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Myelin in Alzheimer's disease: culprit or bystander?

Michel Maitre¹, H el ene Jeltsch-David^{1,2}, Nwifere Getrude Okechukwu¹, Christian Klein¹, Christine Patte-Mensah¹,
Ayikoe-Guy Mensah-Nyagan¹

¹*Biopathologie de la My el ine, Neuroprotection et Strat egies Th erapeutiques, INSERM U1119, F ed eration de M edecine Translationnelle de Strasbourg (FMTS), Universit e de Strasbourg, B atiment CRBS de la Facult e de M edecine, 1 rue Eug ene Boeckel, 67000 Strasbourg, France*

²*Biotechnologie et signalisation cellulaire, UMR 7242 CNRS / Universit e de Strasbourg, 300 Boulevard S ebastien Brant CS 10413, 67412 Illkirch cedex, France*

Corresponding authors: Michel Maitre : maitre@unistra.fr, phone: (+33) 368853096 or Ayikoe-Guy Mensah-Nyagan : gmensah@unistra.fr, phone: (+33) 368853124

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20 Abstract

21 Alzheimer's disease (AD) is a neurodegenerative disorder with neuronal and synaptic losses due to the accumulation
22 of toxic amyloid β ($A\beta$) peptide oligomers, plaques, and tangles containing tau (tubulin-associated unit) protein. While
23 familial AD is caused by specific mutations, the sporadic disease is more common and appears to result from a complex
24 chronic brain neuroinflammation with mitochondriopathies, inducing free radicals' accumulation. In aged brain,
25 mutations in DNA and several unfolded proteins participate in a chronic amyloidosis response with a toxic effect on
26 myelin sheath and axons, leading to cognitive deficits and dementia. $A\beta$ peptides are the most frequent form of toxic
27 amyloid oligomers. Accumulations of misfolded proteins during several years alters different metabolic mechanisms,
28 induce chronic inflammatory and immune responses with toxic consequences on neuronal cells. Myelin composition
29 and architecture may appear to be an early target for the toxic activity of $A\beta$ peptides and others hydrophobic misfolded
30 proteins. In this work, we describe the possible role of early myelin alterations in the genesis of neuronal alterations
31 and the onset of symptomatology. We propose that some pathophysiological and clinical forms of the disease may
32 arise from structural and metabolic disorders in the processes of myelination/demyelination of brain regions where the
33 accumulation of non-functional toxic proteins is important. In these forms, the primacy of the deleterious role of
34 amyloid peptides would be a matter of questioning and the initiating role of neuropathology would be primarily the
35 fact of dysmyelination.

36

37 **Keywords:** myelin, early biomarker, Alzheimer's disease, oligodendrocytes, $A\beta$ peptides

38 Introduction

39 Sporadic AD typically occurs after the age of 65 and is the most common cause of dementia in older people. We
40 consider here the disease under its main pathophysiological definition that classically consists of extracellular amyloid
41 plaques and intracellular neurofibrillary tangles [70, 71]. These abnormalities lead to a cascade of events eventually
42 conducting to cognitive disorders and dementia. There are, however, a significant number of diverse clinical
43 presentations with ages of onset and evolution in the disease that suggest non-univocal pathophysiological mechanisms
44 [61]. It seems that some cases of sporadic AD involve changes in the constitution and architecture of myelin, and this
45 early in the life of the future patient. In general, extracellular abnormalities of the amyloid cascade predominate,
46 followed most often by other Tau mediated biological mechanisms at the intracellular level, accompanied by
47 inflammatory, neuroimmune and neurochemical disorders that can put dysmyelination at the forefront of
48 neurodegenerative disorders.

49 Myelin consists of a multilayered membrane wrapped around the axons of most central nervous system (CNS) neurons.
50 This membrane is produced by expansions of specialized glial cells of the brain, "the mature oligodendrocytes",
51 derived from oligodendrocytes progenitor cells (OPCs) [22]. This cell line constitutes the precursor cells for the
52 constitution of the myelin sheath through a well-defined program of proliferation, migration, and differentiation to lead
53 to the myelination of neuronal axons [101]. Among the properties of myelin, the best known is the saltatory conduction
54 of nerve impulses, which gives it more speed and efficiency. Furthermore, it is now well acknowledged that

55 oligodendrocytes' expansions display a trophic, plastic, and metabolic influence on the axons they envelop (Fig.1)
 56 [131, 139]. Myelin is constantly reshaping and its alteration in degenerative phenomena such as Alzheimer's disease
 57 (AD) may be a fundamental element for the genesis of pathophysiological and clinical disorders observed in the early
 58 stages of the disease [21].

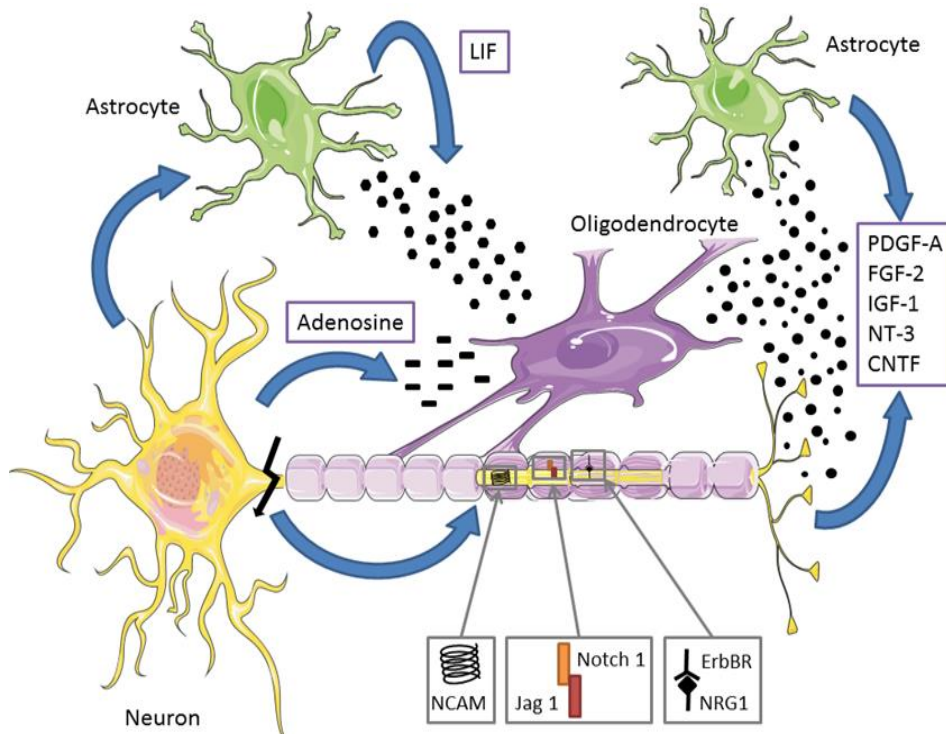


Fig.1 Oligodendrocytes are derived from the differentiation of oligodendrocyte precursor cells (OPCs) and are the main cell for remyelination (modified from [176]). The differentiated oligodendrocytes of OPCs migrate to different axons via positive chemotactism [216]. A variety of growth and trophic factors regulate the development of oligodendrocytes and their temporal and geographical attractions [17]. Many of these factors are produced by both neurons and astrocytes, regulating the proliferation, survival, or degeneration of OPCs. The neuroregulin, which activates Erb-tyrosines kinases receptors, promotes the survival and proliferation of oligodendrocytes. The activation of the Notch 1 cascade inhibits the differentiation of oligodendrocytes, and an integrin/contactin complex coordinates signals from the extracellular matrix and the axonal surface to regulate oligodendrocyte survival and myelination. This also depends closely on the electrical activity propagated in the axons. OPCs express functional adenosine receptors, activated by action potential [150, 184]. Adenosine acts as a powerful transmitter between glia and neurons to inhibit the proliferation of OPCs, stimulate their differentiation and stimulate myelin production. The LIF (leukemia inhibitory factor) is heavily involved in oligodendrocyte development kinetics and in the overall myelination process [134, 198]. Abbreviations: CNTF, ciliary neurotrophic factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor; LIF, leukemia inhibitory factor; NCAM, neural cell adhesion molecule; NT-3, neurotrophin 3; OPCs, oligodendrocyte precursor cells; PDGF-A, platelet-derived growth factor-A.

