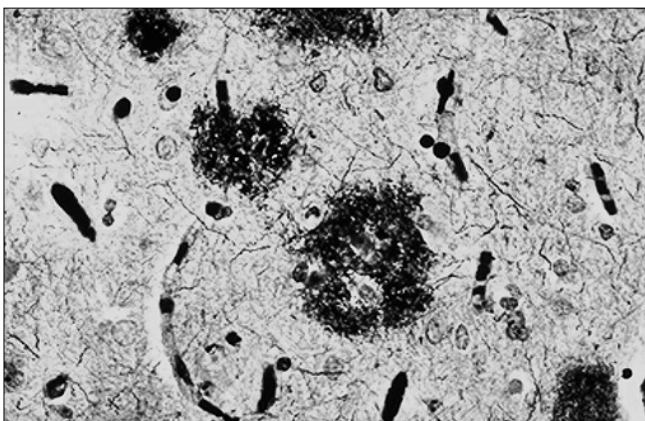


Fig. 1. Microscopic image of senile plaque, bielschowsky silver stain.

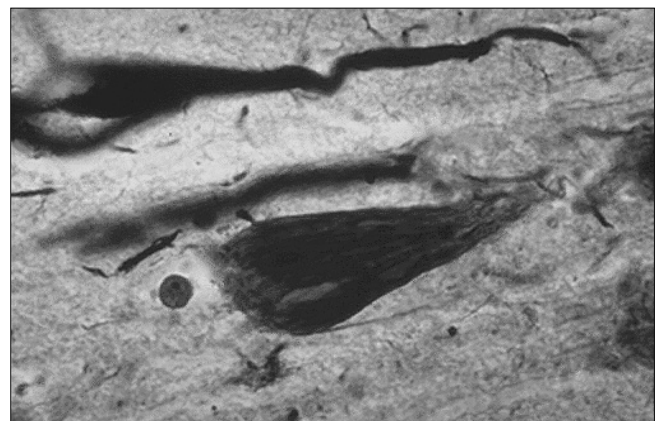


Fig. 2. Microscopic image of neurofibrillary tangle, bielschowsky silver stain.

APP gene 가 6 . Tau kinase
 NFT (Gail Jenkins 1997).
 2. β -amyloid protein
 가
 가 A . A APP
 . APP alternate splicing
 695, 714, 751, 770 4 (isoform)
 가 . N
 C
 20 (Mattson 1997).
 APP molecules A sequence -
 secretase
 'secretary' 가 (Sisodia
 1992). APP molecules가
 'alternate' free calcium 가(Querfurth
 Selkoe 1994) PSN genes
 (Selkoe 1996). -secretase
 A C , 가 A
 . -secretase A C
 39~43 A 가
 .
 protein kinase free radicals
 가
 (Price 1992). ,
 A 가
 .
 가 -secretase
 . -secretase가 A C
 A 40, A 42 가 . A 42
 가 AD
 가 가 . -secretase
 inhibitor AD
 (Sinha Lieberburg 1999).
 A immunization AD
 (Schenk 2000).

MAP tau microtubule network
 axonal transport neuronal plasticity (De-
 lacourte Buee 1997). Tau microtubule
 axonal transport neuronal plasticity
 가 tau cell integ-
 rity 가 (Delacourte Buee 1997).
 CSF tau
 가 가
 (Galasko 1997).

