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REVIEW

Amyloid-β and Parkinson's disease

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Abstract

Parkinson's disease (PD) is the second commonest neurodegenerative disorder in the world with a rising prevalence. The pathophysiology is multifactorial but aggregation of misfolded α-synuclein is considered to be a key underpinning mechanism. Amyloid-β (Aβ) and tau deposition are also comorbid associations and especially Aβ deposition is associated with cognitive decline in PD. Some existing evidence suggests that low cerebrospinal fluid (CSF) $A\beta_{42}$ is predictive of future cognitive impairment in PD. Recent studies also show that CSF Aβ is associated with the postural instability and gait difficulties (PIGD) or the newly proposed cholinergic subtype of PD, a possible risk factor for cognitive decline in PD. The glial-lymphatic system, responsible for convective solute clearance driven by active fluid transport through aquaporin-4 water channels, may be implicated in brain amyloid deposition. A better understanding of the role of this system and more specifically the role of Aβ in PD symptomatology, could introduce new treatment and repurposing drug-based strategies. For instance, apomorphine infusion has been shown to promote the degradation of Aβ in rodent models. This is further supported in a post-mortem study in PD patients although clinical implications are unclear. In this review, we address the clinical implication of cerebral Aβ deposition in PD and elaborate on its metabolism, its role in cognition and motor function/gait, and finally assess the potential effect of apomorphine on Aβ deposition in PD.

Keywords Amyloid · Parkinson · Cognitive decline · PET amyloid · PIGD · Apomorphine

Introduction

History and background

Deposition of amyloid-β (Aβ) plaques is regarded as the hallmark of Alzheimer's disease (AD) [1]. Aβ discovery dates as far back as 1984, when it was first purified [2]. Alongside Aβ also the microtubule-associated protein Tau and its phosphorylated form P-Tau are thought to underlie AD. In PD, cognitive deficits are now known to occur in the prodromal and de novo state [3, 4] and more than 80% of patients who survive more than 10 years will eventually develop dementia with a reported average point prevalence of 40% [5], although the time to develop dementia varies from a few years to many years and even decades after. This phenomenon has led to increased interest in the potential overlap of common pathophysiological pathways between AD and PD and brain Aβ deposition as well as α-synuclein are understood to underpin PD dementia (PDD) [3]. The subpopulation of AD patients with Aβ and Lewy body

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deposition (in about > 50% of AD cases), has been reported to cause a rapid cognitive decline and a shorter lifespan [1]. Supporting this observation, patients with Lewy body spectrum disorders, mainly dementia with Lewy bodies (DLB), and to a lesser extent also PDD patients, have been found to have Aβ plaques along the typical Lewy body deposition [6]. Recent in vitro [7, 8] and transgenic mice models [9, 10] have furthermore found evidence on a synergistic action between Aβ and α-synuclein deposition, the former promoting the aggregation of the latter [9–11] and vice versa [9].

Studies on cerebrospinal fluid (CSF) biomarkers for PD clinical progression have consistently reported decreased Aβ-42 levels among PD patients with gait disturbances, postulating a potential involvement of Aβ deposition not only on cognition, but also on locomotor function [12]. Such abnormalities may also underpin the emerging concept of specific non-motor endophenotypes of PD [13]. Along with decreased Aβ in CSF, also high level of Tau and P-Tau in CSF has been found to be potential predictors of motor progression in PD [14], underpinning the multifactorial disease process in PD.

In this review, we address the clinical implication of brain Aβ deposition in PD and will: (1) offer a systematic review of Aβ and its metabolism, (2) how Aβ can be measured in vivo as a potential predictive biomarker in PD, (3 & 4) the clinical associations of brain Aβ deposition and cognition and motor symptoms in PD, (5) Aβ-based therapeutic strategies, including repurposing apomorphine for a potential anti amyloid effect on PD.

Amyloid-β protein: structure, biochemical properties, catabolism, and metabolism

Aβ is a peptide weighing approximately 4 kDa, which is formed from the Aβ precursor protein (APP) and is found pathologically accumulated in two areas only in humans, either in the brain and cerebrovascular system or in the skeletal muscle [15]. Aβ is formed from an initial processing of APP by three enzymes, alpha-, beta-, and gamma-secretase. While the cleavage by the alpha-secretase does not cause amyloidogenic end products preventing Aβ production, the initiation of a beta-secretase cleavage of APP with the subsequent processing through gamma-secretase, will end up producing peptides of 38, 40, or 42 amino acids [16].

These resulting peptides are released into CSF, plasma and interstitial fluid, where they can be measured. Within the healthy population, the liberated Aβ peptides in the CSF consist of about 50% of Aβ-40, 16% of Aβ-38, and 10% of Aβ-42 among other isoforms, the latter having a stronger tendency to aggregate (Fig. 1) and thus to form amyloid plaques and have neurotoxic effects [16, 17]. More recent evidence has, however, shown that neuronal damage and subsequent cognitive dysfunction are caused mainly by the transient oligomers and protofibrils (Fig. 1) rather than mature fibrils [18].

