occurrence of elevated levels of oxidatively modified lipids, proteins, and nucleic acids in vulnerable brain regions of AD subjects when compared with age-matched controls (18, 107, 120, 122, 141). Indeed, increased levels of lipid peroxidation products, such as TBARS, malondialdehyde, 4-hydroxy-2-nonenal (HNE), and F_2-isoprostanes, were documented in the AD brain, particularly in regions where senile plaques and neurofibrillary tangles typically accumulate (106, 118, 119, 148, 158, 206). With regard to protein oxidation, AD is characterized by increased levels of protein carbonyls and widespread nitration of tyrosine residues in brain cortex and hippocampus (81, 112, 167). An increase in 8-hydroxyguanine (8OHG) and 8-hydroxy-2-deoxyguanosine (8OHdG), markers of RNA and DNA oxidation, respectively, and protein adducts were observed in brain regions that were most affected by AD pathology (142, 108, 156). The role of oxidative stress in AD is further reinforced by the existence of a defective antioxidant defense system (5, 11). A decrease was documented in the activities of the antioxidant enzymes copper/zinc superoxide dismutase (Cu/ZnSOD) and catalase in the frontal and temporal cortex of AD subjects (118). AD subjects also exhibit reduced total antioxidant capacity (176), and a negative correlation was observed between the total antioxidant capacity and the duration of the disease (72).

During the course of AD, oxidative damage is also coupled to a progressive decline of the mitochondrial function (127). This notion is supported by an extensive literature which reports that AD is characterized by reduced cerebral energy metabolism (8), impaired activities of the tricarboxylic acid cycle enzymes (25, 121, 162), and defects in the mitochondrial ETC (21, 32, 45, 146, 96, 193). The most consistent defect at ETC level is the decline in cytochrome c oxidase (COX) activity, an effect that is positively correlated with Aβ concentration, as determined by *in vitro* studies (30). During AD progression, Aβ is translocated toward mitochondria (88, 186), enabling its interaction with critical redox centers of the subunit I of COX (6, 7) and Aβ-binding alcohol dehydrogenase (ABAD) (111, 187). The interaction of Aβ with the subunit I of COX and ABAD potentiates mitochondrial dysfunction and further increases ROS production in a vicious cycle. There is also evidence which supports a role for mtDNA mutations in the development and progression of AD (83).

Another important aspect is the role of redox-active metals in AD-related oxidative damage. Indeed, disruption of iron homeostasis has been suggested to be a trigger of oxidative stress and an early neuropathological event in AD (64). It was demonstrated that iron-mediated enhancement of oxidative stress occurs in preclinical AD (168), and increased redox-active iron is found in the cerebrospinal fluid from AD subjects (103). Besides its effects on oxidative status, redox-active metals also potentiate Aβ aggregation, aggravating AD pathology (27). Indeed, iron, zinc, and copper participate in the initiation of Aβ-mediated seeding process and Aβ oligomerization (86).

NOX overactivation is another pathogenic step underlying exacerbated oxidative damage in AD pathology (65). Mounting evidence suggests that the NOX system may be altered in AD, as indicated by the increased levels of p47phox and p67phox in the membrane fraction of AD brains, which foster the idea that NOX is overactivated in AD (55). Microglial expression of NOX subunit p22phox is also enhanced in the AD brain (3). A deficiency of NOX2 in transgenic AD mice reduces oxidative stress and improves cerebrovascular function and memory deficits without affecting Aβ levels or senile plaques (145), which reinforces the role of NOX in AD-associated oxidative damage. Importantly, aggregated Aβ stimulates $O_2^{\bullet -}$ and H_2O_2 production in microglial cells and induces the translocation of Rac from the cytosol to the membrane, supporting the idea that Aβ can affect NOX2-mediated pathways (126, 200).

Overall, these findings indicate that mitochondria, NOX, and oxidative stress are important contributors in AD-related neurodegeneration.

mtDNA Oxidation and Repair Deficiency

mtDNA oxidation and repair mechanisms

Mitochondrial dysfunction and apoptosis can also be triggered by point mutations, nucleic acid modifications, and large-scale deletions in mtDNA (104, 100). It has been reported that mtDNA damage is 10- to 20-fold higher, more extensive and persists longer when compared with nDNA (175, 204). mtDNA is particularly susceptible to oxidative damage, because it is not compacted around histones and is localized near the ETC, which is a major source of ROS. In addition, mtDNA has none or few noncoding regions, increasing the chances of mutagenicity in coding regions (4, 156). Mitochondria are highly enriched in iron microenvironments, thus favoring the formation of $^{\bullet}OH$ that, due to its short half-life, preferentially reacts with mitochondrial components, including mtDNA (192, 130). In addition, the oxidation of HNE can originate epoxide forms that interact with DNA bases (110, 91). During aging and in neurodegenerative disorders, nitric oxide (NO) interacts with $O_2^{\bullet -}$, resulting in the formation of peroxynitrite ($ONOO^-$), which contributes to mtDNA damage, including single-strand breaks (182, 194, 190).

All four bases (purines- adenine, guanine; pyrimidines-cytosine, thymine) and the respective deoxynucleosides are highly susceptible to oxidative damage. The main products of DNA oxidation include 8-hydroxyadenine (8OHA), 8-hydroxyguanine (8OHG, and its deoxynucleoside equivalent, 8OHdG), 5,6-dihydroxy-5,6-dihydrothymine, and ring-opened lesions (4,6-diamino-5-formamidopyrimidine, FapyA, and 2,6-diamino-4-hydroxy-5-formamidopyrimidine, FapyG) (Fig. 2) (117). Overall, more than 20 oxidized base adducts can be formed from ROS attack on the DNA (42, 172). Nevertheless, guanine has the lowest oxidation potential, being the most readily oxidized base (130). 8OHG and 8OHdG, along with FapyG, are the most studied and common forms of oxidized DNA bases (53, 95). While mutagenesis is stimulated by the accumulation of 8OHdG by pairing with adenine as well as cytosine (113), the FapyG lesions inhibit DNA synthesis (143, 114). ◀F2

Base excision repair (BER) is the primary nuclear and mitochondrial repair pathway for oxidative DNA damage. BER is evolutionarily conserved and is responsible for recognizing, excising, and replacing a wide number of DNA modifications that are characterized by small base modifications (99, 82). Generally, the BER machinery consists of several proteins that act in an ordered multistep cascade:(i) the recognition and excision of the damaged base;(ii) the incision of the DNA backbone in the abasic (AP) site; (iii) the generation of a 3′-OH and a 5′-P moieties in the DNA termini; (iv) the synthesis of

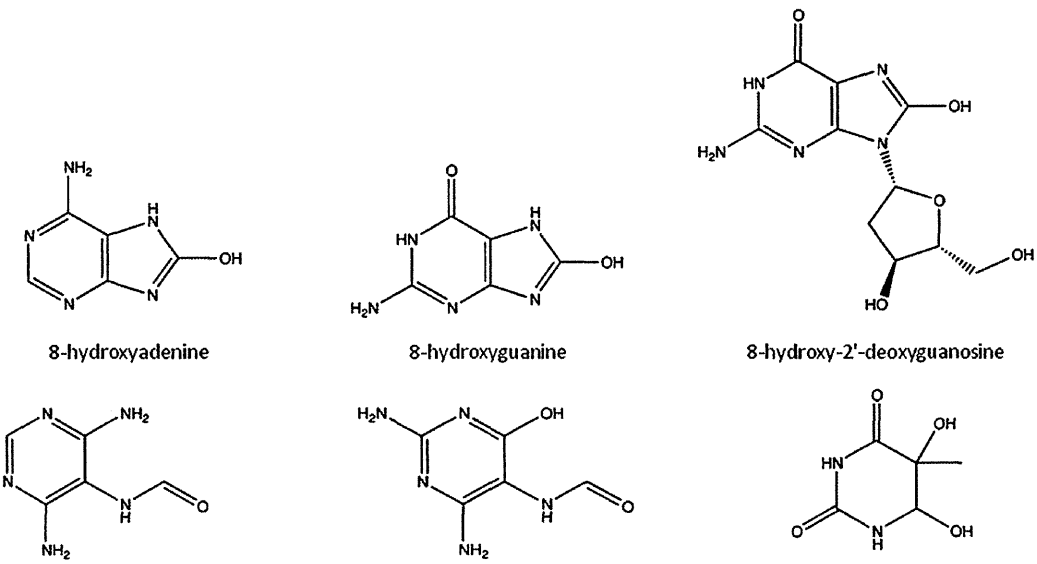

FIG. 2. Molecular structures of some oxidation products of DNA. The products of DNA oxidation result from the attack of reactive oxygen species, mainly $^{\cdot}$OH, to DNA bases.

the missing nucleotide; and (v) the sealing of the remaining DNA nick (Fig. 3) (205). This mechanism is essentially the same for nDNA and mtDNA repair; however, the isoforms of some enzymes involved in the process may differ from the nucleus to the mitochondria, even though all of them are nuclear encoded (199). The initial removal of the damaged base is accomplished by substrate-specific DNA glycosylases that hydrolyze the N-glycosidic bond between the modified base and the DNA backbone (54, 87). DNA glycosylases can be divided into two distinct functional groups: (i) a

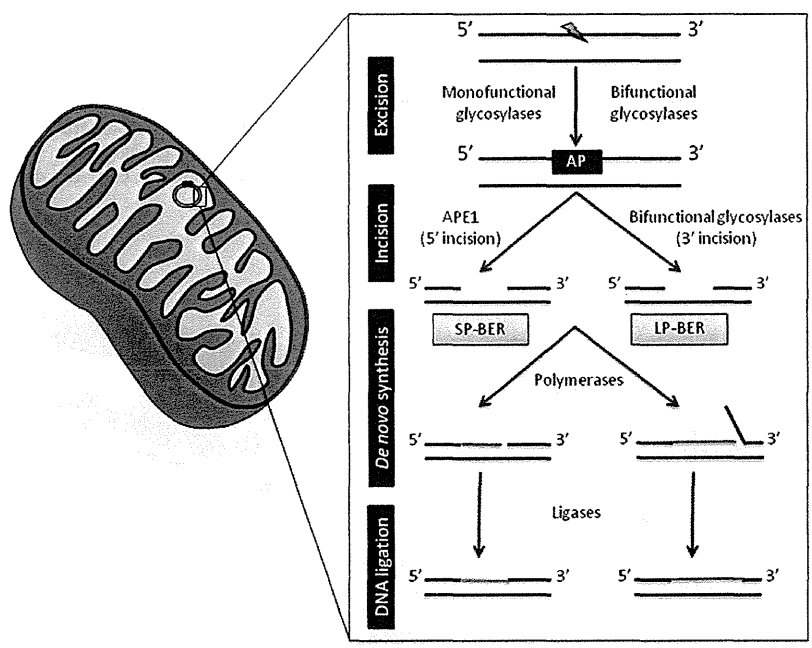

FIG. 3. Base excision repair (BER) machinery. An oxidative lesion (herein represented by the lightning symbol) is removed by DNA glycosylases, which excise the oxidized base from the DNA backbone, leaving an abasic site (AP). Afterward, the DNA backbone is incised in order to create a single-nucleotide gap that is ready for subsequent filling by DNA polymerases. In this step, *de novo* synthesis can follow one of two subpathways; in short-patch BER (SP-BER), 1 nucleotide is inserted and in long-patch BER (LP-BER), 2–7 nucleotides are inserted. The last step involves the ligation of the nick by DNA ligases. APE1, AP endonuclease. See text for further details.

monofunctional group of enzymes with glycosylase activity only, which includes hydroxymethyl-uracyl DNA glycosylase (UDG) whose mitochondrial isoform UDG1 is generated by alternative splicing (31, 136); (ii) a byfunctional group of enzymes with intrinsic 3'AP lyase activity, in addition to glycosylase activity, which include 8OHG DNA glycosylase (OGG1), the human endonuclease III homolog (NTH1), and Nei-like homologs (NEILs)(68). Oxidized bases are generally removed by bifunctional DNA glycosylases. OGG1 has two isoforms, α-OGG1 that localizes to both the nucleus and mitochondria and β-OGG1that localizes in mitochondria (137). NTH1 has a putative mitochondrial targeting sequence, which allows its localization to mitochondria (185, 173, 94). NEILs are localized in the nucleus and mitochondria (132, 77, 89). In human cells, oxidative pyrimidine lesions are generally excised by NTH1 or NEILs; whereas oxidative purine lesions are excised by OGG1 (132, 77, 89). 8OHG lesions are primarily repaired by OGG1 (97, 47). The step after the removal of the damaged base by glycosylases is the incision of the DNA backbone in an adjacent site to the AP site. This stage is characterized by different types of lyase activity, either occurring immediately 5' to the AP site or 3' to the AP site depending on whether the excision step was accomplished by monofunctional or byfunctional glycosylases, respectively (49, 201). Indeed, AP endonuclease (APE1) is responsible for the incision of the DNA backbone after UDG1 removal of the modified base (49, 201). APE1 localizes to both the nucleus and mitochondria (62, 151, 201). Moreover, the byfunctional glycosylases are capable of incising the DNA backbone, leaving a DNA single-strand break. The final steps of the repairing process may undergo two distinct subpathways, the short- or long-patch BER (SP-BER or LP-BER, respectively). The SP-BER involves the incorporation of a single nucleotide into the gap by DNA polymerase. The LP-BER involves the incorporation of several nucleotides, typically 2 to 7, followed by the cleavage of the resulting 5'(91). Finally, the nick left behind by DNA polymerases needs to be sealed, a process performed by ligases, ligase I (nucleus) in the case of LP-BER, and ligase III (nucleus and mitochondria) in the case of SP-BER (70). The polymerase responsible for the mtDNA repair synthesis is polymerase γ (74, 93).

