Clinical Biochemistry 73 (2019) 26–31

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Alzheimer's disease and other neurodegenerative dementias in comorbidity: A clinical and neuropathological overview

Radoslav Matej[a,b], Adam Tesar[c], Robert Rusina[c,d,*]

[a] Department of Pathology and Molecular Medicine, Third Faculty of Medicine, Charles University, Thomayer Hospital, Prague, Czech Republic
[b] Department of Pathology, First Faculty of Medicine, Charles University, General University Hospital, Prague, Czech Republic
[c] Department of Neurology and Centre of Clinical Neuroscience, First Faculty of Medicine, Charles University, General University Hospital, Prague, Czech Republic
[d] Department of Neurology, Third Faculty of Medicine, Charles University, Thomayer Hospital, Prague, Czech Republic

ARTICLE INFO

Keywords:
Neurodegeneration
Alzheimer's disease
Tauopathy
TDP-43
Synucleinopathy
Mixed dementia

ABSTRACT

Neuropathological diagnostic criteria of neurodegenerative disorders are based on the presence of specific inclusions in a specific area of brain tissue that correlate with clinical manifestations. Concomitant neurodegenerative disorders correspond to a combination of two (or more) different fully developed diseases in the same patient. Concomitant neurodegenerative pathology represents the presence of definite neurodegeneration and deposits of pathological proteins specific for another disease, which is not, however, fully developed. Very frequent overlaps include Alzheimer's disease and alpha-synuclein inclusions. Nevertheless, careful neuropathological investigations reveal an increasing frequency of different co-pathologies in examined brains. In Alzheimer's disease, protein TDP-43 may co-aggregate, but it is not clear whether this is atypical isolated Alzheimer's disease or overlap of Alzheimer's disease with early frontotemporal lobar degeneration. Comorbidities of Alzheimer's disease and tauopathies are relatively rare. A combination of vascular pathology with primary neurodegeneration (mostly Alzheimer's disease or dementia with Lewy bodies) is historically called mixed dementia. Overlap of different neuropathologically confirmed neurodegenerations could lead to atypical and unusual clinical presentations and may be responsible for faster disease progression. Several CSF biomarkers have been evaluated for their utility in diagnostic processes in different neurodegenerative dementias; however, evidence regarding their role in neurodegenerative overlaps is still limited.

1. Introduction

Neurodegenerations encompass a large group of diseases with a shared clinical presentation including a combination of cognitive impairment and movement disorders, especially, parkinsonism, or motor neuron diseases.

The common neuropathological background of neurodegeneration is a progressive loss of specific neuronal populations as a consequence of two distinct but parallel pathological hallmarks: i) deposits of pathologically altered proteins into the cell bodies of brain tissue, either neuronal or glial, or extracellularly) [1]; and ii) general mechanisms of programmed cell death like apoptosis and autophagy [2]. The most common proteins forming pathological deposits are beta-amyloid, tau protein, alpha-synuclein, and protein TDP-43. Moreover, other pathophysiological processes are included in neurodegenerations, i.e., genetic and epigenetic changes, metabolism of different metals, and defects of protein degradation.

Neurodegenerative disorders may, therefore, be considered as specific proteinopathies. Clinical manifestations directly result from generalized neuronal loss or neuronal death in specific areas of the brain, reflecting the selective vulnerability of various populations of neurons to specific protein deposits. Selective loss of neuronal subpopulations

Abbreviations: AD, Alzheimer's disease; AGD, argyrophilic grain disease; ARTAG, age-related tau astrogliopathy; bvFTD, behavioral variant of frontotemporal dementia; CJD, Creutzfeldt-Jakob disease; CSF, cerebrospinal fluid; CVD, cerebrovascular disease; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; FTLD, frontotemporal lobar degeneration; FTLD-MND, frontotemporal lobar degeneration with motor neuron disease; GGT, globular glial tauopathies with mainly oligodendroglial and astrocytic inclusions; MSA, multiple system atrophy; NIA-AA, National Institute on Aging–Alzheimer's Association); PART, primary age-related tauopathy; PD, Parkinson's disease; PPA, progressive aphasia; PSP, progressive supranuclear palsy; RT-QuIC, real-time quaking-induced conversion; TDP-43, transactive response DNA binding protein 43

* Corresponding author at: Department of Neurology and Center of Clinical Neuroscience, Charles University in Prague, 1st Faculty of Medicine, General University Hospital in Prague, Katerinska 30, 120 00 Praha 2, Czech Republic.
E-mail address: robert.rusina@lf1.cuni.cz (R. Rusina).

https://doi.org/10.1016/j.clinbiochem.2019.08.005
Received 31 March 2019; Received in revised form 6 August 2019; Accepted 7 August 2019
Available online 07 August 2019

Table 1
Typical clinical and pathological hallmarks in neurodegenerative disease [68].