59 AD involves progressive neurodegeneration with neuronal losses leading to cognitive, memory, emotional, behavioral
 60 disorders, and a progressive dependence [210]. Long considered to primarily affect the grey matter, many studies have
 61 described early lesions of the white matter in patients with nascent and moderate intensity [55]. The main molecular
 62 alterations of the disease are considered to contain essentially a pathology of the production/degradation and an intra-
 63 brain accumulation of amyloid β ($A\beta$) peptides producing deposits in the form of hydrophobic plates of aggregated
 64 toxic peptides (senile plaques) [70, 160]. Another proteinopathy usually accompanies the previous protein in the form
 65 of hyperphosphorylated tau proteins and deposits of neurofibrillary tangles. These toxic proteins maintain chronic
 66 inflammation and oxidative stress accompanied by neuronal and synaptic losses at the origin of the symptomatology

67 [31]. This paper reviews the fundamental importance of myelin and correct CNS myelination for its development,
68 functional adaptations, and permanent reshuffling. During aging in the human patient, sporadic AD has plurifocal
69 impairments that induces various clinical presentations depending on the intensity of inflammatory and immune
70 reactions, and ischemic, mitochondrial, and free radical disorders. In many cases, the hypothesis of an alteration of the
71 amyloid cascade A β as a primitive mechanistic etiology is questionable and multiple proteinopathies can be implicated,
72 which depend on somatic mosaicism, transcriptional and translational alterations. In many cases, myelin and its
73 integrity appear to be a preferential and early target in multiple forms of AD, and oligodendrocytes represent a cell
74 population highly sensitive to A β and other proteinopathies. These misfolded proteins result in multiple dysmetabolism
75 that accentuate and modify the course and clinical forms of the disease.

76 Multiple causes, multiple targets

77 AD as an heterogeneous disease

78 The amyloid hypothesis as the essential cause of neuronal loss and brain atrophy is a matter of discussion mainly
79 because removal or reduction of amyloid plaques by immunological treatments display no significant effect on clinical
80 symptoms of AD [37, 140]. However, before aggregation, the soluble oligomeric forms of A β peptides possess strong
81 toxic properties against myelin integrity and neuronal survival [161, 189]. White matter lesions are commonly found
82 in magnetic resonance imaging (MRI) scans of elderly people and are associated with cognitive decline [129]. Whether
83 or not a primary role of A β peptides is fundamental in these lesions is a matter of debate.

84 Increase in the concentration of A β peptides in brain has also been described because of head trauma or cerebral
85 ischemia [179, 220]. This increase in the concentration of A β peptides is additional evidence for the existence of
86 various forms of Alzheimer's like diseases with various clinical pictures and various mechanisms of neurodegenerative
87 processes in term of pathophysiological evolution and biological markers [41, 212]. In addition to A β peptides
88 accumulation and toxicity, hyperphosphorylation of tau proteins, which disturbs microtubules assembly and axonal
89 transport, could have some impact on the trophic effect on the myelin envelop [209]. These basic alterations are also
90 supplemented with several others biological modifications of many molecular pathways and functions namely in the
91 domain of energy metabolism and cholesterol transports [19]. Cholesterol is fundamental for oligodendrocytes survival
92 and for synthetis of myelin, this compounds represent a large proportion of the human brain and abnormalities in
93 cholesterol metabolism are present and associated with brain age and in Alzheimer's disease [12, 106]. Regarding
94 cholesterol delivery to axons and synapses, the ϵ 4 allele of the apolipoprotein E (*APOE*) gene is the less effective factor
95 for cholesterol transport compared to ϵ 3 and ϵ 2. Interestingly, normal adults at the cognitive level show microstructural
96 changes in myelin architecture when carrying homozygous alleles ϵ 4 that is a major marker for late AD [129, 146,
97 147].

98 Sporadic AD is a multifactorial disease

99 While familial AD has essentially genetic causes expressed in amyloid precursor protein (APP) and presenilin leading
100 early in life to specific proteinopathies and inducing neurodegenerative pathologies [64], these mechanisms are less
101 consistent in the sporadic AD of elderly subjects. In these patients displaying accumulations of cerebral amyloid

102 peptides, the question arises as to whether this accumulation is the cause or the consequence of other factors inducing
103 neurodegeneration. Over the years, many mutations are present in brain neurons, generating multiple proteinopathies
104 after transcriptional, translational, or post-translational errors. Some of these are of exogenous origin and enter the
105 CNS due to the pathological porosity of the blood-brain barrier (BBB). The accumulation of these abnormal proteins
106 generates inflammatory and immune responses that lasts for many years. Such accumulation is increased by
107 mitochondriopathies, and the genesis of free radicals related to the disruption of oxidative phosphorylation and the
108 depreciation of energy metabolism. The most deleterious and widespread proteinopathy is that affecting the regulated
109 proteolysis of the APP, giving rise to toxic peptides interfering with many neuronal functions and leading to synaptic
110 and neuronal losses, as well as inducing profound cognitive and behavioral functional abnormalities. These peptides
111 exhibit amyloid properties and accumulate over time into hydrophobic plaques, which can be detected by PET scan
112 ligands or post-mortem histology.

113 Accumulating evidence supports a multi-factor for the origin of many forms of sporadic AD. Multi-organ alterations
114 could initiate or worsen neurodegeneration [8, 194, 208]. Developing heart failure promoting hypoxia, intestinal and
115 hepatic disorders altering brain metabolism through the microbiome, ischemic symptoms due to vascular deposits and
116 chronic inflammation, could also contribute to the decrease in neuronal survival [115, 197].

117 [Metabolic disorders and AD](#)

118 Many metabolic alterations have often been encountered in AD with varying severities. Most of these alterations
119 concern or affect brain energy metabolism, these phenomena being aggravated by cerebral hypoperfusion and blood
120 sugar abnormalities [10]. Carbohydrate metabolism and dysfunctions in intestinal absorption phenomena, nutritional
121 abnormalities and deficiencies, resistance to glucose utilization via decreased insulin sensitivities combined with fatty
122 acid metabolism disorders, induce energy deficiencies deleterious to neuronal functioning and survival [86]. The
123 slowing down of the tricarboxylic cycle generates the accumulation of acetyl-CoA coming from the increased fatty
124 acids degradation and the synthesis of ketone bodies that could have a positive role on neuronal survival. White matter
125 degeneration in AD could be in part due to the accelerated degradation of lipids in this context of decreased energetic
126 metabolism coming from reduced glucose utilization (Fig.2) [142, 206].

127 At the hepatic level, functional alterations (cirrhosis, hepatitis) could aggravate the elimination of deleterious proteins
128 including A β [203]. Modifications of bile acids synthesized by the altered liver tissue exhibit impaired neuroprotective
129 functions. Frequently, the accumulation of mutations in the mitochondrial genome accelerates pathological phenomena
130 at the level of the tricarboxylic cycle or the respiratory chain and increase ROS production [74]. Metabolic disorders
131 of the periphery of the body often affect brain metabolism via abnormal permeability of BBB and the presence of
132 abnormal metabolites in the cerebrospinal fluid (CSF). This mainly concerns certain intermediates of amino acids
133 metabolism, particularly regarding the catabolites of tryptophan degradation [171]. This essential amino acid is the
134 precursor not only of melatonin and serotonin, but also of the intermediates of the kynurenine cycle, some of which
135 possess neuroprotective or neurotoxic properties or interfere with the elimination of amyloid peptides from the brain
136 [117].