The mechanism thought to underlie the transport of Aβ across the blood–brain barrier is a bidirectional transport system based on diffusion. Dysfunctional diffusion process has also been potentially accounted to contribute to pathological Aβ deposition in the brain [19, 20]. The accumulation of Aβ in the brain of AD patients has been attributed to decreased clearance from the brain parenchyma by the proposed glial-lymphatic ('glympathic') system. This system appears to be responsible for convective solute clearance driven by active fluid transport through the aquaporin-4 water channels [21]. Whether this system could be involved in PD has yet to be determined. A recent study, however, showed a negative correlation between alpha-synuclein deposition and aquaporin-4 expression in the temporal cortex of PD patients [22], suggesting that the glymphatic system may be involved in reduced clearance of alpha-synuclein. Absence of aquaporin-4 results in the impaired clearance of Aβ deposition and increased brain deposition of Aβ in rodents [23]. In a cross-sectional observational study in cognitively normal elderly people showed that Aquaporin-4 mutations are associated with poorer overall sleep quality as assessed by the Pittsburgh sleep quality index (PSQI) [24], underlining the possible relationship between Aβ, the glymphatic system and sleep.

Two enzymes, neprilysin and insulysin, responsible for catalysis of insulin, several neuropeptides and other polypeptides, have been found to play a role in the catabolism of Aβ. The enzymes stimulate the degradation of Aβ, resulting in a reduction of both intracellular and extracellular Aβ accumulation. Both enzymes are reported to decrease in normal aging and the decline is more pronounced in topographically more vulnerable brain areas associated with cognitive decline, such as the hippocampus and the cortex, while the cerebellum maintains more elevated levels in comparison [15, 20]. Furthermore, in early cases of AD, neprilysin has been found to be reduced in the CSF [20, 25]. Of these two enzymes, only insulysin has been recently linked to PD in a laboratory in vitro model, finding an interaction between insulysin and α-synuclein, leading to the arresting of α-synuclein oligomers and increase in insulysin proteolytic activity [26]. However, it is yet to be explored whether a similar mechanism will apply for Aβ.

The interaction between AD and PD-associated proteins: APP and LRRK2

Recent evidence has shown that there is interaction between APP and PD-related protein, called Leucine-rich repeat kinase 2 (LRRK2). LRRK2 is a protein which has been associated with diverse cellular mechanisms such as

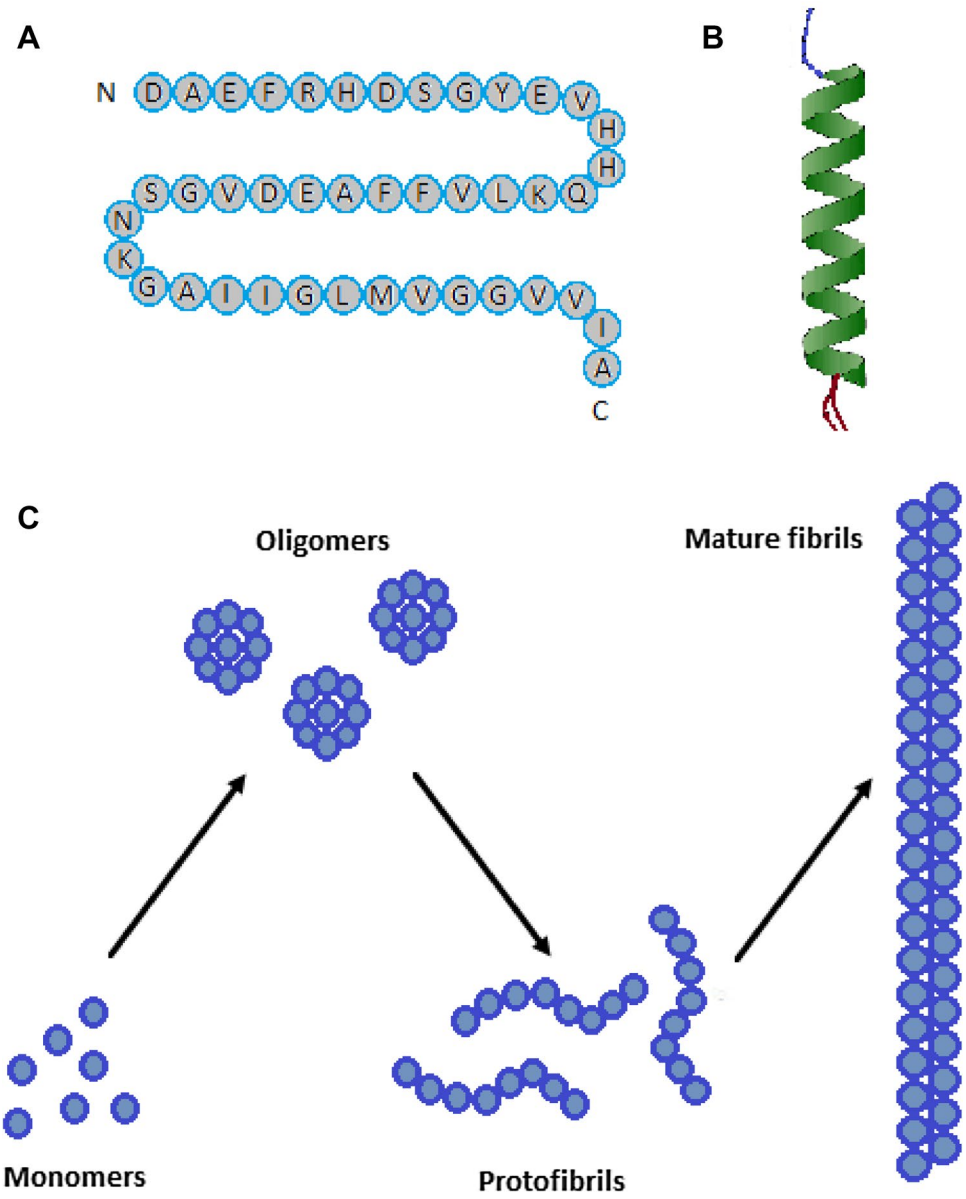

Fig. 1 Structures of Aβ monomer, fibril and oligomers. **a** The primary amino acid sequence of the 42 amino acid Aβ isoform $Aβ_{42}$. **b** The structure of Aβ peptide (1–28), which forms a predominately alpha-helical structure. **c** Proposed pathway for the conversion of Aβ monomers to higher order oligomers, protofibrils and fibrils