Proteinopathy	Disease	Clinical manifestations	Most affected region	Pathological hallmark	Aggregated protein
Alzheimer's disease	Alzheimer's disease	Episodic memory loss; impairment of other cognitive domains (speech, visuospatial, executive function)	Brainstem and limbic structures, hippocampus, neocortex Neocortex, subcortical nuclei, brainstem, cerebellum	Neurofibrillary tangles Amyloid aggregates and cerebral amyloid angiopathy	Tau protein (3R and 3R isoform) Beta-amyloid
Synucleinopathy	Parkinson's disease Dementia with Lewy bodies	L-dopa sensitive parkinsonism Dementia with fluctuating cognition, visual hallucinations, parkinsonism, neuroleptic sensitivity	Brainstem, limbic structure, subcortical nuclei, cortex	Lewy bodies, Lewy neurites	Alpha-synuclein
	Multiple system atrophy	Parkinsonism, cerebellar signs, dysautonomia	Brainstem, cerebellum, basal ganglia, limbic structures, cortex	Oligodendroglial inclusions, neuronal inclusion	
Tauopathy	Frontotemporal dementia	Frontal lobe signs, aphasia, behavioral changes	Hippocampus, limbic and cortical structures	3R tau neuronal and astrocytic inclusion	Tau protein (3R dominantly)
	Primary progressive aphasia, nonfluent/agrammatic variant	Impaired speech production and dysarthria; late dementia	Periinsular cortex, frontal and temporal areas mostly in the dominant hemisphere		
	Progressive supranuclear palsy	Atypical parkinsonism with axial rigidity, supranuclear ophthalmoplegia, falls, dementia	Basal ganglia brainstem, cerebellum, white matter, and neocortex	4R tau neuronal inclusions, "tufted "astrocytes and oligodendroglial inclusion	Tau protein (4R dominantly)
	Corticobasal degeneration	Dementia with apraxia, aphasia, frontal signs, myoclonus, alien hand, asymmetric parkinsonism	Basal ganglia, neocortex and subcortical white matter, brain stem, and cerebellum	4R tau neuronal inclusions, astrocytic plaques, oligodendroglial inclusions, dystrophic fibers in white and grey matter	
TDP-43 proteinopathy	Frontotemporal dementia Primary progressive aphasia, semantic variant	Frontal lobe signs, aphasia, behavioral changes Fluent aphasia, severe comprehension deficits	Limbic structures, hippocampus, cortex	Neuronal cytoplasmatic oligodendroglial inclusion Neuronal and oligodendroglial inclusion	Protein TDP-43
	Amyotrophic lateral sclerosis	Muscular weakness, amyotrophy, spasticity, cognitive impairment	Spinal and brainstem motor neurons, limbic structures	Neuronal cytoplasmatic oligodendroglial inclusion	

plus the spread, over time and space, of specific protein deposits reflects different disease manifestations and progression.

Neuropathological diagnostic criteria of neurodegenerative disorders are based on the presence of specific lesions in different areas of brain tissue, with selective damage to vulnerable cellular subpopulations that correlate with specific clinical symptoms.

Current diagnostic criteria for the most common neurodegenerative diseases encompass three levels of diagnostic certainty: "possible" (based mainly on a characteristic clinical presentation); "probable" (clinical symptoms and results of neuroimaging, laboratory methods, and/or biochemical biomarkers); and "definite" (requires neuropathological verification with immunohistochemical demonstration of specific neuronal and/or glial inclusions). The main clinical and neuropathological findings of the most common neurodegenerations are summarized in Table 1.

There is increasing evidence that neurodegenerative diseases may overlap, i.e., the brain tissue of a given patient may show two (and even more) distinct neurodegenerations simultaneously. Such comorbidities may lead to more severe impairment of cognitive and motor manifestations, a faster disease progression, atypical or troublesome clinical presentations, lower sensitivity to treatment, and a worse prognosis [3]. Epidemiological data concerning the frequency of neurodegenerative disease overlap is still sparse, but comorbidities may occur more often than previously thought, as can be seen from the increasing number of published case series [4,5] and published experience in our single center cohort [6–10].

2. Clinical, biochemical, and neuropathological aspects of the principal neurodegenerative disorders

2.1. Alzheimer's disease

Hallmarks of Alzheimer's disease (AD) are neuritic plaques (extracellular deposits of beta-amyloid in brain tissue) and neurofibrillary tangles (intraneuronal deposits of insoluble hyperphosphorylated tau proteins) mostly predominating in the hippocampal and temporal cortical regions. Typical clinical manifestations include early loss of episodic memory, progressing later to impairment in other cognitive domains (language, executive, and visuospatial functions), and finally the development of various behavioral manifestations in conjunction with impaired daily activities.