Despite the current knowledge on the mechanisms that maintain the genomic integrity, particularly mitochondrial genome, it is of great interest to gain more insight into the real importance of each enzyme and each subpathway involved in the repair process. Indeed, the repair of mtDNA oxidative damage was thought to be mediated solely by SP-BER (17, 177); however, in recent years, LP-BER was also demonstrated to counteract the accumulation of oxidative damage to mtDNA (Fig. 3)(2, 105, 184, 207).

Aging

Aging has been established as being the main risk factor for the development of late-onset neurodegenerative disorders such as AD. The accumulation of oxidative damage plays a key role in the aging process, as postulated by the free radical theory of aging (75). Age-associated oxidation of mtDNA results from an increased oxidative attack to the nucleic acids and a reduced efficacy in mtDNA repair machinery, namely BER (Fig. 4). Indeed, the aging brain is characterized by an increased oxidative damage to mtDNA noticed by the formation of 8OHdG, which is the most common marker of oxidative DNA damage (123). Notably, in human subjects (42–97 years), a progressive augment in 8OHdG was reported in both nDNA and mtDNA with aging; however, the extent of increase of 8OHdG is ten-fold more in mtDNA compared with nDNA (123). The increased susceptibility of mtDNA, compared with nDNA, was also observed in aged brains of other mammalian species (12). An age-associated impairment of mitochondrial BER machinery, particularly OGG1, UDG, APE1, and polymerase γ, has been reported (90, 39). Moreover, five specific brain areas were shown to have deficits in mitochondrial BER, namely caudate nucleus, frontal cortex, hippocampus, cerebellum, and brain stem (90). A recent study demonstrated that brain cortical and hippocampal mtDNA glycosylases behave differently in cortical and hippocampal mitochondria of rodents (68). Hippocampal mtDNA glycosylases present lower activity when compared with cortical glycosylases. Importantly, brain cortical mtDNA glycosylases show an age-dependent decrease in their activity; while hippocampal glycosylases present only minor alterations (68). These findings highlight how mitochondrial heterogeneity influences the susceptibility of these organelles to damage. In fact, it was also shown that synaptic mitochondria are more susceptible to Ca^{2+} overload and the induction of MPTP than

◀ F4

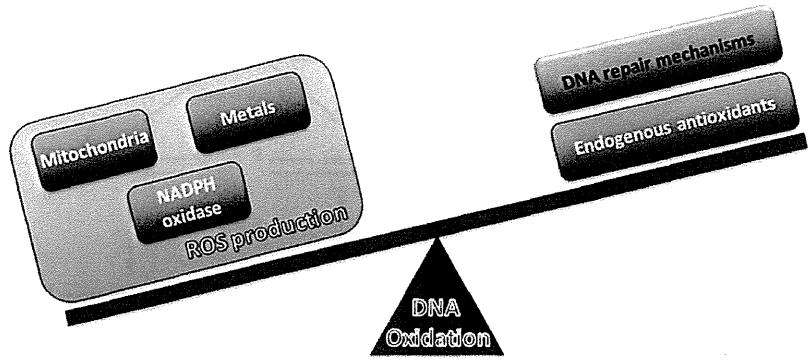

FIG. 4. Redox imbalance, DNA repair, and oxidation. Increased DNA oxidation in aging and AD results from an imbalance between ROS production and ROS scavenging as well as from the failure of DNA repair mechanisms.

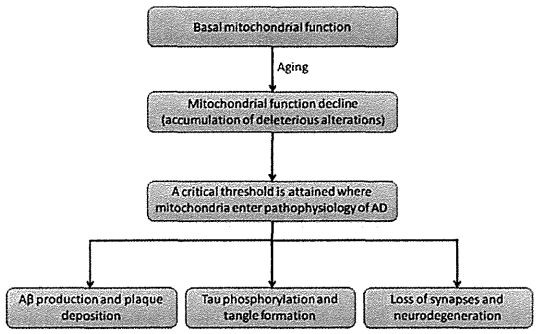

FIG. 5. Mitochondrial cascade hypothesis for AD. The accumulation of damage and consequent decline of mitochondrial function with aging are hypothesized to be the triggers of sporadic (late onset) AD. This hypothesis postulates that amyloidosis, tangle formation, synapse, and neuronal loss are consequences of mitochondrial defects (Swerdlow and Khan 2009).

nonsynaptic mitochondria (24, 134), which reinforces the idea that synaptic mitochondria, including their DNA, are more vulnerable to injury.

BER enzymes are negatively modulated by covalent modifications in an age-dependent manner putatively due to decreased acetylation (183) or iron/copper dyshomeostasis (79). Notably, a general trend toward increasing heteroplasmy with the aging process has been observed, due to a gradual accumulation of alterations in mtDNA throughout life (166). These results are in accordance with previous observations of increased mtDNA deletions (15, 98) and somatic mutations (164) with age in the substantia nigra. A causal relation between the malfunction of BER machinery and neurodegeneration has been established, which is further associated with behavioral alterations (102).

Alzheimer's disease

Mitochondrial dysfunction and exacerbated generation of ROS are well known features of AD. Moreira (130) and de la Monte (46) reported that AD brains present increased fragmentation of mtDNA, reduced mtDNA content and mass, reduced level of COX, and evidence of apoptotic cell loss. Despite no causative mtDNA mutations being linked to AD, some polymorphic variations can occur, having implications in enzymatic activities, such as COX (109). Some mtDNA mutations have been associated with increased incidence of AD (195, 43). Likewise, a reduction in the level of ND6 complex I transcript in AD has been reported (43). AD brains present increased mtDNA mutations that are enhanced in an age-dependent manner, when compared with control cases (43). Nevertheless, and despite no causative mutations in mtDNA being currently known, mitochondrial dysfunction has been proposed to precipitate Aβ deposition, neurofibrillary tangle formation, and, ultimately, neurodegeneration (Fig. 5) (179, 180). ◀F5

Although several studies demonstrate that oxidation of both nDNA and mtDNA is increased in AD brains (63, 124, 197), mtDNA oxidation has been found to be 10-fold higher than nDNA in frontal, parietal, and temporal lobes of AD patients (197). The simultaneous increased oxidation of mtDNA and deficiency of DNA repair could enhance the lesion to mitochondrial genome, potentially leading to neuronal loss. Indeed, Shao *et al.* (161) demonstrated that mitochondrial OGG1 activity is decreased in the frontal and temporal lobe of late-stage AD, and in the temporal lobe of MCI patients, compromising the removal of oxidatively damaged bases from mtDNA. Opposing results were recently reported in the brains of the triple transgenic model of AD (3×Tg-AD), in

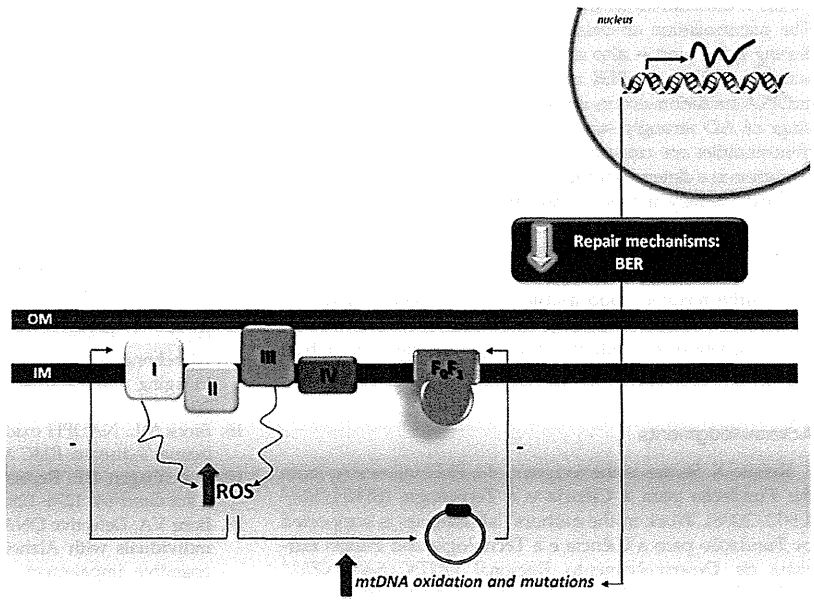

FIG. 6. Putative vicious cycle of mitochondrial ROS production in aging and AD. Since 13 subunits of the electron transport chain (ETC) are encoded by mtDNA, it is likely that mtDNA oxidation resulting from the increased ROS production leads to ETC dysfunction, which exacerbates ROS production. This vicious cycle is potentiated by the decline in BER efficiency that occurs in the aged and AD brains.

which no changes between the synaptosomal BER activities of presymptomatic and symptomatic AD mice were found (69). The contradictory observations reported in human and mice AD brains can be easily explained by the fact that the disease process in 3×Tg-AD mice is the result of a genetic manipulation, as those animals harbor the human amyloid precursor Swedish mutation, presenilin-1 M146V (PS1(M146V)) knock-in mutation, and tau (P301L) mutation; whereas in sporadic AD patients, mitochondria malfunctioning and oxidative stress are considered causative agents (155). Notably, rodents that were engineered to express an inducible mutant form of UDG1 show a decline in cognitive performance, as evaluated by the Morris water maze test (102). Furthermore, and similarly to that described in AD (198), rodents expressing mutant UDG1 also display abnormal mitochondrial dynamics (101), which supports the idea that impaired BER machinery may also play a role in AD.

More studies are needed to clarify the involvement of defects in mtDNA and its repair mechanisms in AD development. Furthermore, caution should be taken in the analysis and interpretation of results obtained with AD transgenic mice, as these animals mimic the familial cases of the disease, which represent less than 5% of all AD cases. In this line, it would be interesting to perform studies in rodents subjected to the intracerebroventricular administration of streptozotocin (icvSTZ), which are considered animal models of sporadic AD.

Conclusion

Mitochondria are major producers of ROS that under low/moderate levels act as second messengers. However, during aging and age-related diseases, an increased production of mitochondrial ROS associated with a defective scavenging system culminate in a redox imbalance and high levels of oxidatively damaged biomolecules. Mitochondrial dysfunction is currently accepted as a pathological hallmark of AD, which is considered an early event in disease pathogenesis. The accumulation of oxidative lesions to mtDNA occurs during aging and is also a prominent feature in AD, along with the failure in BER machinery. The observation that mtDNA oxidation occurs during aging and in the prodromal stage of AD strongly supports the idea that mitochondrial abnormalities are causative agents in AD. Whether mtDNA oxidation is a determinant for the onset of disease is yet to be clarified, namely if there is any threshold that triggers the disease process. Nonetheless, it is tempting to propose that the impairment in OXPHOS results in an exacerbation of ROS generation that increases the probability of mtDNA mutations in a positive feedback loop, a situation which is potentiated by a defective BER machinery (Fig. 6). The clarification of BER in AD also opens new windows for therapeutic intervention that are aimed at effectively repairing damaged mtDNA.