alpha-synuclein phosphorylation, autophagy-lysosomal pathway, microtubule dynamics, synthesis and trafficking of vesicles, mitochondrial function and ubiquitin–proteasome system (UPS) [27, 28]. The interaction between LRRK2 and APP occurs at intracellular domain of APP(AICD), causing phosphorylation of APP at Thr 668 which promotes the transcriptional activity of AICD and its translocation to the nucleus. Transcription of AICD, which is involved in cytoskeletal dynamics, and apoptosis has been tightly regulated. However, in the excess expression of AICD (for instance in the of presence of G2019S mutation of LRRK2), dopaminergic neuronal loss has been observed [29]. This has provided new insight into the mechanisms linking both AD and PD.

Aβ physiological characteristics: effect in the healthy?

While Aβ accumulation in the brain or skeletal muscle can lead to pathological conditions, healthy subjects have also been found to have Aβ accumulation by PET imaging [30] and upon brain autopsy [31]. This raises the question, whether Aβ also possesses physiological characteristics and benefits, which only become detrimental when an imbalance occurs. Several lines of evidence point toward a potential role of Aβ in the modulation of synaptic transmission [32], with the inhibition of Aβ production in primary cultures leading to a neuronal cell death [32, 33]. An interaction between increased Aβ production after hypoxic events and its direct effect exerted on Calcium channels upregulating

and thus facilitating Calcium signalling, has also been reported [32]. However, it remains unclear whether this altered effect on Calcium channel trafficking is due to a physiological protective effect or accounts for later pathological cell death [32]. Other roles of Aβ in the physiological regulation of neuronal channels, such as voltage-gated potassium channels have also been reported [34].

In vivo Aβ measurement

In vivo measurement of Aβ can pose a challenge and requires specific technique to visualise it. Several techniques have been developed to assess cerebral Aβ load, including blood, CSF and nuclear imaging techniques. Aβ proteins can be measured in plasma, but the correlation with cerebral β-amyloidosis is weak, at least in AD [35], and the plasma levels are likely influenced by Aβ production in platelets and other extracerebral tissues [36]. This is reflected by the contradictory results that have been reported based on different molecular detection methods; nonetheless, a recent assessment of plasma Aβ, after treatment with protease and phosphatase inhibitors could establish significant differences among the subjects with Aβ-positive and -negative nuclear imaging results [37]. Recently, Nakamura et al. has reported a high-performance blood-based method to predict Aβ burden in AD using immunoprecipitation coupled with mass spectrometry [38]. APP699-711/$Aβ_{1–42}$ ratio, $Aβ_{1–40}$/$Aβ_{1–42}$ ratio and their composites have been compared with amyloid PET imaging in two data sets in Japan and Australia with high sensitivity and specificity [38]. Further validation studies, optimal cut-off values and its performance in PD will need further research.

Modern imaging technique with Positron Emission Tomography (PET)-based scan and the use of radiotracers which bind to Aβ have been and are being developed with only a few of them showing a sufficient blood–brain barrier passage together with a high binding affinity for Aβ. The common tracers reported include [^{11}C] Pittsburgh compound B (PiB), [^{18}F] Florbetapir, [^{18}F] Florbetaben, [^{18}F] Flutemetamol and fluoroethyl-methylamino-2-naphthylethylidene malononitrile ([^{18}F] FDDNP). Pooled sensitivity of 90–96% and specificity of 58–85% have been reported for the above tracers in AD literature [39]. Abnormal Aβ deposition was only reported up to one-third of PDD [6, 40–43].

CSF $Aβ_{42}$ has been shown to be a reliable marker of Aβ pathology in the brain through autopsy or Aβ PET studies in AD population [44]. In PD, CSF Aβ is also a more promising biomarker with robust evidence compared with blood biomarker and PET imaging. Both longitudinal studies and cross-sectional studies mostly suggest that reduced level of CSF $Aβ_{42}$ is correlated with PDD and baseline value is predictive of future cognitive decline [45–53]. Further details about PET imaging and CSF Aβ biomarker will be discussed in the following section.

Aβ and cognition

Parkinson's disease dementia (PDD) is common in advanced stages of PD and leads to significant caregivers' burden and hence, institutional care. The spectrum of cognitive impairment in PD ranges from subjective cognitive impairment, mild cognitive impairment (MCI) to dementia. 25–30% of non-demented PD patients may be troubled with MCI [54], which is one of the main risk factors of dementia, in addition to age, male sex, postural instability gait difficulty (PIGD) subtype, the cholinergic non-motor endophenotype of PD [55], and presence of other non-motor symptoms [56]. Progression to dementia, particularly the rate of progression, is variable and therefore a biomarker to predict this progression is of utmost importance to better manage patients effectively and to select patients into drug trials. Current literature suggests that Aβ pathology in PD is a potential biomarker to predict cognitive decline in PD.