The neuropathological ABC classification proposed by the National Institute on Aging – Alzheimer's Association (NIA-AA) evaluates both the distribution and density of amyloid deposits (A – amyloid, C – CERAD) and tau protein deposits (B – Braak). The final result estimates the probability (low-intermediate-high) of neuropathological findings to justify the observed cognitive impairment [11]. Several subtypes of AD have been observed: the typical form (60–80% of AD patients); the limbic predominant form with pronounced mediotemporal atrophy, while other areas remain spared for long periods of time (its clinical presentation includes early hippocampal amnesia and mild executive dysfunctions); the hippocampal-sparing form with lesser hippocampal involvement but more pronounced frontal and parietal involvement (early executive and visuospatial manifestations, although episodic memory is relatively spared); and focal AD forms, which predominantly involve different circumscribed cortical areas (e.g., frontal variant of AD, logopenic variant of primary progressive aphasia, corticobasal syndrome, and posterior cortical atrophy) [12,13].

The clinical NIA-AA diagnostic criteria from 2011 [14] were revised in 2018. The most important change in this so-called "research framework" [15] was that AD can be explored in the living as a biological status defined by biomarkers and independently of the clinical presentation. Cerebrospinal fluid (CSF) biomarkers are among the most important and frequently used to support an AD diagnosis [16]. CSF amyloid beta 1–42 (Aβ42), total tau (t-tau), and phosphorylated tau (p-tau) have shown their diagnostic utility in differentiating AD patients

from healthy controls. A decrease in Aβ42 and a low Aβ42 to amyloid beta 1–40 ratio (i.e., Aβ42/Aβ40), together with an increase in both t-tau and p-tau, contribute to the definition of an "Alzheimer's signature" [17]. Additionally, a variety of other CSF analytes relevant to neurodegeneration are now available. These include markers of amyloid processing (AβX-38, AβX-40, AβX-42, and soluble amyloid precursor protein), large fiber axonal degeneration (light chain neurofilaments), and neuroinflammation (chitinase-3-like protein 1, also known as YKL-40), and many others [18]. Moreover, the first published research regarding the potential diagnostic utility of real-time quaking-induced conversion (RT-QuIC) has yielded promising results in detecting seeded tau protein polymerization in AD [19].

RT-QuIC is a new ultrasensitive method related to seeded polymerization of pathologically changed proteins linked to different neurodegenerations. In the field of prion diseases, this method has reached the level of diagnostic inclusion criteria with a high level of sensitivity and specificity. In brief, RT-QuIC is based on cell-free conversion systems emulating protein replication in vitro. Recombinant protein fragments used as a reaction substrate in the reaction mixture are heated and intermittently shaken to provide the necessary energy input. Positive signals consist of fluorescence coming from the amyloid-specific dye Thioflavin T (ThT), which is also present in the reaction mixture. If a protein containing sample is present, it leads to a conformational change in the recombinant substrate and forms ThT binding-protein aggregates, which provide easily detectable fluorescent signals [20].

2.2. Synucleinopathies

Intracellular deposits of alpha-synuclein were first reported in Parkinson's disease (PD), then in dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). The main clinical features of synucleinopathies are parkinsonism (bradykinesia, rigidity, tremor, and postural instability) and cognitive impairment; REM-associated behavioral disorder (RBD) is common and may precede parkinsonism; other manifestations include cerebellar and pyramidal signs and dysautonomia [21].

Pathological alpha-synuclein inclusions may share features with neuronal Lewy bodies, i.e., Lewy neurites and oligodendroglial Papp-Lantos inclusions [22]. There are, however, still no established biomarkers of synucleinopathies in current clinical practice. Several potential markers have been proposed, such as CSF total α-synuclein, CSF oligomeric α-synuclein, phosphorylated α-synuclein, and the seeding activity of α-synuclein from cerebrospinal fluid measured using α-synuclein RT-QuIC) [23,24] and lysosomal enzyme activities [25,26]. CSF total α-synuclein is lower and CSF oligomeric α-synuclein and phosphorylated α-synuclein are higher in PD patients compared with other, non-synucleinopathy, neurodegeneration. Lysosomal enzyme activities in the CSF are reduced in patients with PD. The clinical use of these findings is still limited since blood contamination of CSF samples can affect the accuracy of assays [25]. However, none of these markers (even seeding assays) can distinguish between different synucleinopathies (e.g., PD vs. DLB vs. MSA) [26]. In one study, the levels of fatty acid binding protein 3 were significantly increased in patients with AD and DLB compared with PD patients and controls [27]. Levels of Aβ42 may be used as a marker of cognitive impairment in PD, and serum and plasma levels of urate correlate with slower rates of motor progression [28].