F6 ▶

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References

◀AU3

◀AU4

1. Addabbo F, Montagnani M, and Goligorsky MS. Mitochondria and reactive oxygen species. *Hypertens* 53: 885–892, 2009.
2. Akbari M, Visnes T, Krokan HE, and Otterlei M. Mitochondrial base excision repair of uracil and AP sites takes place by single-nucleotide insertion and long-patch DNA synthesis. *DNA Repair (Amst)* 7: 605–616, 2008.
3. Akiyama H, Barger S, Barnum S, *et al.* Inflammation and Alzheimer's disease. *Neurobiol Aging* 21: 383–421, 2000.
4. Anderson S, Bankier AT, Barrell BG, *et al.* Sequence and organization of the human mitochondrial genome. *Nature* 290: 457–465, 1981.
5. Ansari MA and Scheff SW. Oxidative stress in the progression of alzheimer disease in the frontal cortex. *J Neuropathol Exp Neurol* 69: 155–167, 2010.
6. Atamna H and Frey WH, 2nd. A role for heme in Alzheimer's disease: heme binds amyloid beta and has altered metabolism. *Proc Natl Acad Sci USA* 101: 11153–11158, 2004.
7. Atamna H. Heme binding to Amyloid-beta peptide: mechanistic role in Alzheimer's disease. *J Alzheimers Dis* 10: 255–266, 2006.
8. Azari NP, Pettigrew KD, Schapiro MB, *et al.* Early detection of Alzheimer's disease: a statistical approach using positron emission tomographic data. *J Cereb Blood Flow Metab* 13: 438–447, 1993.
9. Bagh MB, Thakurta IG, Biswas M, Behera P, and Chakrabarti S. Age-related oxidative decline of mitochondrial functions in rat brain is prevented by long term oral antioxidant supplementation. *Biogerontology* 12:119–131, 2010.
10. Balaban RS, Nemoto S, and Finkel T. Mitochondria, oxidants, and aging. *Cell* 120: 483–495, 2005.
11. Baldeiras I, Santana I, Proença MT, *et al.* Oxidative damage and progression to Alzheimer's disease in patients with mild cognitive impairment. *J Alzheimers Dis* 21: 1165–1177, 2010.
12. Barja G and Herrero I. Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals. *FASEB J* 14: 312–318, 2000.
13. Baughman JM, Perocchi F, Girgis HS, Plovanich M, *et al.* Integrative genomics identifies MCU as an essential component of the mitochondrial calcium uniporter. *Nature* 476: 341–345, 2011.
14. Benard, G and Karbowski M. Mitochondrial fusion and division: regulation and role in cell viability. *Semin Cell Dev Biol* 20: 365–374, 2009.
15. Bender A, Krishnan KJ, Morris CM, *et al.* High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat Genet* 38: 515–517, 2006.
16. Block ML. NADPH oxidase as a therapeutic target in Alzheimer's disease. *BMC Neurosci* Suppl 2: S8, 2008.
17. Bogenhagen DF. Repair of mtDNA in vertebrates. *Am J Hum Genet* 64: 1276–1281, 1999.
18. Bohr VA. Defective DNA base excision repair in brain from individuals with Alzheimer's disease and amnestic mild cognitive impairment. *Nucleic Acids Res* 35: 5545–5555, 2007.

19. Bohr VA. Repair of oxidative DNA damage in nuclear and mitochondrial DNA, and some changes with aging in mammalian cells. *Free Radic Biol Med* 32: 804–812, 2002.
20. Bokov A, Chaudhuri A, and Richardson A. The role of oxidative damage and stress in aging. *Mech Ageing Dev* 125: 811–826, 2004.
21. Bosetti F, Brizzi F, Barogi S, *et al.* Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease. *Neurobiol Aging* 23: 371–376, 2002.
22. Bowling AC, Mutisya EM, Walker LC, Price DL, Cork LC, and Beal MH. Age-dependent impairment of mitochondrial function in primate brain. *J Neurochem* 60: 1964–1967, 1993.
23. Brand MD. The sites and topology of mitochondrial superoxide production. *Exp Gerontol* 45: 466–472, 2010.
24. Brown MR, Sullivan PG, and Geddes JW. Synaptic mitochondria are more susceptible to Ca2+ overload than nonsynaptic mitochondria. *J Biol Chem* 28: 11658–11668, 2006.
25. Bubber P, Haroutunian V, Fisch G, Blass JP, and Gibson GE. Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. *Ann Neurol* 57: 695–703, 2005.
26. Buchholz JN, Behringer EJ, Pottorf WJ, Pearce WJ, and Vanterpool CK. Age-dependent changes in Ca2+ homeostasis in peripheral neurones: implications for changes in function. *Aging Cell 6:* 285–296, 2007.
27. Budimir A. Metal ions, Alzheimer's disease and chelation therapy. *Acta Pharm* 61: 1–14, 2011.
28. Cakatay U, Telci A, Kayalì R, Tekeli F, Akçay T, and Sivas A. Relation of oxidative protein damage and nitrotyrosine levels in the aging rat brain. *Exp Gerontol* 36: 221–229, 2001.
29. Camandola S and Mattson MP. Aberrant subcellular neuronal calcium regulation in aging and Alzheimer's disease. *Biochim Biophys Acta* 1813: 965–973, 2011.
30. Canevari L, Clark JB, and Bates TE. Beta-Amyloid fragment 25–35 selectively decreases complex IV activity in isolated mitochondria. *FEBS Lett* 457: 131–134, 1999.
31. Caradonna S, Ladner R, Hansbury M, Kosciuk M, Lynch F, and Muller S. Affinity purification and comparative analysis of two distinct human uracil-DNA glycosylases. *Exp Cell Res* 222: 345–359, 1996.
32. Cardoso SM, Proenca MT, Santos S, Santana I, and Oliveira CR. Cytochrome c oxidase is decreased in Alzheimer's disease platelets. *Neurobiol Aging* 25: 105–110, 2004.
33. Carreras MC, Franco MC, Peralta JG, and Poderoso JJ. Nitric oxide, complex I, and the modulation of mitochondrial reactive species in biology and disease. *Mol Aspects Med* 25: 125–139, 2004.
34. Castellani RJ, Rolston RK, and Smith MA. Alzheimer disease. *Dis Mon* 56: 484–546, 2010.
35. Celsi F, Pizzo P, Brini M, Leo S, Fotino C, Pinton P, and Rizzuto R. Mitochondria, calcium and cell death: a deadly triad in neurodegeneration. *Biochim Biophys Acta* 1787: 335–344, 2009.
36. Chakrabarti S, Munshi S, Banerjee K, Thakurta IG, Sinha M, and Bagh MB. Mitochondrial dysfunction during brain aging: role of oxidative stress and modulation by antioxidant supplementation. *Aging Dis* 2: 242–256, 2011.
37. Chakraborty H, Ray SN, and Chakrabarti S. Lipid peroxidation associated protein damage in rat brain crude synaptosomal fraction mediated by iron and ascorbate. *Neurochem Int* 39: 311–317, 2001.
38. Chan, DC. Mitochondria: dynamic organelles in disease, aging, and development. *Cell* 125: 1241–1252, 2006.
39. Chen D, Cao G, Hastings T, Feng Y, Pei W, O'Horo C, and Chen J. Age-dependent decline of DNA repair activity for oxidative lesions in rat brain mitochondria. *J Neurochem* 81: 1273–1284, 2002.
40. Chen H and Chan DC. Physiological functions of mitochondrial fusion. *Ann NY Acad Sci* 1201: 21–25, 2010.
41. Cocco T, Sgobbo P, Clemente M, *et al.* Tissue-specific changes of mitochondrial functions in aged rats: effect of a long-term dietary treatment with N-acetylcysteine. *Free Radic Biol Med* 38: 796–805, 2005.
42. Cooke MS, Evans MD, Dizdaroglu M, and Lunec J. Oxidative DNA damage: mechanisms, mutation, and disease. *FASEB J* 17: 1195–1214, 2003.
43. Coskun PE, Beal MF, and Wallace DC. Alzheimer' s brains harbor somatic mtDNA control-region mutations that suppress mitochondrial transcription and replication. *Proc Natl Acad Sci USA* 101: 10726–10731, 2004.
44. Crompton M. The mitochondrial permeability transition pore and its role in cell death. *Biochem J* 341: 233–249, 1999.
45. Curti D, Rognoni F, Gasparini L, *et al.* Oxidative metabolism in cultured fibroblasts derived from sporadic Alzheimer's disease (AD) patients. *Neurosci Lett* 236: 13–16, 1997.
46. de la Monte SM, Luong T, Neely TR, Robinson D, and Wands JR. Mitochondrial DNA damage as a mechanism of cell loss in Alzheimer's disease. *Lab Invest* 80: 1323–1335, 2000.
47. de Souza-Pinto NC, Eide L, Hogue BA, *et al.* Repair of 8-oxodeoxyguanosine lesions in mitochondrial DNA depends on the oxoguanine dna glycosylase (OGG1) gene and 8-oxoguanine accumulates in the mitochondrial dna of OGG1-defective mice. *Cancer Res* 61: 5378–5381, 2001.
48. De Stefani D, Raffaello A, Teardo E, Szabò I, and Rizzuto R. A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter. *Nature* 476: 336–340, 2011.
49. Demple B and Sung JS. Molecular and biological roles of Ape1 protein in mammalian base excision repair. *DNA Repair (Amst)* 4: 1442–1449, 2005.
50. Detmer SA and Chan DC. Functions and dysfunctions of mitochondrial dynamics. *Nat Rev Mol Cell Biol* 8: 870–879, 2007.
51. DiMauro S and Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med* 348: 2656–2668, 2003.
52. Dimroth P, Kaim G, and Matthey U. Crucial role of the membrane potential for ATP synthesis by F(1)F(o) ATP synthases. *J Exp Biol* 203: 51–59, 2000.
53. Dizdaroglu M, Kirkali G, and Jaruga P. Formamidopyrimidines in DNA: mechanisms of formation, repair, and biological effects. *Free Radic Biol Med* 45: 1610–1621, 2008.
54. Dizdaroglu M. Base-excision repair of oxidative DNA damage by DNA glycosylases. *Mutat Res* 591: 45–59, 2005.
55. Dumont M and Beal MF. Neuroprotective strategies involving ROS in Alzheimer disease. *Free Radic Biol Med* 51: 1014–1026, 2011.
56. Evans JL, Goldfine ID, Maddux BA, and Grodsky GM. Oxidative stress and stress-activated signaling pathways: a unifying hypothesis of type 2 diabetes. *Endocr Rev* 23: 599–622, 2002.
57. Fang H, Chen M, Ding Y, *et al.* Imaging superoxide flash and metabolism-coupled mitochondrial permeability transition in living animals. *Cell Res* 21: 1295–1304, 2011.
58. Ferrándiz ML, Martínez M, Juan ED, Díez A, Bustos G, and Miquel J. Impairment of mitochondrial oxidative