More recently, specific non-motor symptoms (NMS) dominant clinical endophenotypes of PD has been reported [57]. Among those being discussed, early presentation of cognitive impairment is seen in Park cognitive subtype. Titova et al. has also recently described cholinergic syndrome /subtype which encompasses both motor and non-motor symptoms such as 'ON' related freezing, MCI and dementia [58]. Whether in vivo imaging or measurement of Aβ could serve as a biomarker of this subtype is yet to be ascertained. Such measurements could also form a basis for the definition of complex Parkinson's disease as biomarkers to define this stage are still an unmet need [59].

From the literature, the pathologies reported in PDD and PD–MCI seem to be heterogeneous. While Lewy body being the most important pathological substrate in the development of cognitive impairment, other factors such as Aβ, tau, cerebrovascular disease have their role as well. Multiple neurotransmitters such as dopamine, noradrenaline, serotonin, and acetylcholine have been correlated with these pathologies. The exact mechanisms and the timing of these complex relationships need further research.

Post-mortem studies contribute to the understanding of the role of Aβ in the pathogenesis of cognitive impairment in PD. However, post-mortem studies are cross-sectional by definition, resulting in the inability to look at the real-time pathological changes in correlation to the clinical severity. Aβ PET imaging and CSF biomarkers are therefore important for us to examine its role in de novo patients and to monitor the natural progression of cognition in PD. The relationship of the above three types of studies with amyloid pathology has been summarized in Fig. 2. The understanding

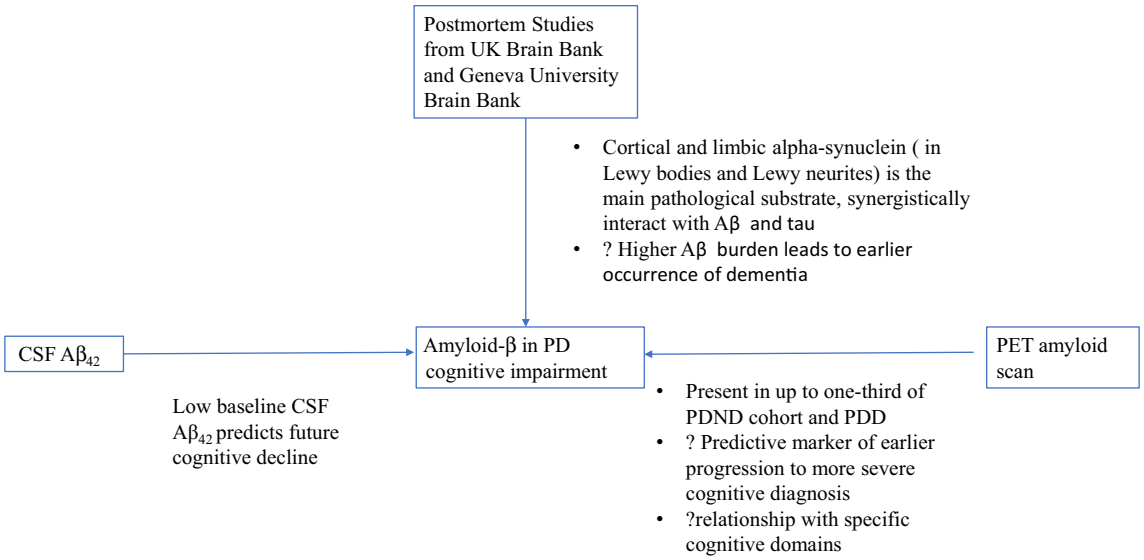

Fig. 2 Summary of the relationship of Aβ and cognition in PD. *CSF* cerebrospinal fluid, *PD* Parkinson's disease, *Aβ* amyloid-β, *PDND* non-demented Parkinson's disease, *PDD* Parkinson' disease dementia, *PET* positron emission tomography

of the natural history and pathogenesis of cognitive impairment in PD is imperative for further research with the hope of finding cutting-edge treatment.

Pathological studies (see Table 1)

Limbic and neocortical Lewy body pathology have been shown to be the main pathological substrate in the PDD since almost two decades ago [60–66]. In contrast, few studies did report the absence of dementia even in the presence of widespread cortical Lewy bodies [64, 67, 68].

Besides Lewy body pathology, tau pathology and significant role of amyloid plaque pathology in PDD has been reported [69]. Higher burden of Aβ, Lewy body and tau pathologies are found in PDD. The three key pathologies are positively correlated to each other [63, 64, 70, 71]. Combination of pathologies has higher predictive value of development of dementia in PD [70, 72], suggesting the multifactorial origins of cognitive decline in PD.

Time-to-dementia is of great interest and concern. Higher cortical Aβ score/burden has been reported as a significant predictor of shorter latency to dementia by several studies [63, 70, 71, 73, 74]. Cohort with synucleidopathy plus Aβ deposition reported by Kotzbauer et al. had significantly shorter survival from both the PD onset and the dementia onset until death [75], as also shown by others [76]. What have been discussed so far support the synergistic interaction of three key pathologies, highlighting to us the complex overlapping mechanisms. This is also in line with transgenic mice models [9, 10].