2.3. Tauopathies

These diseases are characterized by abnormal metabolism of tau protein (i.e., the associated tubulin unit, a structural component of the microtubules system) and subsequent tau deposits in neurons and glial elements.

In the healthy brain, tau is present in six isoforms, with three (3R tau), or four (4R tau) predominant microtubule binding sites. Tauopathies present with neuronal loss, intraneuronal cytoplasmic globose 4R-tau immunoreactive inclusions, pre-tangles (diffuse granular cytoplasmic inclusions), and tufted astrocytes with argyrophilic and tau immunoreactive inclusions.

Tauopathies are an essential part of frontotemporal lobar degenerations (FTLD), which is a very heterogeneous group of neurodegenerative diseases [29]. Common clinical manifestations include frontal lobe signs, early behavioral changes, aphasia with decreased speech production, apraxia of speech, parkinsonism, axial rigidity, oculomotor palsy, asymmetry, early falls, and dementia. The most common tauopathy is progressive supranuclear palsy (PSP) with a clinical presentation of early gait disturbances and falls, axial rigidity, vertical gaze palsy, and subcortical dementia. Tau-positive frontotemporal dementia (including Pick's disease) manifests as predominant frontal lobe dementia with early behavioral features, personality changes, and memory loss due to hippocampal lesions, and in some cases speech and language impairment. The non-fluent/agrammatic variant of primary progressive aphasia typically progresses from isolated aphasia with impaired speech production and dysarthria to frontal lobe dementia. Asymmetric cortical and extrapyramidal signs with limb apraxia, alien limb phenomenon, dopa-unresponsive akinesia with rigidity, and dystonia, are typical of corticobasal syndrome. When the underlying neuropathology is a four-repeat (4R) tauopathy, the term corticobasal degeneration is used. Recently, neuropathologically defined new entities have been added to the list of tauopathies; their clinical manifestation, however, remains poorly determined. Some of the most common are argyrophilic grain disease (AGD) [30], primary age-related tauopathy (PART) [31], age-related tau astrogliopathy (ARTAG), and globular glial tauopathies with mainly oligodendroglial and astrocytic inclusions (GGT) [32]. As with synucleinopathies, fluid CSF biomarkers have only limited value in clinical practice relative to tauopathies [33], however, detection of increased levels of the different sub-forms of tau protein, especially using the new ultrasensitive RT-QuIC method, have initially provided promising results [34].

2.4. TDP-43 proteinopathies

The transactive response DNA binding protein (TDP-43) is a pathological hallmark of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration with TDP-43-positive inclusions (FTLD-TDP) [35]. TDP-43 is physiologically detected in the nucleus as diffuse staining; however, when misfolded it can form neuronal intranuclear inclusions (NII's), neuronal cytoplasmic inclusions (NCI's), and stain different types of dystrophic neurites [36].

Frontotemporal lobar degenerations with TDP-43 inclusions (FTLD-TDP) may present with frontal lobe signs, early behavioral changes, and dementia; aphasia is often fluent with severe comprehension deficits (a semantic variant of primary progressive aphasia), and an unusual affinity of TDP-43 for motor neurons results in muscle weakness, amyotrophy, spasticity, and bulbar signs. FTLD-TDP has been classified neuropathologically into subtypes A, B, C, and D, which are associated with pathogenic mutations in genes *GRN* and *C9orf72*, *VCP* or others and are frequently characterized by atypical clinical presentations, such as the behavioral variant of frontotemporal dementia (bvFTD), the semantic variant of primary progressive aphasia, frontotemporal dementia with motor neuron disease, or inclusion body myopathy with early-onset Paget disease and frontotemporal dementia, respectively [35]. Low-grade dyslipidemia (lipoprotein metabolism alteration) can precede ALS manifestation, but there is still insufficient evidence regarding the role of lipid metabolism in ALS pathology [37]. Exosomal mRNAs, e.g., CUEDC2 (CUE domain-containing 2), in CSF have also been suggested as potential disease biomarkers for amyotrophic lateral sclerosis [38]. In FTLD-TDP caused by the GRN mutation, both CSF and plasma progranulin concentrations are reduced and an assay of dipeptide protein poly(GP) repeats in the CSF has already been established

Table 2
Overlap of neurodegenerative diseases [68].

Variants of overlap	Neuropathology	Clinical examples
Concomitant neuropathology	One neurodegenerative disease and deposits of other neuropathology	FTLD and alpha-synuclein deposits AD and TDP 43 deposits
Concomitant neurodegenerative diseases	Two or more fully developed neurodegenerative diseases	AD and MSA AD and bv-FTD AD and PSP AD and DLB
Mixed dementia	Vascular pathology and neurodegenerative disease	AD and vascular dementia

for ALS-FTD caused by expansions in *C9orf72* [37]. Despite the first promising results regarding the diagnostic utility of the levels of the CSF protein TDP-43 [39], its real value is still a matter of debate [40].