phosphorylation in the brain of aged mice. *Brain Res* 644: 335–338, 1994.
59. Filosto M, Scarpelli M, Cotelli MS, *et al.* The role of mitochondria in neurodegenerative diseases. *J Neurol* 258: 1763–1774, 2011.
60. Finefrock AE, Bush AI, and Doraiswamy PM. Current status of metals as therapeutic targets. *J am Geriatr Soc* 51: 1143–1148, 2003.
61. Floyd RA and Hensley K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. *Neurobiol Aging* 23: 795–807, 2002.
62. Fung H, Kow YW, Van Houten B, *et al.* Asbestos increases mammalian AP-endonuclease gene expression, protein levels, and enzyme activity in mesothelial cells. *Cancer Res* 58: 189–194, 1998.
63. Gabbita SP, Lovell MA, and Markesbery WR. Increased nuclear DNA oxidation in the brain in Alzheimer's disease. *J Neurochem* 71: 2034–2040, 1998.
64. Gallagher JJ, Finnegan ME, Grehan B, Dobson J, Collingwood JF, and Lynch MA. Modest amyloid deposition is associated with iron dysregulation, microglial activation, and oxidative stress. *J Alzheimers Dis* 28: 147–161, 2012.
65. Gao HM, Zhou H, and Hong JS. NADPH oxidases: novel therapeutic targets for neurodegenerative diseases. *Trends Pharmacol Sci* 33: 295–303, 2012.
66. Gemma C, Mesches MH, Sepesi B, Choo K, Holmes DB, and Bickford PC. Diets enriched in foods with high antioxidant activity reverse age-induced decreases in cerebellar β-adrenergic function and increases in proinflammatory cytokines. *J Neurosci* 22: 6114–6120, 2002.
67. Gilmer LK, Ansari MA, Roberts KN, and Scheff SW. Age-related changes in mitochondrial respiration and oxidative damage in the cerebral cortex of the Fischer 344 rat. *Mech Ageing Dev* 131: 133–143, 2010.
68. Gredilla R, Garm C, Holm R, Bohr VA, and Stevnsner T. Differential age-related changes in mitochondrial DNA repair activities in mouse brain regions. *Neurobiol Aging* 31: 993–1002, 2010.
69. Gredilla R, Weissman L, Yang JL, Bohr VA, and Stevnsner T. Mitochondrial base excision repair in mouse synaptosomes during normal aging and in a model of Alzheimer's disease. *Neurobiol Aging* 33: 694–707, 2012.
70. Gredilla R. DNA damage and base excision repair in mitochondria and their role in aging. *J Aging Res* 2011: 257093, 2010.
71. Green K, Brand MD, and Murphy MP. Prevention of mitochondrial oxidative damage as a therapeutic strategy in diabetes. *Diabetes* 53 Suppl 1: S110–S118, 2004.
72. Guidi, I, Galimberti D, Lonati S, Novembrino C, *et al.* Oxidative imbalance in patients with mild cognitive impairment and Alzheimer's disease. *Neurobiol Aging* 27: 262–269, 2006.
73. Hamanaka RB and Chandel NS. Mitochondrial reactive oxygen species regulate cellular signaling and dictate biological outcomes.*Trends Biochem Sci* 35: 505–513, 2010.
74. Hansen AB, Griner NB, Anderson JP, Kujoth GC, Prolla TA, Loeb LA, and Glick E. Mitochondrial DNA integrity is not dependent on DNA polymerase-beta activity. *DNA Repair (Amst)* 5: 71–79, 2006.
75. Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 11: 298–300, 1956.
76. Harman D. The free radical theory of aging. *Antioxid Redox Signal* 5: 57–56, 2003.
77. Hazra TK, Izumi T, Boldogh I, *et al.* Identification and characterization of a human DNA glycosylase for repair of modified bases in oxidatively damaged DNA. *Proc Natl Acad Sci U S A* 99: 3523–3528, 2002.
78. Head E, Liu J, Hagen TM, Muggenburg BA, Milgram NW, Ames BN, and Cotman CW. Oxidative damage increases with age in a canine model of human brain aging. *J Neurochem* 82: 375–381, 2002.
79. Hegde ML, Hegde PM, Holthauzen LM, Hazra TK, Rao KS, and Mitra S. Specific Inhibition of NEIL-initiated repair of oxidized base damage in human genome by copper and iron: potential etiological linkage to neurodegenerative diseases. *J Biol Chem* 285: 28812–28825, 2010.
80. Hengartner MO. The biochemistry of apoptosis. *Nature* 407: 770–776, 2000.
81. Hensley K, Hall N, Subramaniam R, *et al.* Brain regional correspondence between Alzheimer's disease histopathology and biomarkers of protein oxidation. *J Neurochem* 65: 2146–2156, 1995.
82. Hoeijmakers, JH. Genome maintenance mechanisms for preventing cancer. *Nature* 411: 366–374, 2001.
83. Howell N, Elson JL, Chinnery PF, and Turnbull DM. mtDNA mutations and common neurodegenerative disorders. *Trends Genet* 11: 583–586, 2005.
84. Hu J, de Souza-Pinto NC, Haraguchi K, *et al.* Repair of formamidopyrimidines in DNA involves different glycosylases: role of the OGG1, NTH1, and NEIL1 enzymes. *J Biol Chem* 280: 40544–40551, 2005.
85. Huang X, Atwood CS, Hartshorn MA, *et al.* The A beta peptide of Alzheimer's disease directly produces hydrogen peroxide through metal ion reduction. *Biochem* 38: 7609–7616, 1999.
86. Huang X, Moir RD, Tanzi RE, Bush AI, and Rogers JT. Redox-active metals, oxidative stress, and Alzheimer's disease pathology. *Ann N Y Acad Sci* 1012: 153–163, 2004.
87. Huffman JL, Sundheim O, and Tainer JA. DNA base damage recognition and removal: new twists and grooves. *Mutat Res* 577: 55–76, 2005.
88. Humpel C and Marksteiner J. Cerebrovascular damage as a cause for Alzheimer's disease. *Curr Neurovasc Res* 2: 341–347, 2005.
89. Ide H and Kotera M. Human DNA glycosylases involved in the repair of oxidatively damaged DNA. *Biol Pharm Bull* 27: 480–485, 2004.
90. Imam SZ, Karahalil B, Hogue BA, Souza-Pinto NC, and Bohr VA. Mitochondrial and nuclear DNA-repair capacity of various brain regions in mouse is altered in an age-dependent manner. *Neurobiol Aging* 27: 1129–1136, 2006.
91. Jeppesen DK, Bohr VA, and Stevnsner T. DNA repair deficiency in neurodegeneration. *Prog Neurobiol* 94: 166–200, 2011.
92. Jomova K and Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicol* 283: 65–87, 2011.
93. Kaguni LS. DNA polymerase gamma, the mitochondrial replicase. *Annu Rev Biochem* 73: 293–320, 2004.
94. Karahalil B, de Souza-Pinto NC, Parsons JL, Elder RH, and Bohr VA. Compromised incision of oxidized pyrimidines in liver mitochondria of mice deficient in NTH1 and OGG1 glycosylases. *J Biol Chem* 278: 33701–33707, 2003.
95. Kasai H and Nishimura S. Hydroxylation of deoxyguanosine at the C-8 position by ascorbic acid and other reducing agents. *Nucleic Acids Res* 12: 2137–2145, 1984.
96. Kish SJ, Bergeron C, and Rajput, A. Brain cytochrome oxidase in Alzheimer's disease. *J Neurochem* 59: 776–779, 1992.

97. Klungland A, Rosewell I, Hollenbach S, Larsen E, Daly G, Epe B, Seeberg E, Lindahl T, and Barnes DE. Accumulation of premutagenic DNA lesions in mice defective in removal of oxidative base damage. *Proc Natl Acad Sci U S A* 96: 13300–13305, 1999.
98. Kraytsberg Y, Kudryavtseva E, McKee AC, Geula C, Kowall NW, and Khrapko K. Mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra neurons. *Nat Genet* 38: 518–520, 2006.
99. Krokan HE, Nilsen H, Skorpen F, Otterlei M, and Slupphaug G. Base excision repair of DNA in mammalian cells. *FEBS Lett* 476: 73–77, 2000.
100. Kruman II, Wersto RP, Cardozo-Pelaez F, Smilenov L, Chan SL, Chrest FJ, Emokpae R Jr, Gorospe M, and Mattson MP. Cell cycle activation linked to neuronal cell death initiated by DNA damage. *Neuron* 41: 549–561, 2004.
101. Lauritzen KH, Cheng C, Wiksen H, Bergersen LH, and Klungland A. Mitochondrial DNA toxicity compromises mitochondrial dynamics and induces hippocampal antioxidant defenses. *DNA Repair (Amst)* 10: 639–653, 2011.
102. Lauritzen KH, Moldestad O, Eide L, *et al.* Mitochondrial DNA toxicity in forebrain neurons causes apoptosis, neurodegeneration, and impaired behavior. *Mol Cell Biol* 30: 1357–1367, 2010.
103. Lavados M, Guillon M, Mujica MC, Rojo LE, Fuentes P, and Maccioni RB. Mild cognitive impairment and Alzheimer patients display different levels of redox-active CSF iron. *J Alzheimers Dis* 13: 225–232, 2008.
104. Linnane AW, Marzuki S, Ozawa T, and Tanaka M. Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. *Lancet* 1: 642–645, 1989.
105. Liu P, Qian L, Sung JS, *et al.*. Removal of oxidative DNA damage via FEN1-dependent long-patch base excision repair in human cell mitochondria. *Mol Cell Biol* 28: 4975–4987, 2008.
106. Lovell MA, Ehmann WD, Butler SM, and Markesbery WR. Elevated thiobarbituric acid-reactive substances and antioxidant enzyme activity in the brain in Alzheimer's disease. *Neurology* 45: 1594–1601, 1995.
107. Lovell MA, Ehmann WD, Mattson MP, and Markesbery WR. Elevated 4-hydroxynonenal in ventricular fluid in Alzheimer's disease. *Neurobiol Aging* 18: 457–461, 1997.
108. Lovell MA, Gabbita SP, and Markesbery WR. Increased DNA oxidation and decreassed levels of repair products in Alzheimer's disease ventricular CSF. *J Neurochem* 72: 771–776, 1999.
109. Lu J, Wang K, Rodova M, *et al.* Polymorphic variation in cytochrome oxidase subunit genes. *J Alzheimers Dis* 21: 141–154, 2010.
110. Luczaj W and Skrzydlewska E. DNA damage caused by lipid peroxidation products. *Cell Mol Biol Lett* 8: 391–413, 2003.
111. Lustbader JW, Cirilli M, Lin C, *et al.* Abeta to mitochondrial toxicity in Alzheimer's disease. *Science* 304: 448–452, 2004.
112. Lyras L, Cairns NJ, Jenner A, Jenner P, and Halliwell B. An assessment of oxidative damage to proteins, lipids, and DNA in brain from patients with Alzheimer's disease. *J Neurochem* 68: 2061–2069, 1997.
113. Maki H. Origins of spontaneous mutations: specificity and directionality of base substitution, frameshift, and sequence-substitution mutageneses. *Annu Rev Genet* 36: 279–303, 2002.
114. Malins DC, Hellstrom KE, Anderson KM, Johnson PM, and Vinson MA. Antioxidant-induced changes in oxidized DNA. *Proc Natl Acad Sci U S A* 99: 5937–5941, 2002.
115. Mancuso M, Calsolaro V, Orsucci D, Carlesi C, Choub A, Piazza S, and Siciliano G. Mitochondria, cognitive impairment, and Alzheimer's disease. *Int J Alzheimers Dis* 2009: 951548, 2009.
116. Mannella, CA. Structural diversity of mitochondria: functional implications. *Ann N Y Acad Sci* 1147: 171–179, 2008.
117. Mao P and Reddy PH. Aging and amyloid beta-induced oxidative DNA damage and mitochondrial dysfunction in Alzheimer's disease: implications for early intervention and therapeutics. *Biochim Biophys Acta* 1812: 1359–1370, 2011.
118. Marcus DL, Thomas K, Rodriguez C, *et al.* Increased peroxidation and reduced antioxidant enzyme activity in Alzheimer's disease. *Exp Neurol* 150: 40–44, 1998.
119. Markesbery WR and Lovell MA. Four-hydroxynonenal, a product of lipid peroxidation, is increased in the brain in Alzheimer's disease. *Neurobiol Aging* 19: 33–36, 1998.
120. Markesbery WR. Oxidative stress hypothesis in Alzheimer's disease. *Free Radic Biol Med* 23: 134–147, 1997.
121. Mastrogiacomo F, Bergeron C, and Kish SJ. Brain alpha-ketoglutarate dehydrogenase complex activity in Alzheimer's disease. *J Neurochem* 61: 2007–2014, 1993.
122. Mattson MP. Metal-catalyzed disruption of membrane protein and lipid signaling in the pathogenesis of neurodegenerative disorders. *Ann N Y Acad Sci* 1012: 37–50, 2004.
123. Mecocci P, Beal MF, Cecchetti R, *et al.* Mitochondrial membrane fluidity and oxidative damage to mitochondrial DNA in aged and AD human brain. *Mol Chem Neuropathol* 31: 53–64, 1997.
124. Mecocci P, MacGarvey U, and Beal MF. Oxidative damage to mitochondrial DNA is increased in Alzheimer's disease. *Ann Neurol* 36: 747–751, 1994.
125. Melov S, Schneider JA, Day BJ, *et al.* A novel neurological phenotype in mice lacking mitochondrial manganese superoxide dismutase. *Nat Genet* 18: 159–163, 1998.
126. Milton RH, *et al.* CLIC1 function is required for beta-amyloid induced generation of reactive oxygen species by microglia. *J Neurosci* 28: 11488–11499, 2008.
127. Moreira PI, Carvalho C, Zhu X, Smith MA, and Perry G. Mitochondrial dysfunction is a trigger of Alzheimer's disease pathophysiology. *Biochim Biophys Acta* 1802: 2–10, 2010.
128. Moreira PI, Nunomura A, Nakamura M, *et al.* Nucleic acid oxidation in Alzheimer disease. *Free Radic Biol Med* 44: 1493–1505, 2008.
129. Moreira PI, Zhu X, Wang X, *et al.* Mitochondria: a therapeutic target in neurodegeneration. *Biochim Biophys Acta* 1802: 212–220, 2010.
130. Moreira PI. Alzheimer's disease and diabetes: an integrative view of the role of mitochondria, oxidative stress, and insulin. *J Alzheimers Dis* 30: 199–215, 2012.
131. Moreira, PI, Duarte AI, Santos MS, Rego AC, and Oliveira CR. An integrative view of the role of oxidative stress, mitochondria and insulin in Alzheimer's disease. *J Alzheimers Dis* 16: 741–761, 2009.
132. Morland I, Rolseth V, Luna L, Rognes T, Bjoras M, and Seeberg E. Human DNA glycosylases of the bacterial Fpg/MutM superfamily: an alternative pathway for the repair of 8-oxoguanine and other oxidation products in DNA. *Nucleic Acids Res* 30: 4926–4936, 2002.