137

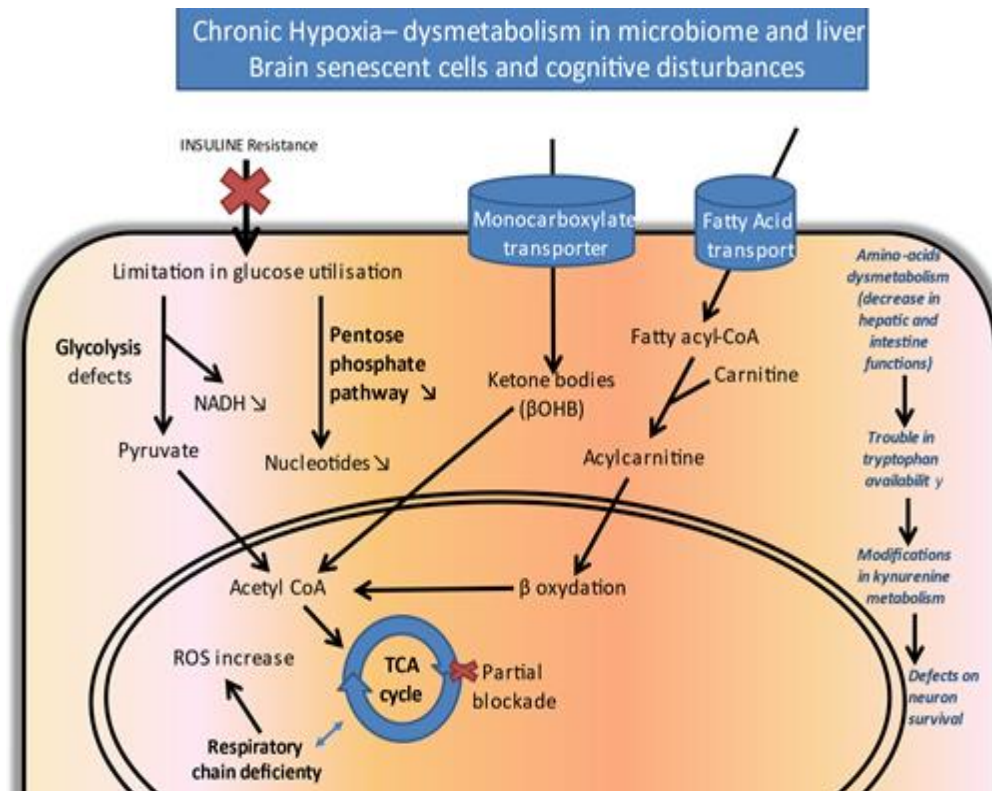


Fig.2 Dysregulation in multiple biochemical pathways underlie the pathogenesis of AD. Metabolomic approaches conducted from the blood or CSF of AD patients compared to controls highlighted abnormalities in the energy metabolism of patients. A diabetic-type pathology is often evoked with a decrease in insulin sensitivity. In addition to disorders in glycolysis and the respiratory chain, abnormalities involving accumulations of ketone bodies resulting from the metabolism of acetyl-CoA residues, a product of the accelerated degradation of fatty acids by β -oxidation, have been described. The bioavailability and metabolism of several amino acids could also be affected, especially concerning tryptophan degraded in the kynurenine cycle and resulting in the formation of neuroprotective (kynurenic acid) or neurotoxic (quinolinic acid) compounds. Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; NADH, nicotinamide-adenine-dinucleotide; ROS, reactive oxygen species; TCA, tricarboxylic acid; β OHD, beta-hydroxybutyrate.

138 Myelin has morphological alterations in the early stages of AD

139 Change of the lipid composition of myelin over time [128]

140 Oligodendrocytes-derived myelin accounts for about 40% of CNS lipids, consisting of 50% phospholipids, 40%
 141 glycolipids, 10% cholesterol and cholesterol esters, and polyunsaturated long-chain fatty acids (Fig.3) [84].

142 Synthesized by oligodendrocytes, cholesterol comes almost exclusively from ketone bodies as precursors. This lipid
 143 has structural functions at the level of the myelin by regulating the fluidity and permeability of this membrane around
 144 the axons, and it regulates the speed of myelination according to its uptake by the membrane in formation. The typical
 145 lipids of myelin are essentially galactosyl ceramides and sulfatides. They stabilize and organize myelin in direct
 146 association with the basic protein.

147 Changes in the configuration of myelin are observed with age but are more accentuated in AD. Not all regions of the
 148 brain are affected in the same way. In general, the volume of white matter decreases over time and the phenomena of
 149 demyelination/remyelination accentuated by pathology leads to the decrease in the size of axons and the reduction in
 150 the size of the internodal distances. These structural changes induce functional consequences for conduction rates and

151 vulnerability to traumatic, ischemic, dysmetabolic conditions and toxic factors such as oligomers A β peptides. These
152 processes are commonly encountered as factors favoring Alzheimer's genesis and pathology.

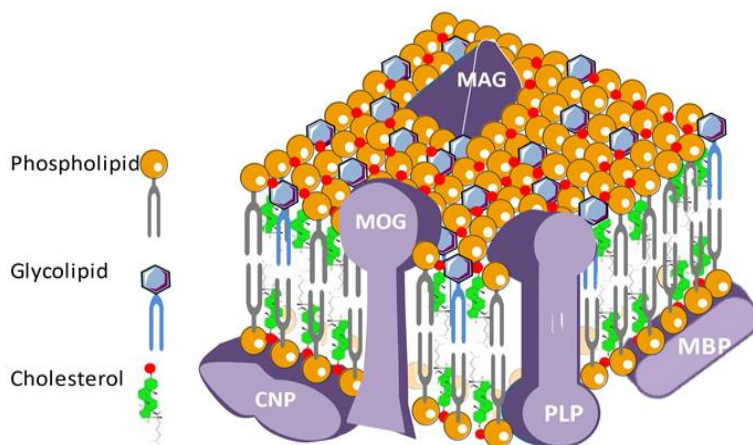


Fig.3 Myelin composition and organization. The myelin wrapping around most of the CNS axons includes a large majority of complex lipids and 15-30% of specific proteins. Lipids are essentially made up of cholesterol, galactocerebrosides and phospholipids. This envelope is constantly reshuffled in time and space from the oligodendrocytes that make up the bulk of the glial cells of the CNS. Chronic inflammatory and autoimmune reactions, mutations in certain constituent proteins, attacks by free radicals or ischemic, and metabolic problems related to aging alter the myelin sheath that releases its constituents into the CSF and the bloodstream. In AD, myelin is one of the first bulwarks for the anatomical and functional integrity of the axons it surrounds and undergoes early toxic action of misfolded extracellular toxic proteins or peptides. Abbreviations: AD, Alzheimer' disease; CNP, C-type natriuretic peptide; CNS, central nervous system; CSF, cerebrospinal fluid; MAG, myelin-associated glycoprotein; MBP, myelin basic protein; MOG, myelin oligodendrocyte glycoprotein; PLP, proteolipid protein.

153 [A step for the conversion of mild cognitive impairment \(MCI\) into dementia?](#)

154 Studies of myelin sheath's conformation in AD were mostly conducted by electron microscopy and MRI both in
155 animals and humans. The 5XFAD mouse is a transgenic model that expresses three different mutations in the *APP* and
156 two in presenilin 1 (*PS1*). In this mouse, amyloid deposits can be detected with synaptic losses at an age as early as
157 1.5 months [143] and myelin abnormalities can be seen even earlier accompanying the first alterations in spatial
158 memory occurring around the age of 1 month [68]. Several studies conducted in humans suggest that myelin disorders
159 strongly contribute to the onset of AD symptoms. Neuroimaging shows myelination defects in several brain regions,
160 but especially and firstly in the hippocampus and corpus callosum [55, 138, 148, 201]. Conformation abnormalities
161 accompanied by thinning of the myelin sheath are frequently encountered even before the onset of axonal lesions,
162 which may indicate premises for demyelination. In the pre-clinical stages of the disease, MRI shows altered
163 longitudinal and transverse relaxation times and increased myelin hydration degrees [18]. In general, abnormalities in
164 the structure and formation of the cerebral white matter have been identified in many presentations of Alzheimer's
165 disease that can be warning signs for a disease in progress [157]. Variations in T1w/T2w ratios in patients with risk
166 factors (close family history, *APOE4* phenotypes) were identified compared to control individuals. In addition,
167 individuals at risk had an association with altered patterns of resting-state functional connectivity (rs-FC) [53]. These
168 abnormalities support the idea of significant alterations in myelin developing with age and constituting signals of
169 vulnerability [52]. Interestingly, some studies have shown a relationship between structural abnormalities of myelin in
170 ADs in the pre-clinical period and peptide concentrations of A β 1-42 in patients' CSF [34, 36].

171 Studies of cortical stratification in the human brain provide important knowledge on the level of degeneration, in
172 addition to the information given by the level of volumetric atrophy [148, 156]. MRI studies show hyper-densities in
173 the white matter with volume increase consistent with the abnormalities of amyloid peptides and tau proteins in CSF.
174 At the histological level, it appears that these stratification disorders are mainly due to alterations in myelin architecture
175 in which iron ions could play an important role [43]. Vascularization and oxygen supply in injured hyper-dense regions
176 are decreased and are related to axonal lesions and inflammatory disorders, BBB permeability abnormalities and
177 multiple disseminated micro-hemorrhagic structures [89, 103].

178 Potential involvements of epigenetic mechanisms in myelin reshuffle

179 GWAS (genome-wide association study) has identified about 40 loci associated with AD in the European population
180 and in these respective loci, several genes involved directly in the causative mechanism of the disease have been
181 described (*APOE*, *CRI*, *BINI*, *TREM2*, *CLU*, *SORL1*, *ADAM10*, *ABCA7*, *CD33*, *SP11*, *PIRLA*). It remains to identify
182 the functions of many genes in the identified loci. Many risk genes are involved in the innate immune response and
183 neuroinflammation. The CD33 and TREM2 microglia receptors, implicated in microglial pathology, represent new
184 targets for the development of therapeutic tools. It is possible in many cases that the activation of innate immunity,
185 like that encountered in other myelin pathologies, associated with long-term inflammatory mechanisms, is responsible
186 for subtle alterations of myelin during the incubation period of the disease [5, 66].