2.5. Cerebrospinal fluid biomarkers for differentiation between comorbidities

Most prior studies have focused on differentiating patients with neurodegenerative diseases from controls or predicting disease conversion/progression rates; however, a major challenge in clinical practice is to distinguish different neurodegenerative disorders or different subtypes having the same proteinopathy [41]. In these settings, the use of biomarkers is promising. The best-established CSF biomarkers: Aβ42, t-tau and p-tau, and serum level of neurofilaments (NF) are overall markers of general neurodegeneration (axonal damage in case of neurofilaments) [42], which makes it complicated to establish diagnostic cut-off values [43]. That said, levels of neurofilaments increase in the CSF and blood proportionally with disease progression [42] and can also discriminate PD from PSP, MSA, and CBS in cases with confounding clinical presentations [26]. On the other hand, CSF Aβ42 tends to be higher in patients with PD than in LBD and AD patients [26] and can predict cognitive impairment in DLB or PD [28]. In FTD, Alzheimer biomarkers (Aβ42, p-tau, and t-tau) are only positive in a small percentage of patients, which leads in combination with increased NF to high diagnostic sensitivity 75–86% and specificity of 94–100% compared to AD patients and healthy controls. Moreover, recent data suggest that a reduction in the plasma Aβ42/Aβ40 ratio reflects the presence of AD-associated brain pathology. Additionally, neurofilaments have been shown to be higher in FTD, compared to AD [33].

There are no established biomarkers for vascular dementia since changes in MRI scans are used worldwide to estimate the severity of vascular impairment (for example the Fazekas scale) [44]. Circulating inflammatory biomarkers, such as C-reactive protein, interleukin-6, and alpha 1-antichymotrypsin, have been shown to be related to microinfarcts, microbleeds and white matter hyperintensities on MRI scans [45], but their clinical reliability remains to be confirmed.

3. Overlap of neurodegenerative diseases

Despite the use of recent diagnostic methods and biomarkers (MRI, SPECT with ioflupane, amyloid and tau PET, detection of beta-amyloid, tau protein, synuclein, and other proteins in the cerebrospinal fluid), autopsy finding (definite diagnosis) are often different from clinical conclusions (i.e., the probable diagnosis, accordingly to current diagnostic criteria for the given neurodegenerative disease) in up to 20–40% of cases (for example, Parkinson's disease vs. progressive supranuclear palsy). Therefore, neuropathological verification is crucial for a better understanding, better descriptions, and better tests for neurodegeneration [46].

The last few years have shown that more than one neurodegenerative disease can be found in the same brain during an autopsy. There is increasing evidence that a concomitant occurrence of additional markers for different neurodegenerative disorders is quite common and increases with age, and can impact clinical presentations [47,48]. On the other hand, the increasing frequency of neuropathologically diagnosed neurodegenerations may result from deeper neuropathological investigations of the brains using a widening spectrum of specific antibodies.

The neurodegenerative overlap (Table 2) can have two distinct forms: 1) concomitant neurodegenerative diseases: a true comorbidity of two or more fully developed neurodegenerative diseases (corresponding to neuropathological diagnostic criteria); and 2) concomitant neuropathology: one neuropathologically confirmed neurodegenerative disease and specific deposits characteristic of another neuropathological disorder, although, it is not a fully developed disease, i.e., present only in some brain areas, and thus not fulfilling the required neuropathological diagnostic criteria in terms of inclusion distribution (for example, TDP-43 deposits only in hippocampal areas but not widespread in the frontal and temporal regions as suggested for FTLD-TDP). AD is the most frequent cause of neurodegenerative dementia, and thus AD comorbidities are more frequently found in post mortem case series than other disorders.

3.1. Alzheimer's disease pathology and synucleinopathy

Alzheimer pathology co-occurs with deposits of alpha-synuclein in up to 80% of patients with neuropathologically confirmed Lewy body dementia [49]. On the other hand, up to 60% of patients with AD display at least some Lewy-body type synucleinopathy [50]. Beta-amyloid and tau deposits can be detected in other synucleinopathies, such as Parkinson's disease (in approximately 40% of cases) or multiple system atrophy [51].

The underlying interaction between both pathologies is still unclear, but intraneuronal tau and alpha-synuclein coaggregation is more frequent in the amygdala and entorhinal cortex than in the frontal cortex and is independent of the Braak stage. Therefore, this process is probably synergic but only locally [52]. Moreover, AD with amygdala Lewy bodies was established as a new distinct entity [53]. Recent studies also identified a difference in clinical characteristic between pure AD and patients with comorbid AD and synucleinopathy. These patients have more severe motor impairment (based on the UPDRS scale), have lower scores on dysexecutive and visuospatial function tests, and also have a higher tendency toward depression [15].