신경전달물질과 그 수용체들

. 가
 (innervate)
 Meynert (nucleus basalis of Meynert)
 (cholinergic neurons) (Arendt 1983 ; Saper
 1985). (choline acetyltransf-
 erase) , (acetylcholine esterase)
 .
 5-HT1 receptors 5-HT2 re-
 ceptors 가 (Jansen 1990).
 noradrenergic receptor binding 2
 receptors 가 (Meana 1992).
 (nucleus accumbens)
 D1 receptors (Cortes 1988) D2 recep-
 tors (Cross 1984) .
 glutamate
 . Glutamate receptors N-Methyl-
 D-aspartate(NMDA) receptor alpha-amino-3-hydro-
 xy-5-methyl-4-isoxazole-propionic acid(AMPA) rece-
 ptor calcium ions 가 ion channels
 가 . 가
 가 ; long-term
 potentiation(LTP) excitotoxicity. LTP
 (presynaptic fibers) (brief tetanic sti-
 mulation) (postsynaptic hipp-
 ocampal neurons)
 (Harris
 1984 ; Morris 1986). LTP
 . NMDA
 AMPA receptors neurons calcium

influx (excitotoxicity) 가 (Blass Wisniewski 1991).
 Garthwaite 1990). (Meldrum 가
 (Dodd 1994). 가 (Banati 1993 ;
 GABA가 Giulian 1993) T
 synaptosome GABA cytokines
 biosynthetic enzyme (McGeer 1989 ; Tooyama 1990).
 glutamic acid decarboxylase cytokines interleukin - 6(IL - 6)가
 (Chu 1987a ; Chu 1987b). (Altstiel Sperber
 GABA_A receptor 1991) IL - 1 APP (Goldgaber
 GABA_B receptor 1989) A (Buxabaum 1992)
 GABA_B receptor binding 가 (Chu (Down syndrome)
 1987a ; Chu 1987b). IL - 1 (Griffin
 1989) IL - 1, IL - 2, IL - 6
 가 가 (Van-
 denabeele Fiers 1991 ; Yamata 1995).

가 (Chan - Palay Asan 1989)
 (cortisol) 가(Davis 1986), T
 (Raskind Peskind 1994 ; Zubenko (suppressor T cell) (Skias 1985),
 1991). (natural killer cell) (Araga 1991)

nicotinic acetyl-
 holine receptor(nAChRs) 가 (Sahakian
 Coull 1993 ; Nordberg 1994). nAChRs ligand - gated
 ion channels 가 ion pore 가 pentameric
 가 nAChR 2
 7 , 2 4 가 (Elliot
 1996 ; Chavez - Noriega 1997).
 nAChRs 가
 (Newhouse 1997). nAChR 4 2 subtype
 가 가 (Warpman
 Nordberg 1995). Guan (2000)
 3, 4 7
 2
 nAChRs가

Genetics

60
 (early onset Alzheimer 's disease : EOAD)
 60
 (late onset Alzheimer 's disease : LOAD) . EOAD
 가
 . EOAD 가 10% .
 EOAD 21 APP
 gene (Selkoe 1996 ; Sisodia Price 1995), 14
 PSN1 (Campion 1995),
 1 PSN2 (Levy - Lahad
 1995), trisomy 21 EOAD
 30~40% (1). LOAD

염증반응과 면역기제

A (Farrer 1990 ; Van Broeckho-
 ven 1995). 가 LOAD (sporadic
 Alzheimer 's disease) 19
 Apo - E gene (Strittmatter Roses 1995).
 platelet membrane fluidity(PMF) locus

Table 1. AD susceptibility loci

Locus	Chromosome	Proportion of all AD cases affected	Clinical phenotype	A phenotype
Genes with pathogenic mutations				
APP mutations	21	<1%	Rare early-onset FAD, autosomal dominant	Production of total A and A ₄₂₍₄₃₎ peptides
Presenilin 1 mutations	14	<5%	Majority of early- onset FAD, some with intermediate onset (60 - 70yr), autosomal dominant	Production of total A ₄₂₍₄₃₎ peptides
Presenilin 2 mutations	1	<1%	Early-onset FAD, volga germans, autosomal dominant	Production of total A ₄₂₍₄₃₎ peptides
Genes with polymorphisms that increase risk				
ApoE, 4 allele	19	- 50%	Typical-onset (60s+) FAD and sporadic AD, dose effect on risk	Density of A plaques and vessel wall deposits
PMF locus, increased fluidity allele	?	- 50%	Onset 65 to early 70s, FAD and sporadic AD, dose effect on risk	Density of A plaques ; suggested N-terminal APP derivatives
α-1-Antichymotrypsin, single sequence polymorphism	14	- 75%	Modulate risk of AD conferred through APOE ε4 allele	Role in promoting A aggregation
CYP2D6B allele	22	- 50% of ADLBV only	Association with Lewy body disorders, not "pure"AD	No change in density of A plaques or nfts