187 Over 20 AD risk loci falling mainly in noncoding regions of the genome have been identified by genome-wide
188 association studies, explaining the complexity of the disease at the genetic level [82, 99, 127]. The regulation of gene
189 expression by microRNA is a promising issue for the diagnostic and treatment of several kind of MCI and AD at the
190 beginning of the symptoms, as well as to discriminate with other myelin pathologies like multiple sclerosis [104, 226].
191 In such diseases, the dynamics of the myelination/demyelination/remyelination balance is continuously evolving under
192 normal conditions of plasticity of the nervous system, but also under pathological conditions, where this balance is
193 affected [46]. In this respect, the process of myelin degeneration are particularly concerned both in multiple sclerosis
194 and in the early phases of AD. Oligodendrocytes and their progenitors are directly involved in membrane and metabolic
195 interactions with neurons during the different phases of destruction and regeneration of the myelin sheath, driven by
196 the dynamic and fluctuating expression of many transcription factors [180]. The activity of the nervous system is
197 intimately linked to the epigenetic regulation of the activity of these factors and to the neo-expression of certain genes
198 involved in the functional dynamics of the production/destruction of myelin [159]. Correct myelination is essential for
199 the proper development and evolution of neuronal connections and the adaptation of brain function to the environment.
200 It constantly reshapes neuron/oligodendrocytes interactions following many factors such as learning, social
201 relationships, emotional stimuli (emotions, anxiety) [167, 217]. These stimuli can induce epigenetic modifications that
202 alter the physiology and functionality of precursors and oligodendrocytes [166].

203 Changes in the epigenome have a role in the manifestations of AD [13]. Social isolation impacts the intensity of
204 neuronal activity and reduces the importance of myelination [6, 139]. Modifications in the acetylation and methylation
205 of histones were detected, as well as in DNA [132]. These adaptations participate in the regulation of genes involved
206 in the processes of myelination/demyelination and in the pathophysiology of certain neurodegenerative diseases where

207 these processes play a central role (AD, but also multiple sclerosis) [30]. This last pathology of myelin includes
208 analogies with those existing in some phenotypic form of AD and may be the consequence of a combined alteration
209 of genetic and epigenetic factors, the latter involving DNA methylations, histone modifications, chromatin remodeling
210 and modified regulation of non-coding RNA [16].

211 Brain markers of myelin in Alzheimer's patients

212 Looking for myelin components in biological fluids

213 At the genetic markers level, several genes associated with the corpus of the oligodendrocyte ecosystem have been
214 described as risk factors in late-onset AD [125]. In genomic association studies, the *BINI* (bridging integrator 1) gene
215 is considered to be significantly involved in late AD behind the *APOE* gene [169]. It is mainly expressed in mature
216 oligodendrocytes and white matter in rodents and humans, where it regulates membrane dynamics in the phenomena
217 of endocytosis and membrane remodeling [35]. Histologically, *BINI* is mostly expressed at the Ranvier nodes.

218 *BACE1* (beta-site amyloid precursor protein cleaving enzyme 1) codes for a transmembrane β secretase expressed in
219 several cell types including oligodendrocytes. It cleaves *APP* giving birth to amyloid peptides, but also neuroregulin 1,
220 which modulates the myelination and differentiation of oligodendrocytes [49, 195]. Many β -secretase inhibitors have
221 effects on myelin abnormalities caused by AD. Finally, several other genes that are also expressed in oligodendrocytes
222 (*PICALM*, *NME8*, *PSEN*, for example) possess a special responsibility as genetic factors associated with the
223 development of AD [124].

224 *LINGO 1* (leucine rich repeat and Immunoglobulin-like domain-containing protein 1) codes for a transmembrane
225 protein primarily expressed in the cortex, hippocampus, thalamus, and amygdala. The protein acts primarily as a
226 negative regulator of myelination and its inhibition may have potential applications for the treatment of myelin damage
227 in neurodegenerative diseases [202]. As such, anti-LINGO 1 antibodies promote the action of oligodendrocytes and
228 the repair of myelin disease [211].

229 The biochemical markers of the white matter indicating the evolution of late AD are of many natures and depend on
230 the stage of the disease. Since myelin is mainly composed of complex lipids synthesized by oligodendrocytes, reduced
231 levels of galactosyl ceramide (cerebroside) and sulfatide can be found in both the grey and white matters of AD brains
232 [90]. These compounds are the most specific lipids of myelin, decreasing in parallel with the severity of the disease
233 and altering long before fibrillary deposits of tau protein [28, 88]. Cholesterol concentrations, another majority lipid
234 compound of myelin sheaths, is known to decrease with the onset of cerebral atrophy [42].

235 Myelin proteins are also involved in relatively early stages of the disease (Braak stage I and II), in which alterations
236 of oligodendrocytes and myelin are noted even before the onset of clinically detectable cognitive disorders [55]. The
237 level of most myelin proteins is likewise decreased in more advanced stages of AD (Braak stages V and VI). Lowered
238 concentrations of basic myelin protein (MBP), proteolipid (PLP) and 2'-3' cyclic nucleotide phosphodiesterase
239 (CNPase) are observed, specifically in several regions of the cerebral cortex.

240 In the field of protein markers present in patients' CSF, there is a wide heterogeneity and variability, which confirm
241 the impression that sporadic AD may be the consequence of multiple and varied alterations in many metabolic circuits.

242 This reinforces the idea that the pathophysiological mechanisms leading to late AD are multifactorial and reveal a
243 disease of great complexity [205]. Many cognitive pathologies with MCI are often accompanied in a non-specific way
244 by the presence of inflammatory markers and proteins associated with the complement cascade in the CSF or blood of
245 patients.

246 Oligodendrocyte's dysfunction: A major risk factor in AD and a process in the onset of the 247 disease?

248 Before the appearance of amyloid and tau pathology, many forms of AD showed a breakdown of myelin due to the
249 vulnerability of oligodendrocytes under this neurodegenerative pathology. In many cases, the loss of myelin sheaths
250 appears to be the initiating step in the earliest stages of the disease. Extensive evidence has indicated that the breakdown
251 of myelin is associated with AD since the vulnerability of oligodendrocytes under Alzheimer's pathology easily induces
252 the myelin breakdown and the loss of the myelin sheath.

253 Aging itself is already an important factor of myelin alterations and multiple cellular partners are involved in this
254 process. Brain MRI often reveals signs including several hyper signal outbreaks in T2-weighted images (T2WI) with
255 chronic cerebral hypoperfusion often associated with carotid stenosis [113]. These alterations appear more massive at
256 the stage of MCI both in animal models and in human pathology than in established AD. In myelin abnormalities,
257 association of oligodendrocytes' losses with axonal alterations are commonly encountered in post-mortem patients
258 [138]. The accumulation of A β peptides is considered a princeps factor in the neurodegenerative process even before
259 the appearance of aggregates in the form of amyloid plaques [23, 76]. The response of oligodendrocytes to the presence
260 of amyloid peptides or plaques has been the subject of several studies. During aging, the spontaneous involution of
261 these cells is important, and their disappearance is close to 25 % from the age of 50 years, this phenomenon being
262 potentiated by the presence of the *APOE* ϵ 4 allele in the genomic baggage of the individual [108, 133, 135].
263 Furthermore, the importance of increase in the expression of myelinating genes in oligodendrocytes from Alzheimer's
264 patients is related to the severity of the disease [65, 80]. In transgenic animals over-expressing the APP, the myelin
265 sheath has an increased thickness and a modified architecture [54, 68, 214].

266 Originating mostly from the ventricular and subventricular regions of the brain, OPCs are present in the brain, even in
267 the adult stage [62, 165, 188, 218]. OPCs control the angiogenesis of the white matter, its vascularization/oxygenation,
268 and the myelination of axons according to spatial-temporal parameters, which contribute to their stability, functions,
269 and integrity [97, 154]. Intimate exchanges between neurons regulate ionic homeostasis, making of real synaptic
270 connections and activity of OPCs via numerous neurotransmitters [58, 69, 173]. These cells are also the target for
271 several mitogens produced by neurons and trophic factors like neuroregulin 1 and brain-derived neurotrophic factors
272 (BDNF), whose release depends on neuronal activity [78, 204]. Many studies have been conducted to explore early
273 oligodendrocyte alterations in AD in association with changes in myelination and early symptoms of the disease. Most
274 commonly, oligodendrocyte differentiation abnormalities are associated with disruption of oxidative stress phenomena
275 associated with excitotoxicity, mediated by glutamatergic metabotropic receptors in large amounts in oligodendrocyte
276 precursors [21, 138]. Other factors, such as high iron ion levels and disorders in the glutathione cycle, would accentuate
277 the presence of free radicals, without forgetting the mitochondrial chain disorders induced by the toxicity of A β

278 peptides [191]. Mitochondria pathologies are at the forefront of axonal survival for functional and metabolic exchanges
279 with the myelin envelope [67, 219].