Apart from cortical deposition, a few other studies have explored the relationship between neuropathology of the striatum and dementia. The striatum is believed to play a role in cognition and behaviour [77]. Contradicting evidence has been published about the correlation of Aβ deposition at striatum and dementia in PD [78–81]. Kalaitzakis et al. published a cohort of 30 cases (16 PDD, 14 PD) which demonstrated significant higher burden of Aβ pathology in striatum (including caudate nucleus, putamen, and nucleus accumbens) in PDD cases which was not attributed to age [78]. The authors again reported greater Aβ deposition in the striatum of both PDD and dementia with Lewy body (DLB) cases when compared to PD, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) groups [80]. On the

Table 1 Summary of the key findings of the pathological studies

PDD group has higher burden of Aβ, Lewy body and tau pathologies
Positive correlation between three key pathologies
Higher predictive values of combination of pathologies compared to single pathology
Higher Aβ burden predicts shorter latency to dementia
Questionable role of deposition of Aβ at striatum and claustrum and cognition
Association of Aβ plaques and neurofibrillary tangles with visual hallucination

PDD Parkinson's disease dementia, *Aβ* amyloid-β

contrary, Halliday et al. and Jellinger et al. demonstrated that striatal Aβ pathology was a consistent feature in DLB cases while it was absent in 8/12 and 14/17 PDD cases, respectively [79, 81]. Deposition of Aβ in the claustrum has been shown by one study to be correlated with the occurrence of dementia in PD and DLB [82]. Claustrum is a subcortical structure with multiple connections with neocortical areas and limbic structure. Its physiological function is largely unknown and has been reported to be related to the presence of visual hallucinations occurring in DLB [83] and cognitive impairment in AD [84].

Jacobson et al. reported greater Lewy-type alpha-synucleinopathy, Aβ plaques (total plaque density, neuritic plaque density, and plaque density in frontal, parietal, and hippocampal areas) and neurofibrillary tangle densities in PD with visual hallucinations [85]. There was association between early-onset PD psychosis and reduced baseline CSF $A\beta_{42}$ [4]. PD patients who had visual hallucinations were found to have increased risk of dementia at follow-up [86]. This suggests potential links between Aβ pathology, cognition and visual hallucination.

Amyloid-β PET imaging

The advance of nuclear imaging has not only contributed to the understanding of the complex mechanisms of different pathologies and neurotransmitter systems, but also provided us a new mean to measure in vivo amyloid pathology. Most of the studies discussed here used [^{11}C] Pittsburgh compound B (PiB) as tracer. Other tracers being less used are [^{18}F] Florbetaben (FBB), [^{18}F] Florbetapir and [^{18}F] FDDNP.

The prevalence of positive amyloid PET studies in PDND is variable, ranging from 0% [6, 87–89] to 38%[90–93] while 16.6–33% were reported in PDD [6, 40–43]. Shah et al. reported that combination of striatal and cortical β-amyloidopathy is correlated with worse cognitive impairment in PD [90]. 16.7% (11/66) of a subgroup of PD patients with elevated PiB binding was found to have significantly lower CSF $A\beta_{42}$ level [93].

Gomperts et al. reported a one longitudinal study [94] which involved 35 PD patients with normal cognition and 11 with MCI. There was no difference in the baseline PiB binding between these two groups. However, significant higher baseline PiB uptake ($p = 0.048$) was found in the group who progressed to a more severe cognitive diagnosis. Baseline PiB uptake also predicted deterioration in executive function over time.

On a smaller scale, there is also evidence from PD patients to support the significant negative correlation of [^{18}F] FDDNP binding in lateral temporal region with CSF Aβ. Longitudinally, higher baseline lateral temporal [18F] FDDNP binding was associated to longitudinal worsening in cognitive performances and progression to dementia among subjects classified as PDND at baseline, as well as a reduction in CSF Aβ and an increase in CSF tau levels [95].

A recent study by Rizwan et al. [91] suggested the association of regional brain Aβ accumulation with domain-specific cognitive deficits in PDND. The ^{18}F-florbetapir retention values in the frontal cortex, precuneus, and anterior cingulate gyrus is inversely correlated with naming performance while the retention values in the posterior cingulate gyrus is inversely correlated with verbal memory performance.

CSF Aβ studies

Apart from Aβ PET imaging, CSF markers are another promising in vivo biomarkers. The low CSF Aβ and high total tau(t-tau) and high phosphorylated tau (p-tau) have been described initially in Alzheimer's disease (AD). Cross-sectional studies mostly showed the decreasing trend of CSF $A\beta_{42}$ level in the following manner: NC > PDND > PDD [96–98]. Consistently, most studies showed the significant association between cognitive impairment and reduced level of CSF $A\beta_{42}$ [99]. Alves group reported low level of CSF Aβ 42, 40, and 38 in a subset of newly diagnosed 109 PD patients [100]. In the same cohort, sequential regression analyses showed significant association between those CSF markers and memory cognitive domain. CSF Aβ had also been shown to be related with phonetic fluency in PDND [96].

Eight longitudinal studies (Table 3) have been published and consistently revealed that low CSF $A\beta_{42}$ at baseline is a predictor for future cognitive decline [45, 47–53].

Summary

In short, the combination of the three pathology substrates, be it synucleinopathy in Lewy body, Aβ pathology or taupathy, seems to exert worsening effect on cognition far beyond any single proteinopathy. Low CSF $A\beta_{42}$ has been consistently shown as a predictive marker of cognitive decline in eight longitudinal studies (Table 2). Though increased Aβ binding in both PDND and PDD cohorts is around one-third, but its correlation with low CSF $A\beta_{42}$ level and the progression to a more severe cognitive state, do concur with the pathological studies and CSF studies.