3.2. Alzheimer's disease pathology and tauopathy

AD in combination with tauopathy is quite rare. Most evidence is related to AD with concomitant argyrophilic grain disease (AGD). This AGD overlap leads to symptomatic cognitive impairment even in patients with lower levels of AD-related pathology relative to pure AD [54]. Other tauopathies, in particular, progressive supranuclear palsy, have sometimes been found in histological sections from patients with AD pathology [55]. On the other hand, there is no relevant estimation about the presence of the PART and ARTAG pathology in fully evolved AD. However, our observations suggest that it could be relatively high and should be clarified by a more comprehensive investigation. The clinical relevance of these newly described entities is waiting for elucidation.

3.3. Alzheimer's disease pathology and TDP-43 pathology

TDP-43 deposits can be identified in 19–57% of AD brains [56] and are considered to contribute to both beta an amyloid dependent and beta-amyloid independent pathways in AD [57].

TDP-43 protein was found in a concomitant AD/DLB (52.6%) pathology and is positively associated with age and mutations in the progranulin gene [58]. It has been suggested that AD itself could trigger or at least aggravate the load of TDP-43 inclusions [59] within both neurons and oligodendroglia AD cases. The frontal cortex is usually spared, but the amygdala and hippocampi are more vulnerable in AD patients than in FTLD cases with ubiquitin deposits [60,61]. These pathological findings agree with the impact of TDP-43 inclusions on cognition impairment, memory loss, and medial temporal atrophy in AD [62] as well as abnormalities on the Boston Naming Test in AD with early involvement of the amygdala [59].

3.4. Alzheimer's disease and vascular dementia – mixed dementia

Concomitant cerebrovascular disease (CVD) and hallmarks of neurodegenerative disorders are common findings in brain autopsies of older subjects with dementia, being most common in AD (up to 84% cases) [63,64].

Fibrinoid necrosis, lipohyalinosis, and arteriosclerosis are typically found in subcortical ischemic vascular dementia, historically called Binswanger disease. In AD, cerebral amyloid angiopathy is the most recognized vascular pathology (affecting almost 90% of Alzheimer's disease brains) [65] and thus, could affect the clinical presentation.

CVD causes a reduction in cerebral blood flow and therefore increases beta-amyloid production by modulating β and γ-secretase. Also, beta-amyloid clearance is affected because of changes in active transport across the blood-brain barrier into the vascular/lymphatic drainage systems.

CVD can also influence tau-pathology in AD, but the exact mechanism is still not clear [65]. Probably, there are compensative mechanisms in the white matter capillaries intended to retain white matter perfusion and integrity during hypoperfusion states that can occur in dementias [66]. There are additional vascular histological changes of white matter such as lacunes, periventricular and diffuse white matter demyelination, and focal and diffuse cortical gliosis, which are commonly believed to be unrelated to cognitive impairment.

Therefore, in concomitant AD and vascular pathology, the clinical impact depends on both the location and type of pathology as well as on the severity of the concomitant AD-related pathology [67]. CVD has additive as well as synergistic effects, and future therapeutic options for AD treatment should take into consideration this comorbid component [62].

4. Conclusion

The overlap of neurodegenerative diseases may be associated with faster progression or, in many patients, with a very atypical presentation. This demonstrates the urgent need for a detailed neuropathological examination of the brain and subsequent clinical-pathological correlations to analyze the role and participation of different comorbid disorders on the manifestation of the final disease. This final analysis may impact novel therapeutic options and consequences and may help in improving prognostic accuracy in neurodegenerative dementias. Moreover, newly described neuropathological entities related to aging, i.e., ARTAG and PART, are more common than expected and a precise definition of the clinical picture of these impairments is still missing.

The existence of two or more neurodegenerative diseases in comorbidity is of increasing importance in understanding neurodegeneration in so far as it may help explain the considerable differences in clinical presentations of what were previously considered homogenous neurodegenerative entities (e.g., AD, tauopathy, and TDP-43 proteinopathy). Furthermore, comorbidity may also contribute to more rapid disease progression and greater resistance to standard therapeutic options. Additionally, they may play a role in the failure of new precisely tailored therapies.

Neurodegenerative comorbidities remain largely underdiagnosed, and their prevalence and incidence remain to be established. Moreover, many neurodegenerative disorders (TDP-43 proteinopathies, tau subgroups, ARTAG, PART, etc.) have only become detectable during the last ten years. Therefore previous neuropathological examinations should be considered incomplete unless current standards were used.