280 Myelination is directly related to the intensity of neural activity, which affects the electrical properties of axons. The
281 toxicity of A β peptides proteinopathy affects immediately the whole myelin-axon, which forms a couple with multiple
282 functional and metabolic relationships [182].

283 The toxicity of proteinopathies, which causes degenerations in AD, mainly concerns oligomeric A β peptides and
284 hyperphosphorylated tau proteins [2, 39, 84]. Senile plaques are rarely seen in the hydrophobic white matter and does
285 not lend itself to the aggregation of toxic oligomers. As a result, it is mainly these latter that exert toxicity on myelin.

286 The therapeutic strategies currently developed for plaque removal seem not to display huge impact on clinical
287 symptomatology [196]. In fact, the degree to which the therapeutic strategies for plaque removal have clinical effects
288 remains an open question, as the reason why such therapies are not working well. For more than twenty years,
289 therapeutic research against AD has focused on reducing the accumulation of pathological amyloid peptides and the
290 substances studied have made it possible to achieve this goal without significant improvement in cognitive impairment
291 in patients. The amyloid hypothesis revised in many cases is questioned, sometimes in favor of primitive alterations
292 of the myelin envelope [61]. Oligodendrocytes are very active cells from a metabolic point of view, especially during
293 the process of myelination or remyelination. A cellular respiratory abnormality that may be related to hypo-
294 vascularization or ischemia may be the source of a myelination disorder [138]. Vascular pathologies affecting the white
295 matter are common in the elderly or with symptomatologically occurring early AD [79, 109]. The human brain is
296 largely myelinated, which may partly explain its vulnerability to neurodegeneration [193].

297 Oligodendrocytes are widely represented in many areas of the human CNS, especially in the neocortex, where they
298 account for about 75% of glial cells [44]. They are considered very fragile, and their density decreases sharply in the
299 brain of the elderly person from 50 years of age [223]. Various methods of labeling these cells have shown a severe
300 loss of oligodendrocytes in several regions of the hippocampus, not correlated with the density of amyloid β deposits
301 [38]. These specific depopulations probably precede the disorganization of the neural connectome that precedes the
302 appearance of AD, and a contemporary demyelination around the outbreaks of amyloid peptide deposits [95]. These
303 dysfunctions are strongly associated with abnormalities in lipoprotein metabolism given that the amyloid
304 oligodendrocytes actively participate in the synthesis of cholesterol constituting synaptic contacts [121]. They secrete
305 apolipoproteins E and J, which are severe risk factors depending on the alleles involved in the onset of AD [86].
306 Interestingly, the production of new oligodendrocytes seems fundamental for motor learning in mice [112].

307 During the development of AD, including in the early stages characterized by mild, worsening memory disorders
308 (MCI), numerous studies have been performed to characterize the changes observable by MRI techniques in the
309 structure and architecture of myelin. Schematically, the results obtained showed very early the existence of a reduction
310 in cerebral myelin levels, with losses of oligodendrocytes and axons, microglial activations accompanied by dilated
311 perivascular regions in the white matter. These studies are essentially based on the contrasts between the aqueous
312 contents of the intra- and extra-cellular spaces at the periventricular level, comparing MCI patients and control persons.

313 It seems that progressive ischemia with vascular and energy losses associated with the toxicity of certain

314 proteinopathies (especially amyloidosis A β) alters the myelin structure very early and hinders proliferation and
315 oligodendrocytic re-myelination [89, 138, 149].

316 **Adaptative immunity to myelin components in AD**

317 **An auto-immune process for degeneration?**

318 Many results support the existence of mutual interactions between immune processes (innate and acquired) and
319 neurodegenerative events, especially those occurring during the incubation of AD [33, 51, 145].

320 Neuroinflammation phenomena are considered to pre-exist for a very long time in the brain before the onset of cellular
321 stigmas of neurodegeneration and clinical symptomatology. Chronic inflammation, microglia activation and
322 lymphocytic infiltration are thought to be the result of intracerebral accumulation of misfolded proteins and/or multiple
323 exogenous attacks of various infectious agents during the individual's lifetime [40]. Amyloid peptides and
324 hyperphosphorylated tau are particularly involved in the inflammatory reaction and progressive onset of autoimmunity
325 [207]. Changes in circulating cytokines as well as disorders in the cascades of the complement and clotting factors
326 testify to changes in the immune response at the periphery [144]. Cleavage fragments of abnormal proteins, numerous
327 glycosylated proteins and a large population of phosphoproteins contribute to microglial activation in the brain and
328 alteration of many resident proteins [24]. This include myelin constituent proteins that are presented as new antigens
329 to the immune system. Studies have shown significant accumulation of autoantibodies in the serum of patients with
330 AD, especially directed against myelin proteins [63, 116]. IgG and IgM immunoglobulins directed against the MOG,
331 MBP, MAG and PLP proteins are frequently present in the CSF and circulating blood [153]. This strongly suggests
332 the involvement of the immune system in myelin alterations observed in many AD patients and in some animal models
333 of the disease.

334 Since the discovery of mutations in *APP*, *PSEN1* and *PSEN2* genes, which induce familial ADs, the hypothesis of the
335 amyloid cascade at the origin of the pathophysiology of AD remains the preferred mechanism of this type of
336 neurodegeneration [137]. The problem is that sporadic AD does not usually present this type of mutation, although
337 similar pathologies of A β peptides and tau proteins are encountered in familial and late forms of the disease [107]. The
338 main hypothesis remains those long-term abnormalities in A β peptide metabolism are the starting point of tau
339 dysfunction and a series of toxic phenomena inducing neuronal and cognitive losses. It appears that during aging,
340 multiple mutations accumulate in the nuclear and mitochondrial DNA of neural cells that add up to the increased loss
341 of editing and quality control of translated proteins [77, 111]. It is estimated that in the normal individual, about 20%
342 of the proteins synthesized by ribosomes have structural and folding abnormalities and must be eliminated by the
343 proteasome, lysosome, or resident proteases of the cell membrane [98, 158, 181]. Overloading these mechanisms leads
344 to chronic neuroinflammation, microglial and macrophagic activation, and immune responses against abnormal non-
345 functional proteins over the long-term [123]. Among the oligomeric peptides that accumulate in the brain and display
346 significant cellular toxicity are A β peptides and particularly the peptide A β 1-42. This accumulation most often comes
347 from a drop in the clearance to the vascular compartment and the CSF.

348 The rupture of the myelin envelope appears to be an early phenomenon in the pathophysiology of AD [36, 151, 201].
349 In humans, the vulnerability of myelin materializes on MRI through morphological changes, thinning and hydration

350 swelling [48, 228]. At the same time, there are elevations of tau, phosphotau, soluble APP β (sAPP β) peptides and A β 1-
351 42 peptides. The latter peptide has a high toxicity to myelin in oligodendrocyte cultures and in animal models of
352 familial AD (*e.g.* 5XFAD mice), where morphological alterations of myelin are the first pathological stigmas to appear
353 in animals at 1 month of age [68]. The mechanisms of toxicity of peptides A β are still the subject of speculation; it
354 seems that the oligomeric A β peptides are the main culprits of this toxicity [76]. Several cellular receptors (glutamates,
355 ephrin's, adrenergic, cholinergic, and immunoglobulins) bind oligomeric A β peptides and could mediate the toxicity
356 of amyloid oligomers during the years of incubation of the disease [172, 215].

357 Multi-proteinopathies are associated with aging brains

358 During lifetime, mutations accumulate in the post-mitotic cells of neurons due to non-replication of DNA, but also
359 within mitochondrial DNA [87, 96]. This results in harmful mitochondriopathies for neuronal survival, as well as
360 increased production of misfolded and non-functional proteins. Deficiencies in quality control and protein structure
361 editing also contribute to the intra-brain accumulation of protease-resistant hydrophobic deposits with intrinsic toxicity
362 [1, 152]. These chronic accumulations lead to long-term inflammatory and phagocytic reactions, as well as immune
363 responses accompanied by infiltration of immunocompetent cells. Gradually, an amyloid reaction develops, in which
364 peptides A β participates largely because of their cerebral accumulation. The elimination of these peptides from the
365 brain is largely conditioned by the effectiveness of the enzymes that degrade them and allow their clearance [222]. The
366 peptide A β 1-42 is particularly toxic to myelin sheaths, axonal and synaptic endings that finally degenerate [76, 138].
367 In several transgenic models of familial forms of Alzheimer's, the first stigmas of the disease result in morphological
368 abnormalities of myelin sheaths, in the form of edema and thinning of the envelope surrounding myelinated axons. At
369 the same time, disturbances in animal behavior appear manifesting as reduced anxiety manifestations and reduction of
370 memory and spatial recognition [56, 57].