Aβ and gait

Gait control involves complex brain processing which integrates coordination, cognitive processes, somatosensory, and visual inputs. Motor symptoms in PD such as bradykinesia, rigidity and tremor are usually controlled well with dopaminergic therapy, but this therapy is not effective for

Table 2 Longitudinal studies involving CSF biomarkers that suggested low baseline CSF $A\beta_{42}$ as predictor for future cognitive decline in PD

Study	Sample size	Disease duration (years)	Baseline MMSE score	Duration of follow-up (years)	CSF biomarkers	Outcome measures of cognition	Main findings	Reference
Siderowf et al.	45 PD	11	DRS score: 133	1.5	Aβ42, total tau, p-tau	DRS-2 score	Reduced CSF42 was an independent predictor of cognitive decline	[45]
Parnetti et al.	44 PD, 25 C	3	27 (PD), 29 [C]	3	Aβ42, total tau, p-tau, α-synuclein	MMSE, MOCA scores	Low CSF Aβ42 was an independent predictor of more rapid cognitive decline	[53]
Modreanu et al.	58 PD patients (21 PDD at baseline)	8	Nil	1.5	CSF Aβ and tau	Dementia	(1) At baseline, CSF tau was higher and CSF Aβ was lower in PDD vs. PDND, (2) 'Dementia-converters' had significantly lower CSF Aβ at baseline, (3) non-motor predominance and CSF Aβ remained as significant predictors of dementia	[47]
Alves et al.	104 PD	1.5 mths	28	5	Aβ42, Aβ40, and Aβ38, total tau, p-tau	Dementia	Low Aβ42 values predicted a substantially increased risk for subsequent dementia at high sensitivity after adjustment for baseline age and MCI status	[48]
Backstrom et al.	104 PDND, 11 MSA, and 13 PSP	1.4	29	5 till 9	Neurofilament light chain protein, Aβ42, total tau, p-tau, α-synuclein, and heart fatty acid-binding protein	Dementia	High neurofilament light chain protein, low Aβ42, and high heart fatty acid-binding protein were related to future PDD	[49]

Table 2 (continued)

Study	Sample size	Disease duration (years)	Baseline MMSE score	Duration of follow-up (years)	CSF biomarkers	Outcome measures of cognition	Main findings	Reference
Compta et al.	50 subjects (19 PDND, 19 PDD, 12C)	10 (PDND), 9 (PDD)	30 (C), 28 (PDND), 19 (PDD)	1.5	Aβ42, total tau, p-tau, α-synuclein	Dementia	Progression to dementia at 18 months was more frequent in patients with moderate-to-severe parieto-occipital WMHs and low CSF Aβ	[50]
Caspell-Garcia et al.	423PD–PPMI cohort	6.7 mths	27.13 (MOCA)	3	Aβ42, total tau, p-tau, α-synuclein	CI (detailed cognitive battery)	Predictors of cognitive impairment include dopamine deficiency, diffuse cortical decreased brain volume or thickness, lower CSF Aβ42 and genes	[51]
Compta et al.	27 PD	10	28	1.5	Aβ42, total tau, p-tau	Dementia	Low CSF Aβ42 predicted dementia	[52]

DRS-2 Mattis Dementia Rating Scale (version 2), *CI* cognitive impairment, *MSA* multiple system atrophy, *PSP* progressive supranuclear palsy, *MOCA* Montreal cognitive assessment, *PDD* Parkinson's disease dementia, *PDND* Parkinson's disease non-demented, *C* controls, *mths* months, *WMH* white matter hyperintensities, *p-tau* phosphorylated tau, *PPMI* Parkinson's progression markers initiative

Table 3 Aβ-based therapeutic strategies

Anti-inflammatory (amyloid-related neuroinflammation)	Nonselective and selective COX inhibitors NSAIDS Mast cell stabilizer Inhibitor of RAGE
Reducing Aβ production	BACE inhibitors Gamma-secretase inhibitors Selective gamma-secretase modulators
Facilitating Aβ clearance	Active immunotherapy (e.g., active vaccine) Passive immunotherapy (e.g., anti-Aβ monoclonal antibody)

Aβ amyloid-β, *BACE* β-site amyloid precursor protein cleaving enzyme, *RAGE* receptor for advanced glycation end products, *COX* cyclooxygenase, *NSAID* nonsteroidal anti-inflammatory drug

gait disturbances such as on-period freezing, increased gait variability, and postural instability. One of the underlying mechanisms of gait disorders in PD is likely a cholinergic deficit resulting from involvement of the pedunculopontine nucleus, thalamus, nucleus basalis of Meynert and the forebrain cortical cholinergic projections [101, 102]. In addition, Aβ pathology has been reported to be associated with gait abnormalities recently in both normal aging population [103] and PD cohorts. There are four cross-sectional studies in PD that demonstrated the relationship between Aβ pathology and the PIGD subtype. Alves et al. [104] had examined the CSF of 39 PIGD cases, 60 patients with tremor-dominant (TD) variant and 46 age-matched normal controls. CSF $A\beta_{42}$, $A\beta_{38}$, $A\beta_{42/40}$ and $A\beta_{38/40}$ using triplex immunoassay were collected together with motor and neuropsychological function and cerebral MRI. Significant lower CSF $A\beta_{42}$, $A\beta_{38}$, $A\beta_{42/40}$ and $A\beta_{38/40}$ levels were detected in PIGD phenotype in comparison to the tremor-dominant (TD) phenotype and normal controls. Further multivariate regression analysis demonstrated significant association between CSF Aβ markers with severity of PIGD and lower limb bradykinesia in PD patients adjusting for age, MRI white matter hyperintensities and cognition. The association of lower CSF $A\beta_{42}$ with the PIGD phenotype has also been replicated by Kang et al. and Ding et al. [105, 106]. The fourth cross-sectional study involved PET imaging using [^{11}C]-PiB and [^{11}C]-dihydrotetrabenazine(DTBZ) [107]. 44 PD patients were recruited. Increased PIGD severity was significantly associated with higher neocortical [^{11}C]-PiB binding for Aβ after adjusting for nigrostriatal dopaminergic denervation, age, and cognition.