AD : Alzheimer's disease
 FAD : familial Alzheimer's disease
 ADLBV : Alzheimer's disease Lewy body variant
 APP : amyloid precursor protein
 PMF : platelet membrane fluidity

(Salzman 1998). Presenilins (endoplasmic reticulum) low - density lipoprotein receptor - related protein (Golgi apparatus) (Haass 1996) A (LRP1) - 2 macroglobulin LOAD apoptosis (Cole (Leavitt 2000). LRP1 apo E APP Frautschy 1997). PSN1 encoding , - 2 macroglobulin - A 1 - 42(43) 가 amyloid LRP1 , amyloid pla- 가 (Haltia 1994 ; Scheuner 1996). que PSN1 - secretase PSN1 (Leavitt 2000). AD PSN1 1. APP 돌연변이 APP EOAD 2~3% (Tanzi PSN1 - secretase APP 1992). 가 APP 717 가 PSN1 residue APP (substitution) . 670 - secretase PSN1 - secretase 671 , A coding sequence (Mullan 1992). PSN2 apoptosis (Tanzi 2. Presenilins Presenilins 465 1997). PSN1 (Van Broeckhoven 가 PSN1 (Mattson 1997 ; Tanzi PSN2 APP (hippocampus), (parahippocampal gyrus), (cerebellar granular cell), (choroids plexus), (cerebral cortex), (stri- atum), (midbrain) (Tanzi 1997). 3. Apolipoprotein E apolipoprotein ApoE가 . Apo E gene (polymorphism) . ApoE gene 2, 3, 4 가 (Strittmatter Roses 1995). 4 LOAD

10% ApoE 4 allele
 (homozygous) 40% (hetero-zygous)
 50% 4 allele
 ApoE 2 allele LOAD 가
 (Chartier - Harlin 1994 ; Corder 1994).
 4 allele 가
 (Marder 1994 ; Zubenko 1994)
 가 . 4 allele
 late - life depression
 가 (Zubenko 1996). 4 allele
 가
 (Petersen 1995).
 4 allele
 . ApoE
 가 2 4
 . 4
 allele

in vitro
 .
 가 (Blass Gibson 1991).
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 .
 가
 estr-
 ogen receptor(ER) gene polymorphism
 P allele X allele 가
 (Urakami 2001). ,
 , PSN 가 ,
 PSN 가
 가 가 (Warrington 2001).
 , ,
 - 2 - macroglobulin LOAD

A 40
 4. PMF locus
 PMF(platelet membrane fluidity) 가가
 (subgroup) . PMF 가 single
 major locus PMF locus
 locus 65~70
 (Zubenko 1996).

가
 EOAD
 (Blennow 2000 ; Koster 2000 ; Nacmias 2001 ; Shibata 2000).
 ,
 가

Energy Metabolism

(Positron Emission Tomography :
 PET)
 (parietal lobe) (temporal lobe)
 (resting glucose metabolism)
 (regional reduction) (Minoshima 1995).
 가
 (Grady 1988).
 가 PET
 late -
 life depression (Parkinson 's disease) 가 가
 . APP A APP
 A 가

결론

가

cytokines

(neuronal injury) (neuronal death)

가 . MAP tau NFT

CSF tau

, GABA

nicotinic acetyl-

choline receptors 가

21 APP

gene , 14 PSN1 ,

1 PSN2 , trisomy 21, 19

Apo - E gene,

LRP1 - 2 - macroglobulin

가 가 가 ,

가

가

중심 단어 : . tau

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