133. Murphy MP. How mitochondria produce reactive oxygen species. *Biochem J* 417: 1–13, 2009.
134. Naga KK, Sullivan PG, and Geddes JW. High cyclophilin D content of synaptic mitochondria results in increased vulnerability to permeability transition. *J Neurosci* 27: 7469–7475, 2007.
135. Neiman M and Taylor DR. The causes of mutation accumulation in mitochondrial genomes. *Proc Biol Sci* 276: 1201–1209, 2009.
136. Nilsen H, Otterlei M, Haug T, *et al.* Nuclear and mitochondrial uracil-DNA glycosylases are generated by alternative splicing and transcription from different positions in the UNG gene. *Nucleic Acids Res* 25: 750–755, 1997.
137. Nishioka K, Ohtsubo T, Oda H, Fujiwara T, Kang D, Sugimachi K, and Nakabeppu Y. Expression and differential intracellular localization of two major forms of human 8-oxoguanine DNA glycosylase encoded by alternatively spliced OGG1 mRNAs. *Mol Biol Cell* 10: 1637–1652, 1999.
138. Nonaka I. Mitochondrial diseases. *Curr Opin Neurol Neurosurg* 5: 622–632, 1992.
139. Nunomura A, Honda K, Takeda A, Hirai K, Zhu X, Smith MA, and Perry G. Oxidative damage to RNA in neurodegenerative diseases. *J Biomed Biotechnol* 2006: 82323, 2006
140. Nunomura A, Moreira PI, Castellani RJ, Lee HG, Zhu X, Smith MA, and Perry G. Oxidative damage to RNA in aging and neurodegenerative disorders. *Neurotox Res* 22: 231–248, 2012.
141. Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, *et al.* Oxidative damage is the earliest event in Alzheimer's disease. *J Neuropathol Exp Neurol* 60: 759–767, 2001.
142. Nunomura A, Perry G, Pappolla MA, Wade R, Hirai K, Chiba S, *et al.* RNA oxidation is a prominent feature of vulnerable neurons in Alzheimer's disease. *J Neurosci* 19: 1959–1964, 1999.
143. O'Connor TR, Boiteux S, and Laval J. Ring-opened 7-methylguanine residues in DNA are a block to *in vitro* DNA synthesis. *Nucleic Acids Res* 16: 5879–5894, 1988.
144. Ojaimi J, Masters CL, Opeskin K, Mckelvie P, and Byrne E. Mitochondrial respiratory chain activity in the human brain as a function of age. *Mech Ageing Dev* 111: 39–47, 1999.
145. Park L, Zhou P, Pitstick R, *et al.* Nox2-derived radicals contribute to neurovascularand behavioral dysfunction in mice overexpressing the amyloid precursor protein. *Proc Natl Acad Sci USA* 105: 1347–1352, 2008.
146. Parker WD Jr, Filley CM, and Parks JK. Cytochrome oxidase deficiency in Alzheimer's disease. *Neurol* 40: 1302–1303, 1990.
147. Patten DA, Germain M, Kelly MA, and Slack RS. Reactive oxygen species: stuck in the middle of neurodegeneration. *J Alzheimer's Dis* 20:S357–S367, 2010.
148. Praticò D, Lee VMY, Trojanowski JQ, Rokach J, and Fitzgerald GA. Increased F2-isoprostanes in Alzheimer's disease: evidence for enhanced lipid peroxidation *in vivo*. *FASEB J* 12: 1777–1783, 1998.
149. Querfurth HW and LaFerla FM. Alzheimer's disease. *N Engl J Med* 362: 329–344, 2010.
150. Rasola A and Bernardi P. Mitochondrial permeability transition in Ca(2+)-dependent apoptosis and necrosis. *Cell Calcium* 50: 222–233, 2011.
151. Rivkees SA and Kelley MR. Expression of a multifunctional DNA repair enzyme gene, apurinic/apyrimidinic endonuclease (APE; Ref-1) in the suprachiasmatic, supraoptic and paraventricular nuclei. *Brain Res* 666: 137–142, 1994.
152. Rizzuto R, Bernardi P, and Pozzan T. Mitochondria as all-round players of the calcium game. *J Physiol* 529: 37–47, 2000.
153. Rizzuto R, Pinton P, Brini M, Chiesa A, Filippin L, and Pozzan T. Mitochondria as biosensors of calcium microdomains. *Cell Calcium* 26: 193–199, 1999.
154. Sabatini BL, Maravall M, and Svoboda K. Ca(2+) signaling in dendritic spines. *Curr Opin Neurobiol* 11: 349–356, 2001.
155. Santos RX, Correia SC, Wang X, *et al.* Alzheimer's disease: diverse aspects of mitochondrial malfunctioning. *Int J Clin Exp Pathol* 3: 570–581, 2010.
156. Santos RX, Correia SC, Zhu X, *et al.* Nuclear and mitochondrial DNA oxidation in Alzheimer's disease. *Free Radic Res* 6: 565–576, 2012.
157. Sayre LM, Perry G, Harris PL, Liu Y, Schubert KA, and Smith MA. *In situ* oxidative catalysis by neurofibrillary tangles and senile plaques in Alzheimer's disease: a central role for bound transition metals. *J Neurochem* 74: 270–279, 2000.
158. Sayre, LM, Zelasko DA, Harris PL, *et al.* 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease. *J Neurochem* 68: 2092–2097, 1997.
159. Scherz-Shouval R and Elazar Z. Regulation of autophagy by ROS: physiology and pathology. *Trends Biochem Sci* 36: 30–98, 2011.
160. Sen T, Sen N, Jana S, Khan FH, Chatterjee U, and Chakrabarti S. Depolarization and cardiolipin depletion in aged rat brain mitochondria: relationship with oxidative stress and electron transport chain activity. *Neurochem Int* 50: 719–722, 2007.
161. Shao C, Xiong S, Li GM, *et al.* Altered 8-oxoguanine glycosylase in mild cognitive impairment and late-stage Alzheimer's disease brain. *Free Radic Biol Med* 45: 813–819, 2008.
162. Sheu KF, Kim YT, Blass JP, *et al.* An immunochemical study of the pyruvate dehydrogenase deficit in Alzheimer's disease brain. *Ann Neurol* 17: 444–449, 1985.
163. Shigenaga MK, Hagen TM, and Ames BN. Oxidative damage and mitochondrial decay in aging. *Proc Natl Acad Sci U S A* 91: 10771–10778, 1994.
164. Simon DK, Lin MT, Zheng L, *et al.* Somatic mitochondrial DNA mutations in cortex and substantia nigra in aging and Parkinson's disease. *Neurobiol Aging* 25: 71–81, 2004.
165. Sinclair, DA. Toward a unified theory of caloric restriction and longevity regulation. *Mech Ageing Dev* 126, 987–1002, 2005.
166. Smith CD, Carney JM, Starke-Reed PE, *et al.* Excess brain protein oxidation and enzyme dysfunction in normal aging and in Alzheimer disease. *Proc Natl Acad Sci USA* 88: 10540–10543, 1991.
167. Smith MA, Richey Harris PL, Sayre LM, Beckman JS, and Perry G. Widespread peroxynitrite-mediated damage in Alzheimer's disease. *J Neurosci* 17: 2653–2657, 1997.
168. Smith MA, Zhu X, Tabaton M, *et al.* Increased iron and free radical generation in preclinical Alzheimer disease and mild cognitive impairment. *J Alzheimers Dis* 19: 363–372, 2010.
169. Soderling TR. CaM-kinases: modulators of synaptic plasticity. *Curr Opin Neurobiol* 10: 375–380, 2000.