371 Depending on the individual, brain aging does not occur unequivocally but depends on multiple factors related to
372 specific genes and environmental situations (Fig.4) [177]. The accumulation of mutations in the nuclear DNA of post-
373 mitotic cells and mitochondrial DNA induce deleterious mitochondriopathies [122, 187], promote the production of
374 abnormal proteins, impair respiratory and energy functions, and amplify cellular and oxidative stress [92]. Toxicity of
375 abnormal oligomers seems to be the result of their misfolded nature, which exposes hydrophobic residues leading to
376 aggregation and abnormal interactions with a large range of cellular components [4]. Membranes like myelin
377 constituted mainly by complex hydrophobic lipids could be an important target for amyloid oligomers for direct
378 interactions andymes modifications inducing inflammatory and immune responses.

379 Several evidence from studies of the population of abnormal proteins in the CSF showed that abnormal proteins in
380 CSF represent a picture close to that of abnormal proteins in the brain [11]. This methodology can provide information
381 on the biochemical and metabolic changes that occur in the CNS of patients with neurodegeneration. CSF amyloid
382 peptides and tau proteins are used for the diagnosis and evolution of AD [155]. A β 1-42 peptides correlation has been
383 described with several CSF proteins belonging to the endocannabinoid and the somatostatin systems [72] with the
384 latter regulating the proteolytic degradation of the amyloid peptide. The presence of other proteins has been linked to
385 the degradation of the myelin [170].

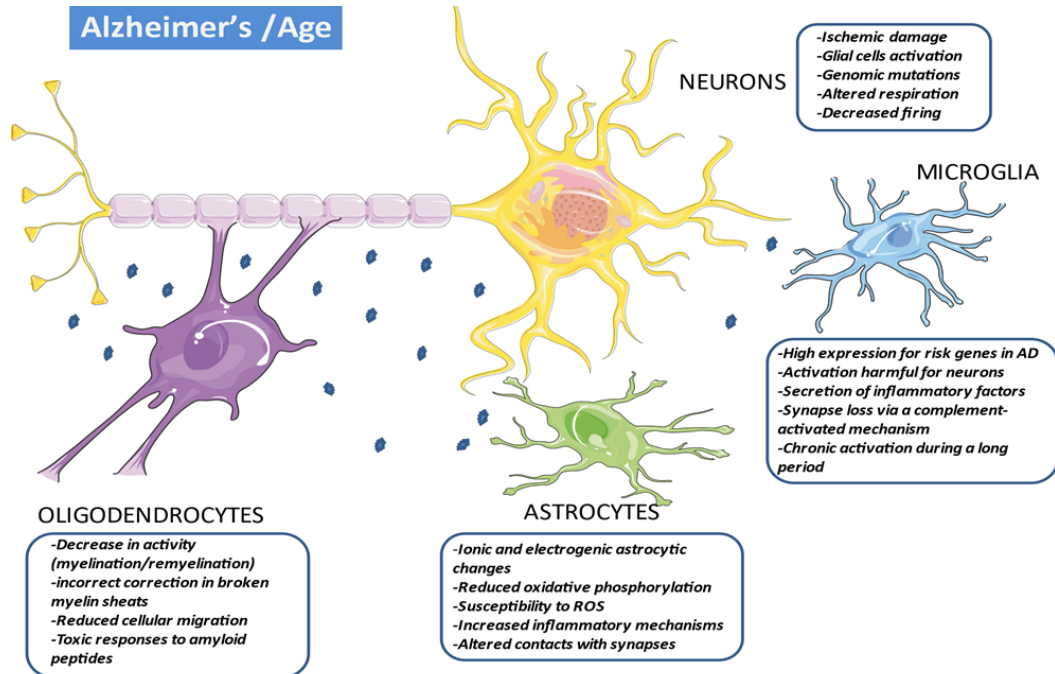


Fig.4 Multiple Alzheimer's disease etiologies and many cellular partners. Deleterious proteinopathies (in the first-place amyloid peptides) are to be integrated into the complex cellular environment of the brain. These multiple cellular elements participate in progressive multi-focal neuro-axonal degeneration leading to the irreversible symptomatology of AD. This is expressed when the toxic peptide removal systems are overwhelmed, which appears only after a long incubation period. Altered neurons express phases of hypo- and hyperexcitability with deficits in axonal transport and synaptic activity that affects myelination / remyelination activity and oligodendrocyte trophism. These are very vulnerable cells whose density decreases sharply with age. There seems to be a link between the intensity of neuronal involvement and the extent of demyelination. This is strongly accentuated in AD in which remyelination processes seem deficient. The activation of astrocytes participates in the elimination of deficient neurons and synapses. They actively participate in the elimination of abnormal proteins and inflammation processes, in the same way that the activation of microglia facilitates the phagocytosis of cellular debris. In the same way, these cells participate in the activation of the innate immune responses, the activation of the complement and the secretion of inflammatory cytokines. Abbreviations: AD, Alzheimer's disease; ROS, reactive oxygen species.

386 The quality control processes of *in vivo* newly formed proteins and the elimination of abnormal proteins are phenomena
 387 with growing alterations with age [93, 141]. This results in the cellular and extra-cellular accumulation of an increasing
 388 number of non-functional proteins that tend to form hydrophobic aggregates [118]. At the brain level, these toxic
 389 aggregates induce significant cellular and functional losses that are the basis of many neurodegenerative diseases [14].
 390 In addition to the amyloid peptides and tau protein that are the canonical proteins of early AD and whose toxic deposits
 391 in brain tissue are the basis of mechanistic theories of neurodegeneration, it has been shown that a wide range of protein
 392 aggregates from other sources exist in the brain of elderly patients displaying a cognitive impairment or at first stages
 393 of AD [163]. Among the proteins significantly altered compared to controls, many are found in the biochemical cascade
 394 of glycolysis that primarily feeds cellular energy and whose intensity decreases with age, even faster in patients with
 395 AD [136]. Other strategic proteins form larger insoluble aggregates depending on symptomatologic impairment. These
 396 include glucose 6 phosphate isomerase creatine kinase B, certain forms of adenylate cyclase and calcium/calmodulin
 397 protein kinase 2. This list is not exhaustive but reflects the importance of metabolic and functional disorders that
 398 develop over time in the brains of patients with mild cognitive impairments that worsen in AD [92].
 399 It could be speculated that the accumulation of misfolded proteins during old age in multiple regions of the brain alters
 400 mitochondrial and metabolic functions, saturates the processes of cleaning and elimination of senescent cells, and

401 slows down the neurogenesis that persists in the older brain [20, 81]. Inflammatory vasculitis, hypoxia, and oxidative
402 stress due to the accumulation of non-functional deleterious proteins are considered the primary factors in myelin
403 envelope impairment. The decrease in electrical and metabolic activity of axons contributes to the decrease in myelin
404 density that surrounds them leading to its gradual dislocation. The toxicity of A β peptides has been demonstrated *in*
405 *vitro* against neurons, endothelial cells, astrocytes, vascular smooth muscle cells and oligodendrocytes [224]. A β
406 peptides cytotoxicity might involve the susceptibility of oligodendrocytes to oxidative stress because of its low content
407 of reduced glutathione and high concentration of iron [191]. The A β peptides activation of the neutral
408 sphingomyelinase-ceramide pathway has been reported to induce oligodendrocyte death [102]. In addition, inhibition
409 of neutral sphingomyelinase 2 in these cells reduces their ceramide content and favor the myelination process by
410 improving the quality of myelin structure [221].

411 Microbiome and myelin dysregulation in the neurodegenerative brain

412 A role for the gut-brain axis and for hepatic metabolism

413 Some arguments favor a view of AD as a disease that is not limited to the CNS alone but reflects multi-organ
414 dysfunctions that contribute to or influence brain neurodegeneration [200]. Multiple proteinopathies, including the A β
415 cascade, may come from peripheral organs that no longer metabolize abnormal proteins properly and allow their
416 dissemination through a permeable BBB. Abnormal communication between various compartments of amyloid
417 proteins can contribute to altering brain disease. Chronic peripheral metabolic abnormalities are suspected to
418 participate or to worsen neurodegeneration. In this regard, intestinal metabolism is often questioned.