Bohnen et al. tested the hypothesis that freezing of gait (FoG) in PD is associated with extra-nigral changes of subcortical and neocortical cholinergic deficit and Aβ deposition [108]. Indeed, a higher frequency of freezing of gait was reported in the subgroup where both neocortical cholinopathy and amyloidopathy were present [108].

Besides this, one prospective study recruiting patients within 5 months of diagnosis by Rochester et al. [12] did not find the difference in worsening of gait between PIGD and TD phenotypes. However, low baseline CSF $A\beta_{42}$ is a significant predictor of dopamine-resistant gait characteristic (step time variability, step length variability) in the first 3 years after diagnosis, not attributed by age and cognition. With the evidence of instability of motor subtypes in the first year of diagnosis [109] and relatively paucity number of studies looking at CSF biomarkers and motor subtypes, definite conclusion at this time is difficult. In summary, amyloid pathology is likely play a role in locomotor network and gait. As discussed in the earlier section of cognition, the role of Aβ pathology in both cognition and gait seems to concur with the cholinergic subtype which includes 'ON' freezing and cognitive impairment [58]. This raises the possible relationship between Aβ pathology and cholinergic subtype and is yet to be explored in future.

Aβ and apomorphine

Apomorphine: affinity and mechanism of action

Apomorphine is a broad-spectrum dopamine agonist activating dopamine D1-like (D1, D5) and D2-like (D2, D3, D4) receptors, along an affinity for serotonin and α-adrenergic receptors [110]. Its use is currently given for rescue of unpredictable Off-periods when administered as a subcutaneous injection or sublingually, having a quick onset of action within 7–10 min and for overall improvement of Off time with no increase in dyskinesia when administered as a continuous subcutaneous infusion [110].

Apomorphine and Aβ deposition

In AD, anti-Aβ drugs (see Table 3) entering Phase III clinical studies consist of inhibitor of the β-secretase cleaving enzyme (BACE), anti-Aβ monoclonal antibodies, inhibitor of receptor for advanced glycation end products and anti-inflammatory compounds [111]. Recent trials failures with Aβ based therapy in mild-to-moderate AD or prodromal AD has casted doubt on the amyloid hypothesis. While Aβ pathway is likely to be one of the complex multiple pathways in the pathogenesis of AD, there are contributions from other mechanisms such as neuroinflammation, tau pathology and oxidative stress. Besides this, there are few other factors to consider, for instance timing of drug being administered in the course of AD, the unclear correlation between the effects of Aβ-based drugs on AD biomarkers and cognition and optimal pathological Aβ molecular species to target [111]. All these factors may explain the failure of the drug trials as precise amyloid-related pathophysiology remain yet to

be elucidated by further research. As an analogy in PD with its pathophysiological heterogeneity the challenge remains to understand the precise interactions between alpha-synuclein, amyloid and tau pathology before specific therapeutic approaches can be developed.

The first description of a potential role of apomorphine came from a mouse model study of AD in 2011, where apomorphine reduced intraneural Aβ as well as p-Tau deposition along with a strong improvement in memory function [112]. This effect was not observed after injection of pramipexole, another dopamine-agonist, postulating that a potential role of non-dopaminergic pathways might at least partially account for the pronounced effect exerted by apomorphine. In humans, an observation of decreased Aβ diffuse and total plaque load in post-mortem brain analysis of PD patients previously exposed to apomorphine ($N=35$) compared to apomorphine-naïve subjects ($N=36$) was reported [113]. In this study, demented and non-demented subjects were included and interestingly, a significant reduction of Aβ load could only be identified in the non-demented group with antemortem apomorphine exposure. Furthermore, a significant negative correlation between maximum apomorphine dose received and Aβ burden was observed in the non-demented group. The potential mechanisms underlying this clearance capacity are to date not fully understood, with current hypothesis postulating an anti-oxidative effect on cells, reducing apoptosis and synaptic injury as well as an enhanced degradation of intracellular Aβ mainly thought to be due to an upregulation of the proteasome system [112, 113]. From a mechanistic viewpoint, Apomorphine might also interfere with Aβ in other ways. Through a Micheal reaction, i.e., the mild formation of carbon bonds between apomorphine and amyloid precursors, apomorphine may reduce the formation of amyloid oligomers from monomers (Fig. 3). In addition, apomorphine seems to interfere with the formation of amyloid fibrils from oligomers [114]. More research is needed to elucidate the mechanisms of apomorphine on Aβ clearance as the current available evidence is still scarce. A single human post-mortem study found reduction of Aβ load in non-demented PD group [113] but not in demented PD group. A prospective longitudinal in vivo study involving PET imaging pre and post apomorphine and detailed neurocognitive assessment may provide us more insight into this interesting mechanistic phenomenon related to apomorphine infusion. Furthermore, whether a reduction of Aβ load within the brain also translates into clinical outcome remains to be seen. If initial studies are positive it could be envisaged that apomorphine infusion or injection could be repurposed as a potential disease modifying compound for early and non-demented stages of PD. A well-designed trial administering apomorphine infusion in an enriched PDND cohort with positive Aβ imaging or low CSF Aβ at baseline may be considered for this purpose and enable amyloid based therapy to be considered a therapeutic option to reduce cognitive burden in PD population and thus delivering personalised medicine [115].