170. Sondheimer N, Glatz CE, Tirone JE, Deardorff MA, Krieger AM, and Hakonarson H. Neutral mitochondrial heteroplasmy and the influence of aging. *Hum Mol Genet* 20: 1653–1659, 2011.
171. Starkov AA, Fiskum G, Chinopoulos C *et al.* Mitochondrial α-ketoglutarate dehydrogenase complex generates reactive oxygen species. *J Neurosci* 24: 7779–7788, 2004.
172. Steenken S. Purine bases, nucleosides, and nucleotides: aqueous solution redox chemistry and transformation reactions of their radical cations and e- and OH adducts. *Chem Rev* 89: 503–520, 1989.
173. Stierum RH, Croteau DL, and Bohr VA. Purification and characterization of a mitochondrial thymine glycol endonuclease from rat liver. *J Biol Chem* 274: 7128–7136, 1999.
174. Stierum RH, Dianov GL, and Bohr VA. Single-nucleotide patch base excision repair of uracil in DNA by mitochondrial protein extracts. *Nucleic Acids Res* 27: 3712–3719, 1999.
175. Stowe DF and Camara AK. Mitochondrial reactive oxygen species production in excitable cells: modulators of mitochondrial and cell function. *Antioxid Redox Signal* 11: 1373–1414, 2009.
176. Straface, E Matarrese P, Gambardella L, *et al.* Oxidative imbalance and cathepsin D changes as peripheral blood biomarkers of Alzheimer disease: A pilot study. *FEBS Lett* 579: 2759–2766, 2005.
177. Subba Rao K. Mechanisms of disease: DNA repair defects and neurological disease. *Nat Clin Pract Neurol* 3: 162–172, 2007.
178. Suzuki YJ, Forman HJ, and Sevanian A. Oxidants as stimulators of signal transduction. *Free Radic Biol Med* 22: 269–285, 1997.
179. Swerdlow RH and Khan SM. A "mitochondrial cascade hypothesis" for sporadic Alzheimer's disease. *Med Hypotheses* 63: 8–20, 2004.
180. Swerdlow RH and Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis: an update. *Exp Neurol* 218: 308–315, 2009.
181. Swerdlow RH. Brain aging, Alzheimer's disease, and mitochondria. *Biochim Biophys Acta* 1812: 1630–1639, 2011.
182. Szabo C. Multiple pathways of peroxynitrite cytotoxicity. *Toxicol Lett* 140–141: 105–112, 2003.
183. Szczesny B, Bhakat KK, Mitra S, and Boldogh I. Age-dependent modulation of DNA repair enzymes by covalent modification and subcellular distribution. *Mech Ageing Dev* 125: 755–765, 2004.
184. Szczesny B, Tann AW, Longley MJ, Copeland WC, and Mitra S. Long patch base excision repair in mammalian mitochondrial genomes. *J Biol Chem* 283: 26349–26356, 2008.
185. Takao M, Aburatani H, Kobayashi K, and Yasui A. Mitochondrial targeting of human DNA glycosylases for repair of oxidative DNA damage. *Nucleic Acids Res* 26: 2917–2922, 1998.
186. Takuma K, Fang F, Zhang W, *et al.* RAGE-mediated signaling contributes to intraneuronal transport of amyloid-beta and neuronal dysfunction. *Proc Natl Acad Scu USA* 106: 20021–20026, 2009.
187. Takuma K, Yao J, Huang J, *et al.* ABAD enhances Abeta-induced cell stress via mitochondrial dysfunction. *FASEB J* 19: 597–598, 2005.
188. Tang S and Huang T. Characterization of mitochondrial DNA heteroplasmy using a parallel sequencing system. *Biotechniques* 48: 287–296, 2010.
189. Taylor RC, Cullen SP, and Martin SJ. Apoptosis: controlled demolition at the cellular level. *Nat Rev Mol Cell Biol* 9: 231–241, 2008.
190. Torreilles F, Salman-Tabcheh S, Guerin M, and Torreilles J. Neurodegenerative disorders: the role of peroxynitrite. *Brain Res Rev* 30: 153–163, 1999.
191. Turrens JF. Mitochondrial formation of reactive oxygen species. *J Physiol* 552: 335–344, 2003.
192. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, and Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol* 39: 44–84, 2007.
193. Valla J, Schneider L, Niedzielko T, *et al.* Impaired platelet mitochondrial activity in Alzheimer's disease and mild cognitive impairment. *Mitochondrion* 6: 323–330, 2006.
194. Virag L, Szabo E, Gergely P, and Szabo C. Peroxynitrite-induced cytotoxicity: mechanism and opportunities for intervention. *Toxicol Lett* 140–141: 113–124, 2003.
195. Wallace DC, Stugard C, Murdock D, Schurr T, and Brown MD. Ancient mtDNA sequences in the human nuclear genome: a potential source of errors in identifying pathogenic mutations. *Proc Natl Acad Sci USA* 94: 14900–14905, 1997.
196. Wallace DC. Animal models for mitochondrial disease. *Methods Mol Biol* 197: 3–54, 2002.
197. Wang J, Xiong S, Xie C, Markesbery WR, and Lovell MA. Increased oxidative damage in nuclear and mitochondrial DNA in Alzheimer's disease. *J Neurochem* 93: 953–962, 2005.
198. Wang W, Fang H, Groom L *et al.* Superoxide Flashes in Single Mitochondria. *Cell* 134: 279–290, 2008.
199. Weissman L, de Souza-Pinto NC, Stevnsner T, and Bohr VA. DNA repair, mitochondria, and neurodegeneration. *Neurosci* 145: 1318–1329, 2007.
200. Wilkinson B, *et al.* Fibrillar beta-amyloid-stimulated intracellular signaling cascades require Vav for induction of respiratory burst and phagocytosis in monocytes and microglia. *J Biol Chem* 281: 20842–20850, 2006.
201. Wilson DM III and Barsky D. The major human abasic endonuclease: formation, consequences and repair of abasic lesions in DNA. *Mutat Res* 485: 283–307, 2001.
202. Wilson TM, Rivkees SA, Deutsch WA, and Kelley MR. Differential expression of the apurinic/apyrimidinic endonuclease (APE/ref-1) multifunctional DNA base excision repair gene during fetal development and in adult rat brain and testis. *Mutat Res* 362: 237–248, 1996.
203. Wojda U, Salinska E, and Kuznicki J. Calcium ions in neuronal degeneration. *IUBMB Life* 60: 575–590, 2008.
204. Yakes FM and Van Houten B. Mitochondrial DNA damage is more extensive and persists longer than nuclear DNA damage in human cells following oxidative stress. *Proc Natl Acad Sci USA* 94: 514–519, 1997.
205. Yang JL, Weissman L, Bohr VA, and Mattson MP. Mitochondrial DNA damage and repair in neurodegenerative disorders. *DNA Repair (Amst)* 7: 1110–1120, 2008.
206. Yao Y, Zhukareva V, Sung S, *et al.* Enhanced brain levels of 8,12-iso-iPF2α-VI differentiate AD from frontotemporal dementia. *Neurology* 61: 475–478, 2003.
207. Zheng L, Zhou M, Guo Z, *et al.* Human DNA2 is a mitochondrial nuclease/helicase for efficient processing of DNA replication and repair intermediates. *Mol Cell* 32: 325–336, 2008.
208. Zimmermann H. Neurotransmitter release. *FEBS Lett* 268: 394–399, 1990.
209. Zoratti M and Szabo I. The mitochondrial permeability transition. *Biochim Biophys Acta* 1241: 139–176, 1995.
210. Zucker RS. Calcium- and activity-dependent synaptic plasticity. *Curr Opin Neurobiol* 9: 305–313, 1999.

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Abbreviations Used

8OHA = 8-hydroxyadenine
8OHdG = 8-hydroxydeoxyguanosine
8OHG = 8-hydroxyguanine
ABAD = Aβ-binding alcohol dehydrogenase
AD = Alzheimer's disease
APE1 = AP endonuclease
Aβ = Amyloid beta
BER = base excision repair
COX = cytochrome c oxidase
ETC = electron transport chain
H_2O_2 = hydrogen peroxide
HNE = 4-hydroxy-2-nonenal
LP-BER = long-patch BER
MCU = mitochondrial Ca^{2+} uniporter
MPT = mitochondrial permeability transition
MPTP = mitochondrial permeability transition pore
mtDNA = mitochondrial DNA
NADPH = nicotinamide adenine dinucleotide phosphate
nDNA = nuclear DNA
NEILS = Nei-like homologs
NOS = nitric oxide synthase
NOX = nicotinamide adenine dinucleotide phosphate oxidase
NTH1 = human endonuclease III homologue
OGG1 = 80HG DNA glycosylase
OXPHOS = oxidative phosphorylation
ROS = reactive oxygen species
SP-BER = short-patch BER
TBARS = thiobarbituric acid reactive substances
UDG = hyderoxymethyl-uracyl DNA glycosylase

1. アルツハイマー病

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Key Point

- 認知症におけるアルツハイマー病（AD）の比率は脳血管性認知症より低いとされてきたが，最近はADが多いという報告が多く，臨床的には約50%がADとされる。
- AD脳の病理学的特徴は，大脳皮質，海馬を中心とした神経細胞脱落，細胞外に沈着するアミロイドを核にもつ老人斑の形成と血管周囲のアミロイド沈着，細胞内に蓄積する神経原線維変化である。
- 最初に起こる臨床症状は記憶障害である。さらに1～3年経つと実行・遂行障害や時間の見当識障害が加わり，以前はあった興味・関心が失われる，日課をしなくなる，怒りっぽくなるなどの性格の変化も出現する。このようになると日常生活の困難さがみられるようになり，家族も気づくようになる。
- スクリーニングテストとしては，MMSEやHDS-Rが用いられる。重症度評価としてはFASTやCDRが，記憶障害を中心とした中核症状の検査としてはWAIS-R，WAIS-Ⅲ，ADASなどが用いられる。

概　念

アルツハイマー病（Alzheimer's disease：AD）は認知症のなかで最も頻度が高く，今後増加が予想される疾患である。そのため日常診療のなかで遭遇する機会が多い。また，一般に認知症という疾患群を理解する際に，ADを基本的な概念として考えることが多く，医療に関わるすべての職種にとって重要な疾患である。なお，アルツハイマー病とアルツハイマー型認知症は同義に扱う。

1．疫学

わが国における認知症の65歳以上の有病率は従来5～8%とする報告が多かったが[1]，最近の新しい報告では10%を超える可能性が示唆されている[2]。認知症におけるADの比率は従来，脳血管性認知症より低いとされてきたが，最近はADが多いという報告が多く，臨床的には約50%がADとされる。また，病理学的な検討でも50%前後がADという報告が多い[3]。

2．危険因子

ADの危険因子としては，表1のような因子があげられている。遺伝的危険因子であるApoE ε4アレルはADの遺伝的危険因子として確立しており，アレルが一つ増えるとリスクが数倍高まり，発症が早まる[4]。ダウン症候群では40歳頃から認知症を呈し，AD類似の脳病理所見を呈する。生活習慣に関わる危険因子としては，高血圧，糖尿病といった動脈硬化を介した血管因子に関する

表1 アルツハイマー病の危険因子

1. 遺伝的危険因子
   ApoEε4，ダウン症候群
2. 血管性因子
   高血圧，糖尿病
3. 生活習慣や環境の危険因子
   食事（抗酸化物質）
   アルコール
4. その他の危険因子
   年齢，頭部外傷

もの，ポリフェノールやフラボノイドなど食品に関連した防御因子が知られているが，単独での発症への影響力は強くない。

病　態——病理学的背景

AD脳の病理学的特徴は，大脳皮質，海馬を中心とした神経細胞脱落，細胞外に沈着するアミロイドを核にもつ老人斑の形成と血管周囲のアミロイド沈着，細胞内に蓄積する神経原線維変化である。

神経細胞脱落は大脳の広い範囲に起こるが，ことにアセチルコリン系の中核であるマイネルト基底核の神経細胞脱落が強く，その結果，記憶との関連が強いアセチルコリン系が障害される。これは治療でアセチルコリン補充薬が使われる根拠となる。老人斑や脳血管内に蓄積するアミロイドの主要成分はアミロイドβ蛋白，ことにアミロイドβ_{42}が重要である。老人斑は正常人にもみられるが，ADではより広範囲にかつ大量に出現することが知られており，この変化は神経細胞の障害が起こる前から始まっていることがわかっている。神経細胞内に起こる神経原線維変化の構成成分はタウ蛋白であり，AD脳ではリン酸化，ユビキチン化されている。タウの蓄積と神経細胞死との関係，アミロイドの蓄積がタウの蓄積とどのように結びつくかに関しては依然として解明されていない。

診　断

1．診断基準

ADの診断基準として代表的なものは，米国精神医学会「精神疾患の診断・統計マニュアル第4版」（DSM-Ⅳ-TR）による診断基準[5]（表2）と，1984年に米国の国立精神研究所（NINCDS）とアルツハイマー病協会（ADRDA）が共同で作成したNINCDS-ADRDA基準[6]（表3）であるが，最近バイオマーカー研究の進展を加え，より早期の診断に重点を置いた新しい診断基準が提唱された[7]（表4）。1984年のNINCDS-ADRDAのprobable AD例は全例この基準を満たすことが確認されている。

DSM-ⅣによるADの診断基準は，米国精神医学会が1994年に作成した診断基準である。記憶を含む複数の認知機能障害とは，記憶以外にa．失語，b．失行，c．失認，d．実行機能の障害を指し，これらのうちの1つ，またはそれ以上の障害があることがA）の基準を満たすことになる。高齢者の認知症では，失語，失行，失認が初期から出現することはまれで，記憶障害＋実行・遂行障害，記憶障害＋見当識障害の組み合わせが多くみられる。DSM-Ⅳでは，AD，脳血管性認知症，一般身体疾患による認知症，物質誘発性の持続性認知症，複数の病因による認知症，特定不能の認知症に分け鑑別診断の基準を示しているのが特徴である。

NINCDS-ADRDA：probable ADの診断基準は，診断が確定（definite），臨床的確診（probable），臨床的疑診（possible）の3段階からなり，診断確定は臨床的にprobableの基準を満たし，かつ病理学的にADの所見があることによる。したがって臨床診断だけではADとは確定できず，臨床診断として最も確度が高いのはprobable ADということになる。この診断基準の特徴は，①診断基準に階層性をもたせたこと，②発症年齢に関する規定があること，③probable ADらしくない病像を取り上げていることがあげられる。具体的にprobable ADらしくない病像としては，a）卒中のような突然の発症，b）初期からみられる局所性の神経所見（片麻痺，感覚障害，小脳性失調，視野障害など），c）発症時あるいは初期にみられる痙攣や歩行障害があげられている。2001年に米国神経アカデミーはNINCDS-ADRDAのprobable ADとDSM-Ⅲ-Rが最も信頼性の高い基準として推奨した[8]。また，この診断基準は病理所見と対比した検討がなされている点がより信頼性を高めている。

表2　米国精神医学会「精神疾患の診断・統計マニュアル第4版」（DSM-Ⅳ）によるアルツハイマー型認知症の診断基準

A）記憶を含む複数の認知機能障害
　1. 記憶障害
　2. 以下の認知障害が1つ以上存在
　　a. 失語　b. 失行　c. 失認　d. 実行機能障害
B）社会的・職業的な機能の障害/病前の機能の著しい低下
C）ゆるやかな発症と持続的な認知機能の低下
D）A）の障害が下記によらない
　1. 中枢神経系疾患（脳血管障害，パーキンソン病，ハンチントン病，硬膜下血腫，正常圧水頭症，脳腫瘍）
　2. 全身性疾患（甲状腺機能低下症，ビタミン$_{12}$/葉酸/ニコチン酸欠乏症，高カルシウム血症，神経梅毒，HIV感染症）
　3. 物質誘発性の疾患
E）せん妄の経過中にのみ現れるものではない
F）障害が他の第1軸の疾患では説明されない
　大うつ病性障害，統合失調症など