A standardized clinical, neuropsychological, and MRI assessment of patients with progressive neurodegenerative dementia will be valuable in more precisely identifying as well as developing a better understanding the clinical manifestations seen in some of the more recently described entities (ARTAG, PART, etc.), which can only be recognized through neuropathology samples.

There is increasing evidence that analysis of the distinct features of disease-associated misfolded proteins related to neurodegenerations, namely their amyloid seeding activity detected by new ultrasensitive method RT-QuIC, may have substantial diagnostic utility in other neurodegenerations. Thus, CSF biomarkers might, in the near future facilitate intravital diagnosis of different overlapping neurodegenerations.

Funding

This work was supported by the Ministry of Health, Czech Republic (Conceptual development of research organization VFN64165, General University Hospital in Prague, DZ1716, Thomayer Hospital in Prague, TN64190), by the Grant Agency of the Ministry of Health, Czech Republic (NV18-01-00399, NV19-04-00090) and by Charles University, Czech Republic (Project Progress Q27 and Q28/LF1).

Declaration of Competing Interest

The authors declare that no competing interests exist.

Acknowledgments

The authors wish to thank Tom Secrest, MSc, for revision of the English version of this article.

References

[1] C.A. Ross, M.A. Poirier, Protein aggregation and neurodegenerative disease, Nat. Med. 10 (7s) (2004) S10.
[2] S. Ghavami, S. Shojaei, B. Yeganeh, S.R. Ande, J.R. Jangamreddy, M. Mehrpour, et al., Autophagy and apoptosis dysfunction in neurodegenerative disorders, Prog. Neurobiol. 112 (2014) 24–49.
[3] A. Kapasi, C. DeCarli, J.A. Schneider, Impact of multiple pathologies on the threshold for clinically overt dementia, Acta Neuropathol. 134 (2) (2017) 171–186.
[4] J.L. Robinson, E.B. Lee, S.X. Xie, L. Rennert, E. Suh, C. Bredenberg, et al., Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated, Brain. 141 (7) (2018) 2181–2193.
[5] G.G. Kovacs, Are comorbidities compatible with a molecular pathological classification of neurodegenerative diseases? Curr. Opin. Neurol. 32 (2) (2019) 279–291.
[6] R. Rusina, K. Sheardová, I. Rektorová, P. Ridzon, P. Kulišťák, R. Matej, Amyotrophic lateral sclerosis and Alzheimer's disease – clinical and neuropathological considerations in two cases, Eur. J. Neurol. 14 (7) (2007) 815–818.
[7] K. Menšíková, R. Matěj, L. Tučková, R. Rusina, J. Ehrmann, P. Kaňovský, Progressive supranuclear palsy phenotype mimicking synucleinopathies, J. Neurol. Sci. 329 (1–2) (2013) 34–37.
[8] R. Rusina, L. Pazdera, P. Kulišťák, O. Vyšata, R. Matěj, Pick and Alzheimer diseases: a rare comorbidity presenting as corticobasal syndrome, Cogn. Behav. Neurol. 26 (4) (2013) 189–194.
[9] T. Picková, R. Matěj, O. Bezdicek, J. Keller, J. van der Zee, C. Van Broeckhoven, et al., Genetic Alzheimer disease and sporadic dementia with Lewy bodies: a comorbidity presenting as primary progressive aphasia, Cogn. Behav. Neurol. 30 (1) (2017) 23–29.
[10] K. Storey, S. Johanidesová, R. Matěj, J. Keller, Z. Rohan, R. Rusina, FTLD-TDP and progressive supranuclear palsy in comorbidity-a report of two cases with different clinical presentations, Neurocase. 23 (1) (2017) 5–11.