Conclusions

A concerted effort from different centres using multi prong approach involving clinical, biochemical, imaging, genetics, and molecular evaluations is needed to help better define the roles of amyloid pathology in PD (see Fig. 4). However, current evidence increasingly points toward the involvement of Aβ in PD and, from recent studies, the role it may have in cognitive deficits in PD patients. Not only cognition seems to be affected by Aβ, but also the dopamine-resistant gait disturbances. In fact, both cognition and gait disturbances in PD may share a common underlying pathological

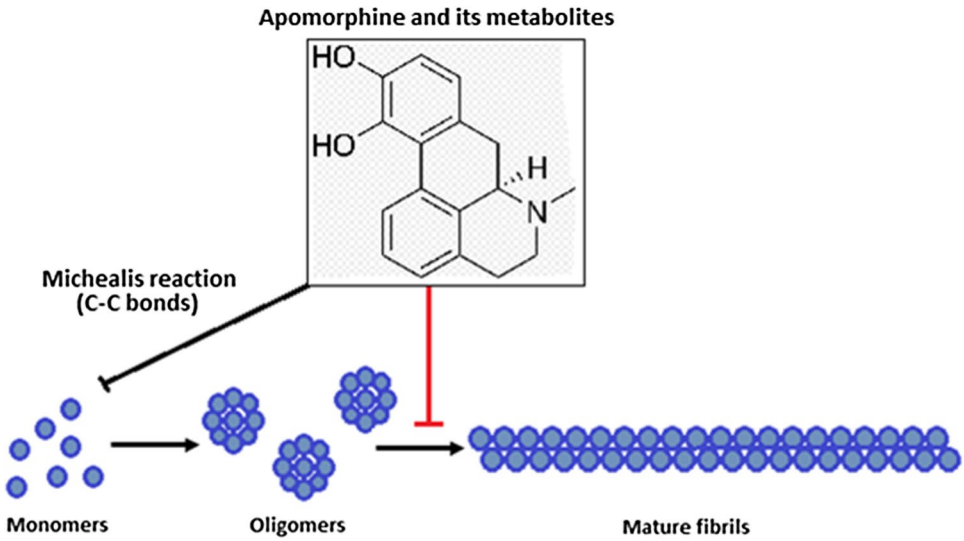

Fig. 3 Possible effects of apomorphine on Aβ which include decreased formation of amyloid oligomers from monomers via Michealis reaction and interfered amyloid fibrils formation from oligomers

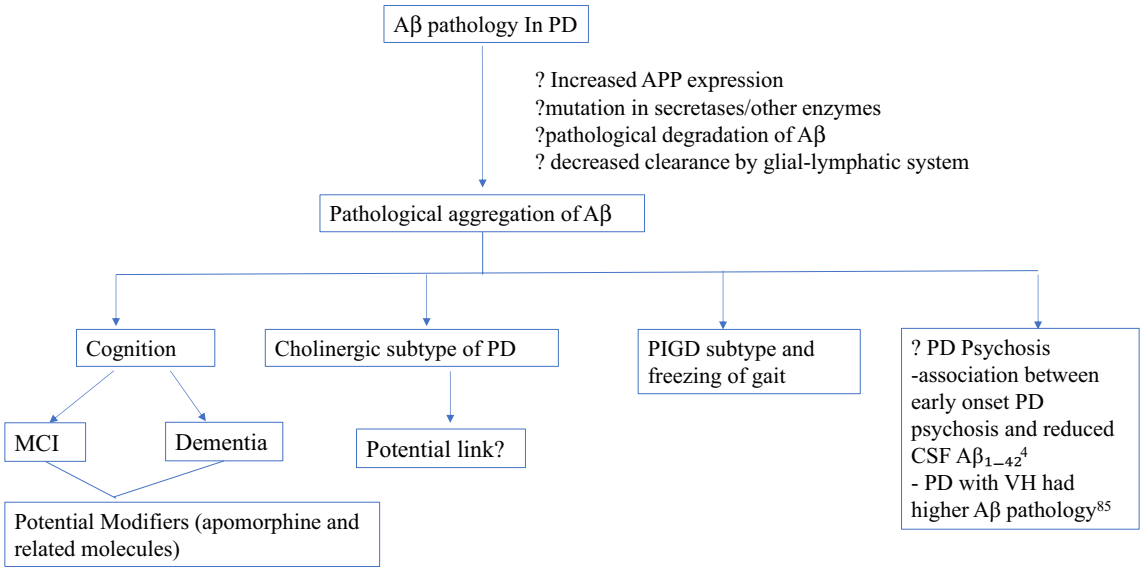

Fig. 4 Summary of the relationship of Aβ and PD APP: amyloid β precursor protein, *CSF* cerebrospinal fluid, *PD* Parkinson's disease, *Aβ* amyloid-β, *PDND* non-demented Parkinson's disease, *PDD* Parkinson' disease dementia, *PET* positron emission tomography, *PIGD* postural instability and gait difficulty

mechanism which is related to Aβ pathology. In the same light, trying to target Aβ seems be a promising strategy of relieving cognitive and axial symptoms in PD. In addition, CSF $Aβ_{42}$ combined with other biomarkers could potentially be used as predictive biomarkers to help us to identify appropriate cohort at risk of cognitive decline, and hence can be selected for future protein targeted therapy.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

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