〔American Psychiatry Association : Diagnostic and Statistical Manual of Mental Disorders 4th edition（DSM-IV）, American Psychiatry Association, 1994より引用，改変〕

表3　NINCDS-ADRDAによるアルツハイマー型認知症の診断基準

臨床的確診（probable AD）の診断基準
- 臨床的および神経心理学的検査で認知症が認められる
- 2つ以上の認知機能の障害
- 記憶と他の認知機能の進行性の悪化
- 意識障害がない
- 40～90歳の間の発症
- 進行性の記憶と認知障害の原因となる全身・脳の疾患がない

臨床的疑診（possible AD）の診断基準
- 認知症を起こすのに十分な他の神経学的，精神医学的，全身的な異常所見がないにもかかわらず認知症が存在
  発症の仕方，症候，臨床経過が典型的でない
- 二次的に認知症を起こすような全身性疾患や脳疾患があっても，それが患者の認知症の原因とはみなしがたい場合
- ほかに特殊な原因がなく，次第に進行する重篤な単独の認知障害の場合は，研究上possible ADとする

〔McKhann, G. et al : Neurology, 34 : 939-944, 1984より引用，改変〕

表4　NIAA（National Institute on Aging-Alzheimer's Association）によるアルツハイマー型認知症の診断基準（Probable AD dementia : Core clinical criteria）

1. 認知症の診断基準を満たしていること。それに加えて以下のような特徴を有すること
　A. 緩徐な発症：月～年の単位での進行であり，時間や日で突然発症しない
　B. 認知機能の悪化の明確な病歴
　C. 以下に示すような最初のそして最も主たる認知機能の低下が存在する
　　a. 健忘：最も一般的な徴候。認知症のクライテリア5で示した領域の障害が1つは存在することが必要
　　b. 非健忘症状：
　　・言語の障害　・視空間認知の障害　・遂行障害
　D. 以下が存在しないこと
　　(a) 認知機能を悪化させたり生じさせたりする脳血管障害：多発脳梗塞，高度の白質病変
　　(b) レビー小体型認知症の存在だけでなく，レビー小体型認知症の中核症状の存在
　　(c) 行動異常型の前頭側頭型認知症の主要症状の存在
　　(d) 語義失語型の進行性失語症，非流暢性/錯語型の進行性失語症
　　(e) その他の神経疾患，内科的疾患，薬物で認知機能に影響を与えるもの

確実性の高いprobable AD dementia
　認知機能検査の進行性低下例：原因遺伝子変異キャリア

ADの病理過程の証拠を伴うprobable AD dementia
　脳アミロイドβ蓄積のバイオマーカー：脳脊髄液アミロイドβ$_{42}$低下，アミロイドPET陽性
　二次性神経変性や障害のバイオマーカー：脳脊髄液タウ，リン酸化タウ増加，FDG-PETでの頭頂側頭葉の糖代謝低下，MRI 統計画像処理での頭頂葉，側頭葉の萎縮（診断目的のルーチン使用は現時点では勧められない。臨床研究や治験，測定可能な施設で，臨床医によって必要とされた場合のみ適応）

〔McKhann GM, et al : Alzheimers Dement, 7 : 263-269, 2011より引用，改変〕

2. 臨床症状

最初に起こる症状は記憶障害である。具体的には，同じことを何度も聞く，置き忘れやしまい忘れが目立つ，人や物の名前が出てこないといった症状がみられる。これらの症状は正常高齢者にもみられ，この段階ではなかなか病気と気がつきにくい（軽度認知機能障害の稿を参照）。この時期が1～3年続いた後に，物事を計画的に段取りよくできない（実行・遂行障害）や時間の見当識障害が加わってくる。また，以前はあった興味や関心が失われる，日課をしなくなる，だらしなくなる，怒りっぽくなるといった性格の変化が出現する。このような症状が出現すると日常生活の困難さがみられるようになり，家族が気づくようになる。この段階でMini-Mental State Examination（MMSE）や改訂長谷川式簡易知能評価スケール（HDS-R）といった標準的なスクリーニングテストを行うと，3単語の再生と時間の見当識で失点するという特徴的なパターンを呈する。また，取り繕い反応がしばしば観察される。具体例を示すと，「今日は何月ですか」という質問に対して，「今日は新聞もテレビも見てこなかったものですから」という。日常生活で家事をしなくなったという情報に対して，最近苦手になったり，困ったりすることはないかと尋ねると「いいえ。何でも普通にやっています。困ることもありません」と答える。前者は時間の見当識障害を，後者は実行・遂行障害があることを取り繕っている。患者はこのようなことを聞かれることが不本意であるという表情を浮かべて，決然と取り繕う。言語機能そのものに問題がない場合には，非常にもっともらしい説明となることがあるので，介護認定の評価や成年後見の診断書を作成する場合には注意が必要である。また，家族は患者が適当なことを言ってつじつまを合わせ，平気な様子でいることにいら立つことが多い。若年の認知症では実行・遂行障害が最も仕事に影響するため気づかれやすい。また，末期になるまで運動症状が出ないのも特徴であるが，最終的には言語の理解や発声が困難になり，歩行障害，嚥下障害が出現し，臥床状態となる。

3. 神経心理学的評価（表5）

スクリーニングテストとしてはMMSEやHDS-Rが用いられる。HDS-Rでは20点以下を認知症としたときに最も鑑別力が高く，感度は0.93，特異度は0.86である。MMSEでは23点以下を認知症と判定した場合に感度0.76～0.87，特異度0.82～0.97を示す。重症度評価としてはFunctional Assessment Staging（FAST）やClinical Dementia Rating（CDR）が用いられる。記憶障害を中心とした中核症状の検査としては，知能全般をみるWechsler Adult Intelligence Scale-Revised（WAIS-R）とその改訂版であるWAIS-Ⅲ，経過観察に有用なAlzheimer's Disease Assessment Scale（ADAS）が代表的な評価尺度である。記憶の評価尺度としてはWechsler Memory Scale Revised（WMS-R）が代表的であり精度も高いが，検査に時間を有するのが欠点である。空間認知機能の評価にはRaven's Colored Progressive Matrices（RCPM）やKohs立方体検査が用いられる。言語機能の評価にはStandard Language Test of Aphasia（SLTA）やWestern Aphasia Battery（WAB）を使用する。前頭葉機能の評価は必ずしも容易ではないが，詳細な検査としてはWisconsin Card Sorting Test（WCST）が，簡易なテストとしてはTrail Making Test（TMT）やFrontal Assessment Battery at bedside（FAB）が用いられる。

このほかにも，精神症状の評価としてNeuropsychiatric

表5 代表的な神経心理学的評価

スクリーニングテスト
- MMSE（Mini-Mental State Examination）
- HDS-R（Hasegawa Dementia Scale-Revised）

重症度評価
- FAST（Functional Assessment Staging）
- CDR（Clinical Dementia Rating）

中核症状の検査（主に記憶障害）
- WAIS-R（Wechsler Adult Intelligence Scale-Rivised），WAIS-Ⅲ
- ADAS（Alzheimer's Disease Assessment Scale）

記憶の評価尺度
- WMS-R（Wechsler Memory Scale-Revised）

空間認知機能の評価
- RCPM（Raven's Colored Progressive Matrices）
- Kohs立方体検査

言語機能の評価
- SLTA（Standard Language Test of Aphasia）
- WAB（Western Aphasia Battery）

前頭葉機能の評価
- WCST（Wisconsin Card Sorting Test）
- TMT（Trail Making Test）
- FAB（Frontal Assessment Battery at bedside）

Inventory（NPI）やBehave-AD，うつの評価としてGeriatric Depression Scale（GDS）やHamiltonの抑うつスコアが，日常生活機能の評価としてはDisability Assessment for Dementia（DAD），介護者の負担度の評価としてZaritの介護負担尺度などが利用される。個々の検査の詳細に関しては成書を参照されたい[9]。

4. 画像診断（□絵図1）

ADを対象に行われる画像診断は，大きく2種類に大別される。すなわち，CT，MRIに代表される，主に脳の形態学的変化をとらえることを目的としたものと，positron emission tomography（PET），single photon emission computed tomography（SPECT）に代表される，脳の機能的側面を画像としてとらえる方法である。MRIはCTに比べ解像力に優れ，微小な脳血管障害を描出しやすく，また種々の方向の断層を得られる点で優れる。しかし，一部の認知症に特異的にみられる石灰化病変や出血性病変の描出などの点ではCTが優れる。また最近では灰白質濃度をもとに標準脳による解剖学的標準化を用いて画像統計解析を行うvoxel-based morphometry（VBM）が可能となり，簡便に利用できるソフトウェア（VSRAD：voxel-based specific regional analysis system for Alzheimer's disease）が開発されている[10]。ADの病理学的変化は，側頭葉内側部の内嗅領皮質に始まるとされ，MRIでは比較的早い時期よりこの近傍の海馬の形態学的な萎縮がみられる。これをとらえるには，水平断画像では側脳室下角の拡大を評価するが，T1冠状断画像がより有効であり，認知症を疑う際にはこの条件での指示が必要となる。高齢発症例では，側頭葉に比較的限局する脳萎縮を呈する例が多いが，初老期発症のADでは，脳萎縮は前頭側頭葉優位に全体に及び病勢の進行も速い。特に高齢者では正常者においても脳萎縮の個人差が大きいため，個々の症例での脳萎縮での判定は注意を要する。また，X線CT，MRI上の白質病変〔いわゆる脳室周囲白質軟化症（PVL），脳室周囲病変（PVH）〕はADをはじめとする変性疾患でもしばしばみられ，これを根拠に血管性認知症と診断することは慎重を要する。ADの初期診断においては後述する機能画像がより有用であるが，他の脳疾患の鑑別のためにも形態画像は必須である。

一方，PET，SPECTは微量の放射性物質（ラジオアイソトープ）で標識した薬剤を生体に投与し，目的部位（脳）に集積した放射線を検出し，画像化する方法であり，投与薬剤により，脳血流量，糖・酸素などのエネルギー代謝，各種神経伝達物質およびそのレセプター量などの測定が可能である。現在，国内においてはSPECT用製剤として^{133}Xe，^{123}I-IMP，^{99m}Tc-PAO，^{99m}Tc-ECDの4種の脳血流測定用製剤が放射性医薬品として企業より供給されている。一方，PETはSPECTより解像力に優れるが，超短半減期（約2～110分）のアイソトープを使用するため，各施設においての薬剤合成が必要となり，サイクロトロンをはじめとする大がかりな設備が必要となる。^{18}F-FDG（^{18}F-fluoro-deoxyglucose）については製薬企業の工場から近隣の病院への配送システムが整備されたが，脳PET検査については脳腫瘍，難治性部分てんかんに対する脳ブドウ糖代謝の測定以外は保険適応となっていないのが現状である。ADの病理学的変化は側頭葉内側部の内嗅領皮質に始まるとされるが，神経投射部位のシナプス活動を反映するPET，SPECTでの血流，代謝の最も早期にとらえられる変化は後部帯状回に始まるとされる[11]。進行した時期になると典型的には，側頭葉外側面より頭頂葉にかけての血流，代謝の低下が明らかとなる。病理学的に萎縮の強い海馬近傍の糖代謝は側頭葉外側面の変化の程度と比べると比較的保たれる。さらに進行した時期になると前頭葉の血流，代謝の低下が明らかとなっていく。一次運動感覚野，一次視覚野は相対的に保たれる場合が多い。近年，アミロイドやタウの画像化が試みられている。ピッツバーグ大学のグループはチオフラビンTの誘導体である^{11}C-6-OH-BTA-1（PIB）を開発した[12]。ADでは前頭前野や大脳皮質でアミロイドの強い集積がみられるが，臨床的に正常例でも集積がみられることがあり，臨床応用は今後の課題である。

5. 診断上の問題点

ADでは初期には精神症状は目立たないことが多いが，前頭葉症状から始まるfrontal variant of Alzheimer's disease[13]や失語症から始まる例があり，その際は前頭