419 The population of microorganisms of the gut microbiota constitutes a true symbiotic organ that has a great inter-
420 individual heterogeneity due to many intrinsic and extrinsic factors dependent on genetic, medication (*e.g.* antibiotics),
421 physical and hormonal activity, and infectious factors [186]. The composition of the microbiome changes with age and
422 the reactivity of the immune system [130]. An active exchange via the bloodstream and intestinal innervation between
423 the microbiome and the nervous system exist, whose influence is important during the neurogenesis, the molecular
424 organization of the connectome, and the variations of CNS myelination. These phenomena are especially different
425 during periods of brain development or during aging [229].

426 In various transgenic models of familial AD, disturbances in the composition and diversity of the intestinal microbiome
427 compared to healthy animals are observed [175]. In humans, it has also been described qualitative and quantitative
428 changes in the population of intestinal bacteria in patients with cognitive disorders associated with cerebral amyloidosis
429 [59, 119]. These disturbances can be the source of chronic neuroinflammation targeting several organs including the
430 brain and a decrease in the immune response inducing neurodegeneration over the long term [27, 75]. These
431 phenomena are increased by the leaky permeability of the BBB as a function of age, allowing the passage at the cerebral
432 level of many toxics present at the periphery (Fig.5) [213].

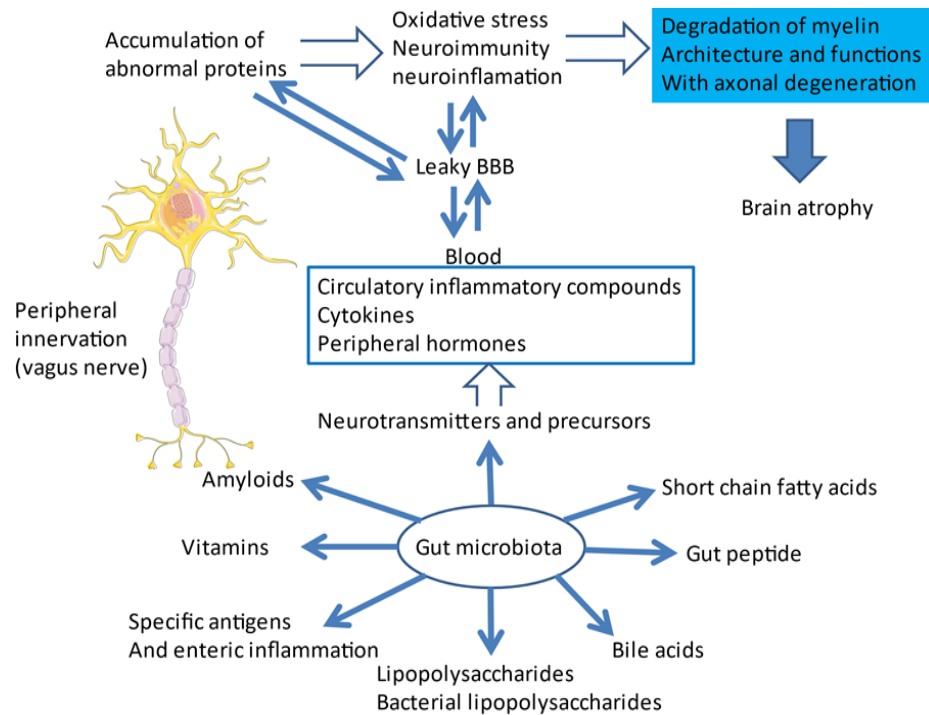


Fig.5 Multiple communication system that includes neural, immune, endocrine, and metabolic pathways lead to degeneration. Continuous fluctuation of the microbiota due to the environment constantly influences the inflammatory, immune, and metabolic responses of the CNS [110]. With age, the permeability of intestinal and BBB is often impaired [85, 162]. The gut microbiota metabolizes and release many growths, metabolic and inflammatory factors which could penetrate the brain via the circulating blood. These substances contribute to increase the inflammatory, immune, and oxidative phenomena that exist in the elderly brain due to the accumulation over time of many abnormal proteins due to their hydrophobic conformation. The very likely origin of these malformed proteins is found in the accumulation during senescence of many mutations in post-mitotic cells that are neurons [9, 77]. In addition, the role of epigenetic dysregulation of gene expression induced by aging or abnormal environmental stimulation is also considered to be an important factor in neurodegeneration and cognitive alterations [126]. Abbreviations: BBB, blood-brain barrier; CNS, central nervous system.

433 The problems of pathological cerebral aging are probably the result either of the evolution of protein targets at the
 434 central level, or the modification of a peripheral immune response [60, 183], the two mechanisms can combine over
 435 time to lead to an autoimmune alteration colonizing the CNS and involving, in the first place, the components of
 436 myelin. Many environmental factors can promote this chronic process by perpetuating the homeostasis of the intestinal
 437 flora and at the origin of certain metabolic and cytotoxic disorders [15, 91]. This primarily affect oligodendrocytes,
 438 which are fragile cells of the CNS, and which adapt their functions throughout the life of the individual. Many factors
 439 contribute to the activity of oligodendrocytes, intrinsic and environmental factors that modify the status of the
 440 epigenome [166]. Among these factors, the composition and activity of the microbiome plays a reweighting role and
 441 interferes with the spatio-temporal character of myelination in the brain. In general, the relationships between the
 442 intestinal sphere and the brain are of primary importance for myelination. This sphere includes not only the intestinal
 443 epithelium, but also hepatic metabolism, sympathetic and parasympathetic nerve activity, endocrine, and cytokine
 444 secretions and metabolites of microbial origin [45]. The microbiota has an important role in the regulation of myelin
 445 plasticity as the existence of hyper-myelinated axons has been demonstrated in germ-free mice or treated chronically
 446 with antibiotics [73]. This abnormality could be a consequence of neuronal hyperactivity in certain regions of the brain
 447 of these mice, such as the amygdala or the prefrontal cortex. The development of myelinating oligodendrocytes is

448 controlled by a set of transcription factors (Sox 10 and Myrf for example) that drive the steps of myelination and re-
449 myelination [7]. The anomalies of these phenomena alter certain brain functions, those concerning cognitive functions.
450 Restoring a normal microbiome in germ-free mice greatly improves their social and executive performance [174, 190,
451 192].
452 It is now recognized that disorders intestinal physiology can influence the risk of Alzheimer's and its rate of
453 progression. Deposits of aggregate of A β peptides at the intestinal level have been detected in AD patients [75], but
454 most of the results involving the intestinal sphere and the progression of AD have been obtained in animal models.
455 The ratios between Firmicutes and Bacteroidetes are considered strategic in the composition of the human intestinal
456 microbiota [168]. The fecal microbiota is the product of a very complex and diverse ecosystem, and its composition
457 can modify the accumulation of intestinal APP in the early phases of AD [29, 120]. In transgenic APP/PS1 animals,
458 an increase in A β peptides levels have been observed in the CNS in relation to changes in the intestinal flora,
459 accompanied by disorders of spatial memory [225]. Oligodendrocytes and myelin sheaths may be the first to be
460 affected by these deleterious deposits. A parallel can be observed between the myelin alterations observed in AD and
461 during normal aging in the elderly. In the latter case, the installation of progressive ischemia could be the cause of this
462 demyelination [138, 178]. The lesions often appear disseminated with a predilection for intracortical axons of small
463 diameters that are myelinated late during development. Myelin dystrophies lead to axonal alterations and neuronal
464 death with different rate in individuals [164].

465 Conclusion and perspectives

466 To conclude, myelin damage and its several possible outcomes (Table 1) is one of the early lesions observed in many
467 clinical forms of AD. Even though many differences exist in the presentations and structural alterations between
468 multiple sclerosis and AD, neurodegenerative alterations between both pathologies have common etiologies and
469 mechanisms [114]: long-standing inflammatory disorders, some autoimmune reactions, cognitive impairments, and
470 mitochondrial alterations [105, 185]. Amyloid disorders are not absent from the pathophysiology of multiple sclerosis
471 and A β peptides levels are generally lower in the CSF of patients with multiple sclerosis who have cognitive
472 impairment [94]. The accumulation of APP in the brain of these patients appears parallel to the worsening of
473 symptomatology and dynamic processes of demyelination/remyelination [25]. These parallels remain hypotheses at
474 present, but there are indications that some mechanistic similarities exist.

475 Current mechanistic hypothesis favors long-term dysfunctions in the proteolysis of APP and in the accumulation of
476 hydrophobic A β peptides with multiple toxicities. These lead to inflammatory, oxidative, and immune reactions
477 leading to massive cellular apoptosis accompanied by post-translational modifications on target proteins inducing
478 profound functional alterations in brain cells activities. It seems possible that a multiplicity of mutations and epigenetic
479 alterations of neuronal genomes, associated with intrinsic or extrinsic predisposing factors, generate metabolic and
480 inflammatory alterations over the long term, inducing a multiplicity of phenotypic and clinical presentations involving
481 secondarily multiple deleterious proteinopathies, including amyloidosis of A β types.