側頭葉変性症との鑑別が困難である。今後，前述のアミロイドPETが鑑別に有用となる可能性がある。

【症例提示】

70歳　女性

主訴：もの忘れ

現病歴：1年ほど前から前日のことを忘れることが多くなった。通帳や大切なもののしまい忘れが目立つようになり，物が見つからないときに夫のせいにする。結婚した娘のところに何度も電話してくるが，前にかけた内容を覚えていない。買い物へは行くが，同じものを大量に買ってきてしまい冷蔵庫内で腐らせてしまう。料理もレパートリーが減り，3日続けて同じ料理を作った。最近，好きで通っていた絵画教室へいろいろ理由をつけては行かなくなった。

初診時所見：診察室では礼節は保たれている。今日の日付を質問すると，同伴の夫を振り返り答えを聞こうとする。「今日は新聞もテレビも見てこなかったものですから」と言い訳する。「薬は飲めていますか」と質問すると，「きちんと飲んでいます。日付を書いてカレンダーに貼り付けて忘れないようにしています」と言う（夫の情報ではできていない）。一般身体所見，神経学的所見には特記すべき所見なし。

MMSEは23/30で，時間の見当識と3単語再生で失点。頭部MRIでは軽度の海馬の萎縮を認めるが年齢相応（VSRAD：1.88）。脳血流シンチグラムでは頭頂側頭連合野の軽度の血流低下，後部帯状回から楔前部での血流低下がみられた。

引用文献

1) 鷲見幸彦，他：痴呆疾患に関する医療経済的検討．日本老年医学会雑誌，41：451-459，2004
2) 朝田　隆：認知症の人はどのくらいいるのか．こころの科学，161：12-16，2012
3) Akatsu H, et al : Subtype analysis of neuropathologically diagnosed patients in a Japanese geriatric hospital. J Neurol Sci, 196 : 63-69, 2002
4) Maestre G, et al : Apolipoprotein E and Alzheimer's disease: ethnic variation in genotypic risks. Ann Neurol, 37 : 254-259, 1995
5) American Psychiatry Association : Diagnostic and Statistical Manual of Mental Disorders 4th edition（DSM-IV）, American Psychiatry Association, 1994
6) McKhann G, et al : Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology, 34 : 939-944, 1984
7) McKhann GM, et al : The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement, 7 : 263-269, 2011
8) Knopman DS, et al : Practice parameter: diagnosis of dementia（an evidence-based review）. Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology, 56 : 1143-1153, 2001
9) 日本臨牀2011年増刊号：認知症学（上）Ⅲ．臨床編 4．認知症診療に用いられる評価法と認知機能検査．pp390-475，2011
10) Hirata Y, et al : Voxel-based morphometry to discriminate early Alzheimer's disease from controls. Neurosci Lett, 382 : 269-274, 2005
11) Minoshima S, et al : Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease. Ann Neurol, 42 : 85-94, 1997
12) Klunk WE, et al : Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol, 55 : 306-319, 2004
13) Johnson JK, et al : Clinical and pathological evidence for a frontal variant of Alzheimer's disease. Arch Neurol, 56 : 1233-1239, 1999

トラックセッション3　認知症の人のための地域包括ケアー2025年に向けたプログラム

認知症の身体合併症医療はどうあるべきか

鷲見幸彦

抄　録

認知症の人がさまざまな身体合併症を生じて，急性期病院を受診し，入院することが今後増加すると推測されるが，その対応方法に関する検討は少ない．本稿では国立長寿医療研究センターでの，認知症高齢者の精神症状や行動障害にも対応可能で，身体合併症にも対応しうる独立したユニット・病棟の試み，認知症を診療するスタッフを支える認知症患者サポートチーム（DST）の試みについて紹介する．

Key words：認知症，身体合併症，認知症患者サポートチーム

はじめに

認知症は，高齢者に多い疾患であると同時に経過の長い疾患であり，その経過中にさまざまな身体疾患や外傷を合併（身体合併症）する．身体合併症の発症は，短期的には行動・心理症状（behavioral and psychological symptoms of dementia；BPSD）を発現させる要因となり，日常生活動作を低下させる．さらに長期的には生命予後に影響する．また認知症では，自己評価の障害や言語機能の障害から自ら症状を訴えることが困難なことがあり身体合併症の発見が遅れる．入院が必要となることもしばしばであるが，体調の悪化に環境変化によるダメージが加わり，せん妄状態となることがある．さらに回復期には離院や転倒といった医療安全の観点からは望ましくない事象が発生することがあり，入院の継続に難渋することが珍しくない．このような状況下で一般病院（ことに急性期病院）においていかに認知症患者に対応していくかは重要である．現在の急性期病院での認知症への対応状況について述べ，国立長寿医療研究センターでの取組みについて紹介する[3]．

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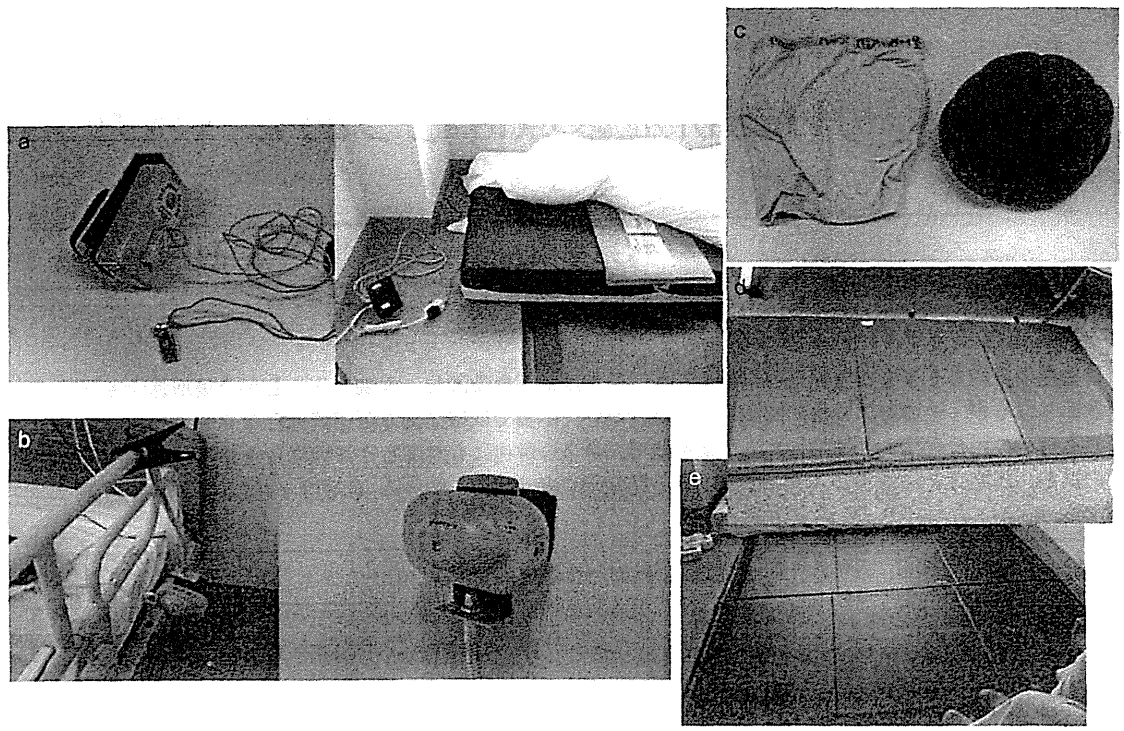
Ⅰ．急性期病院での認知症対応状況

平成20年に愛知県下の臨床研修指定病院81施設にアンケート調査を行った[2]．結果を表1にまとめた．回答は21施設（回答率26%），内訳は大学病院2，名古屋市内の病院9，公的病院2，私立病院7，県内他地域の病院10，公的病院5，私立病院5で，ベッド数は100～1,505床，医師

表1　身体合併症発症時の一般病院での認知症対応，システムの確立（愛知県におけるアンケート調査）

1．認知症の専門外来は60%の施設で存在するが，専門病棟を有する施設はない
2．身体合併症としては内科系では感染症，脳血管障害，外科系では当該科の手術に関連した合併症が多い
3．対応が困難となる原因は過活動症状（徘徊，興奮，夜間の不穏）が圧倒的に多い
4．管理困難な患者に対する治療としては，鎮静薬投与が多い
5．理想的な診療体制としては，認知症高齢者の精神症状や行動障害にも対応可能で，身体合併症にも対応しうる独立したユニットが求められている



a：クリップセンサー，b：赤外線センサー，c：ヒッププロテクター（左）と保護帯（右），d：センサーマット，e：衝撃吸収マット

図1　転倒，傷害予防具

数は17～426人であった．認知症を専門としている医師が所属しているかについては，「所属している」12施設，「していない」9施設であり，専門病棟の有無については有している施設はなかった．一方，専門外来は8施設で「あり」という回答であった．専門として対応しているのは，これらの病院ではほとんどが神経内科医であった．救急外来に認知症患者が受診したときの主たる対応では，「身体合併症に対してのみ対応し，認知症症状については対応しない」6施設，「身体合併症に対して対応し，認知症症状については重症度症状に応じて対応する」11施設，「身体合併症と認知症症状についても対応する」3施設であった．

最も困難を感じる点は「診察時に指示が守れないので身体診察および処置ができない」であった．積極的に受け入れていない理由としては，「徘徊や興奮で周囲の患者さんに迷惑がかかる」が多数を占めたが，「入院するとなかなか退院できず，経営上影響が大きい」という回答もみられた．入院してきた患者に，必要とされている検査や治療を行うことができないときの対応や，入院をしてきた患者に徘徊や興奮がみられ，周囲に迷惑がかかるときの対応ではいずれも「院内で対応を検討する」がほとんどであった．入院の原因となった身体合併症としては，内科系では感染症，脳血管障害，外科系では当該科の手術に関連した合併症が多かった．管理困難となる理由としては患者本人の身体面で危険が多いこと，患者に時間をとられて他患の看護が不十分となることが挙げられた．対応が困難となる原因は過活動症状（徘徊，興奮，夜間の不穏）が圧倒的に多く，それに対しては鎮静薬投与が多かった．

理想的な診療体制としては認知症高齢者のBPSDにも対応可能で，身体合併症にも対応しう

表2　24時間観察チャート

平成　年　月　日（　）　　氏名（　　様）

時間	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
VS（時間）	（　）T			P		BP		SpO_2	（　）T			P		BP		SpO_2	（　）T			P		BP		SpO_2
BS																								
食事（　）																								
in（　ml/日）																								
尿（　ml/日）																								
便（便処置）																								
便の性状・量																								
内服（服用時間）																								
睡眠																								
認知症症状																								

る独立したユニットが求められていた．また同じ研究で長谷川[11]は全国のDPC（診断群分類包括評価）病院700施設に認知症患者への医療提供体制に関するアンケート調査を行った．院内体制の現状と理想に関しての調査では，「現人数での内部医療スタッフで何とか行う」か，「人員を厚くしたユニットが理想」とする結果を得ている．

Ⅱ．国立長寿医療研究センターでの試み

1．認知症ユニットの創設

この結果に基づいて認知症対応病棟を検討した．45床の病棟のうちの18床を認知症対応病棟とし，看護師長を含め16人の看護師が配置された．これは3交代で夜勤を行う最低の人員配置ではあるが，患者・看護師比では1：1に近い配置である．医師は精神科，神経内科，老年科の入院の際は当該科が，それ以外の科が入院する際には，これらの科のいずれかが副科として診療に当たることとした．入院患者数は平成21年4月～平成22年2月28日までの11か月間で延べ174人であり，平均年齢は78.76歳であった．入院の理由は，①外来からBPSDのコントロール目的，②他病棟で認知症への対応が困難なことによる転棟，③認知症を有する患者が慢性硬膜下血腫で入院した際の術後の管理の順であった．他病棟で看護が困難であった理由としては，患者が多動で監視困難，離棟のリスクが高い患者，意欲低下，無為の強い患者への活性化が挙げられた．

この病棟では各種センサーを用いて転倒予防に努めた（図1）．転倒自体は月平均8件で他病棟よりも明らかに高かったが，骨折に至った例は11か月間で1例のみであった．

また専用の24時間で1枚のチャートを用い，睡眠時間，BPSDの種類や発生時間を集中的にモニターした（表2）．BPSD治療の入院では，BPSDを引き起こしそうな薬剤をwash outする