482

483

484 **Table 1.** Examples of different outcomes of myelin damages.

Myelin modifications	References
Demyelination (as evidenced, for example, by decreased myelin water fraction)	[18, 47, 83, 95, 138, 178]
Rupture of the myelin envelope	[36, 151, 201]
Myelin reshuffle	[16, 46, 166, 180]
Defect in myelin biosynthesis (loss of ceramide synthase 2 activity)	[32]
Down-regulation of myelination network	[3]
Morphological abnormalities of myelin sheaths, in the form of edema and thinning of the envelope surrounding myelinated axons	[48, 138, 228]
Myelin degeneration -> driving cognitive and motor impairment	[26, 154]
Changes of myelin organization (q-Space myelin map imaging)	[149]
Myelin instability	[50, 199]
Myelin damage in cortical gray matter (Western blot quantification of MBP and dMBP)	[227]
Decrease of myelin density (multi-echo T2 relaxation time technique)	[100]

485 **Declarations**

486 **Author Contributions**

487 The first draft of the manuscript was written by Michel Maître and H  l  ne Jeltsch-David, who performed the literature
 488 search and data analysis. Idea for the article: Michel Maitre and Ayikoe-Guy Mensah-Nyagan. Table and pictures
 489 design and editing: Christian Klein, Michel Maitre and H  l  ne Jeltsch-David. All authors commented on previous
 490 versions of the manuscript and have approved the manuscript for submission; the content of which is not submitted or
 491 published elsewhere. All authors read and approved the final manuscript.

492 **Author’s information and identification**

493 Michel Maitre : <https://orcid.org/0000-0003-1478-4806>
 494 H  l  ne Jeltsch-David: <https://orcid.org/0000-0003-3630-7242>
 495 Nwife Getrude Okechukwu (PhD student): <https://orcid.org/0000-0001-8678-0850>
 496 Christian Klein: <https://orcid.org/0000-0002-7580-8536>
 497 Christine Patte-Mensah: <https://orcid.org/0000-0002-9970-8214>
 498 Ayikoe-Guy Mensah-Nyagan: <https://orcid.org/0000-0003-4454-511X>

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507 **Consent for publication**

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511 **References**

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1136 Figure legends

1137 **Fig.1:** Oligodendrocytes are derived from the differentiation of oligodendrocyte precursor cells (OPCs) and are the
1138 main cell for remyelination (modified from [176]). The differentiated oligodendrocytes of OPCs migrate to different
1139 axons via positive chemotactism [216]. A variety of growth and trophic factors regulate the development of
1140 oligodendrocytes and their temporal and geographical attractions [17]. Many of these factors are produced by both
1141 neurons and astrocytes, regulating the proliferation, survival, or degeneration of OPCs. The neuroregulin, which
1142 activates Erb-tyrosines kinases receptors, promotes the survival and proliferation of oligodendrocytes. The activation
1143 of the Notch 1 cascade inhibits the differentiation of oligodendrocytes, and an integrin/contactin complex coordinates
1144 signals from the extracellular matrix and the axonal surface to regulate oligodendrocyte survival and myelination. This
1145 also depends closely on the electrical activity propagated in the axons. OPCs express functional adenosine receptors,
1146 activated by action potential [150, 184]. Adenosine acts as a powerful transmitter between glia and neurons to inhibit
1147 the proliferation of OPCs, stimulate their differentiation and stimulate myelin production. The LIF (leukemia inhibitory
1148 factor) is heavily involved in oligodendrocyte development kinetics and in the overall myelination process [134, 198].
1149 *Abbreviations: CNTF, ciliary neurotrophic factor; FGF, fibroblast growth factor; IGF, insulin-like growth factor;*
1150 *LIF, leukemia inhibitory factor; NCAM, neural cell adhesion molecule; NT-3, neurotrophin 3; OPCs, oligodendrocyte*
1151 *precursor cells; PDGF-A, platelet-derived growth factor-A.*

1152 **Fig.2:** Dysregulation in multiple biochemical pathways underlie the pathogenesis of AD. Metabolomic approaches
1153 conducted from the blood or CSF of AD patients compared to controls highlighted abnormalities in the energy
1154 metabolism of patients. A diabetic-type pathology is often evoked with a decrease in insulin sensitivity. In addition to
1155 disorders in glycolysis and the respiratory chain, abnormalities involving accumulations of ketone bodies resulting
1156 from the metabolism of acetyl-CoA residues, a product of the accelerated degradation of fatty acids by β -oxidation,
1157 have been described. The bioavailability and metabolism of several amino acids could also be affected, especially
1158 concerning tryptophan degraded in the kynurenine cycle and resulting in the formation of neuroprotective (kynurenic
1159 acid) or neurotoxic (quinolinic acid) compounds. *Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid;*
1160 *NADH, nicotinamide-adenine-dinucleotide; ROS, reactive oxygen species; TCA, tricarboxylic acid; β OHD, beta-*
1161 *hydroxybutyrate.*

1162 **Fig.3:** Myelin composition and organization. The myelin wrapping around most of the CNS axons includes a large
1163 majority of complex lipids and 15-30% of specific proteins. Lipids are essentially made up of cholesterol,
1164 galactocerebrosides and phospholipids. This envelope is constantly reshuffled in time and space from the
1165 oligodendrocytes that make up the bulk of the glial cells of the CNS. Chronic inflammatory and autoimmune reactions,
1166 mutations in certain constituent proteins, attacks by free radicals or ischemic, and metabolic problems related to aging
1167 alter the myelin sheath that releases its constituents into the CSF and the bloodstream. In AD, myelin is one of the first
1168 bulwarks for the anatomical and functional integrity of the axons it surrounds and undergoes early toxic action of
1169 misfolded extracellular toxic proteins or peptides. *Abbreviations: AD, Alzheimer' disease; CNP, C-type natriuretic*
1170 *peptide; CNS, central nervous system; CSF, cerebrospinal fluid; MAG, myelin-associated glycoprotein; MBP, myelin*
1171 *basic protein; MOG, myelin oligodendrocyte glycoprotein; PLP, proteolipid protein.*

1172 **Fig.4:** Multiple Alzheimer's disease etiologies and many cellular partners. Deleterious proteinopathies (in the first-
1173 place amyloid peptides) are to be integrated into the complex cellular environment of the brain. These multiple cellular
1174 elements participate in progressive multi-focal neuro-axonal degeneration leading to the irreversible symptomatology
1175 of AD. This is expressed when the toxic peptide removal systems are overwhelmed, which appears only after a long
1176 incubation period. Altered neurons express phases of hypo- and hyperexcitability with deficits in axonal transport and
1177 synaptic activity that affects myelination/remyelination activity and oligodendrocyte trophism. These are very
1178 vulnerable cells whose density decreases sharply with age. There seems to be a link between the intensity of neuronal
1179 involvement and the extent of demyelination. This is strongly accentuated in AD in which remyelination processes
1180 seem deficient. The activation of astrocytes participates in the elimination of deficient neurons and synapses. They
1181 actively participate in the elimination of abnormal proteins and inflammation processes, in the same way that the
1182 activation of microglia facilitates the phagocytosis of cellular debris. In the same way, these cells participate in the
1183 activation of the innate immune responses, the activation of the complement and the secretion of inflammatory
1184 cytokines. **Abbreviations:** *AD, Alzheimer's disease; ROS, reactive oxygen species.*

1185 **Fig.5:** Multiple communication system that includes neural, immune, endocrine, and metabolic pathways lead to
1186 degeneration. Continuous fluctuation of the microbiota due to the environment constantly influences the
1187 inflammatory, immune, and metabolic responses of the CNS [110]. With age, the permeability of intestinal and BBB
1188 is often impaired [85, 162]. The gut microbiota metabolizes and release many growths, metabolic and inflammatory
1189 factors which could penetrate the brain via the circulating blood. These substances contribute to increase the
1190 inflammatory, immune, and oxidative phenomena that exist in the elderly brain due to the accumulation over time of
1191 many abnormal proteins due to their hydrophobic conformation. The very likely origin of these malformed proteins is
1192 found in the accumulation during senescence of many mutations in post-mitotic cells that are neurons [9, 77]. In
1193 addition, the role of epigenetic dysregulation of gene expression induced by aging or abnormal environmental
1194 stimulation is also considered to be an important factor in neurodegeneration and cognitive alterations [126].
1195 **Abbreviations:** *BBB, blood-brain barrier; CNS, central nervous system.*