[11] B.T. Hyman, C.H. Phelps, T.G. Beach, E.H. Bigio, N.J. Cairns, M.C. Carrillo, et al., National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease, Alzheimer's & Dementia 8 (1) (2012) 1–13.
[12] J.L. Whitwell, D.W. Dickson, M.E. Murray, S.D. Weigand, N. Tosakulwong, M.L. Senjem, et al., Neuroimaging correlates of pathologically defined subtypes of Alzheimer's disease: a case-control study, Lancet Neurol. 11 (10) (2012) 868–877.
[13] M.E. Murray, N.R. Graff-Radford, O.A. Ross, R.C. Petersen, R. Duara, D.W. Dickson, Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study, Lancet Neurol. 10 (9) (2011) 785–796.
[14] G.M. McKhann, D.S. Knopman, H. Chertkow, B.T. Hyman, C.R. Jack Jr., C.H. Kawas, et al., The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, Alzheimers Dement. 7 (3) (2011) 263–269.
[15] C.R. Jack Jr., D.A. Bennett, K. Blennow, M.C. Carrillo, B. Dunn, S.B. Haeberlein, et al., NIA-AA research framework: toward a biological definition of Alzheimer's disease, Alzheimers Dement. 14 (4) (2018) 535–562.
[16] G.M. Sancesario, S. Bernardini, Diagnosis of neurodegenerative dementia: where do we stand, now? Ann. Transl. Med. 6 (17) (2018) 340.
[17] G.M. Sancesario, S. Bernardini, How many biomarkers to discriminate neurodegenerative dementia? Crit. Rev. Clin. Lab. Sci. 52 (6) (2015) 314–326.
[18] J.L. Molinuevo, S. Ayton, R. Batrla, M. Bednar, T. Bittner, J. Cummings, et al., Current state of Alzheimer's fluid biomarkers, Acta Neuropathol. 136 (6) (2018) 821–853.
[19] A. Kraus, E. Saijo, M.A. Metrick 2nd, K. Newell, C.J. Sigurdson, G. Zanusso, et al., Seeding selectivity and ultrasensitive detection of tau aggregate conformers of Alzheimer disease, Acta Neuropathol. 137 (4) (2019) 585–598.
[20] R. Atarashi, K. Satoh, K. Sano, T. Fuse, N. Yamaguchi, D. Ishibashi, et al., Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion, Nat. Med. 17 (2) (2011) 175–178.
[21] K. Mensikova, P. Kanovsky, M. Kaiserova, I. Nestrasil, M. Bares, Promenliva tvar parkinsonske neurodegenerace, [The Changing Face of Parkinsonian Neurodegeneration] Ceska a Slovenska Neurologie a Neurochirurgie, 76/109(1) (2013), pp. 26–34.
[22] G.M. Halliday, J.L. Holton, T. Revesz, D.W. Dickson, Neuropathology underlying clinical variability in patients with synucleinopathies, Acta Neuropathol. 122 (2) (2011) 187–204.
[23] B.R. Groveman, C.D. Orrù, A.G. Hughson, L.D. Raymond, G. Zanusso, B. Ghetti, et al., Rapid and ultra-sensitive quantitation of disease-associated α-synuclein seeds in brain and cerebrospinal fluid by αSyn RT-QuIC, Acta Neuropathol. Commun. 6 (2018) 7.
[24] K. Sano, R. Atarashi, K. Satoh, D. Ishibashi, T. Nakagaki, Y. Iwasaki, et al., Prion-like seeding of Misfolded α-Synuclein in the brains of dementia with Lewy body patients in RT-QUIC, Mol. Neurobiol. 55 (5) (2018) 3916–3930.
[25] L. Parnetti, L. Gaetani, P. Eusebi, S. Paciotti, O. Hansson, O. El-Agnaf, et al., CSF and blood biomarkers for Parkinson's disease, Lancet Neurol. 18 (6) (2019) 573–586.
[26] L.V. Kalia, Diagnostic biomarkers for Parkinson's disease: focus on α-synuclein in cerebrospinal fluid, Parkinsonism Relat. Disord. 59 (2019) 21–25.
[27] L. Parnetti, S. Paciotti, L. Farotti, G. Bellomo, F.N. Sepe, P. Eusebi, Parkinson's and Lewy body dementia CSF biomarkers, Clin. Chim. Acta 495 (2019) 318–325.
[28] A.S. Chen-Plotkin, Unbiased approaches to biomarker discovery in neurodegenerative diseases, Neuron. 84 (3) (2014) 594–607.
[29] F. Clavaguera, J. Hench, M. Goedert, M. Tolnay, Prion-like transmission and spreading of tau pathology, Neuropathol. Appl. Neurobiol. 41 (1) (2015) 47–58.
[30] I. Ferrer, G. Santpere, F.W. van Leeuwen, Argyrophilic grain disease, Brain. 131 (6) (2008) 1416–1432.
[31] J.F. Crary, J.Q. Trojanowski, J.A. Schneider, J.F. Abisambra, E.L. Abner, I. Alafuzoff, et al., Primary age-related tauopathy (PART): a common pathology associated with human aging, Acta Neuropathol. 128 (6) (2014) 755–766.
[32] Z. Ahmed, E.H. Bigio, H. Budka, D.W. Dickson, I. Ferrer, B. Ghetti, et al., Globular glial tauopathies (GGT): consensus recommendations, Acta Neuropathol. 126 (4) (2013) 537–544.
[33] H. Zetterberg, J.C. van Swieten, A.L. Boxer, J.D. Rohrer, Fluid biomarkers for frontotemporal dementias, Neuropathol. Appl. Neurobiol. b45 (1) (2019) 81–87.
[34] E. Saijo, B. Ghetti, G. Zanusso, A. Oblak, J.L. Furman, M.I. Diamond, et al., Ultrasensitive and selective detection of 3-repeat tau seeding activity in pick disease brain and cerebrospinal fluid, Acta Neuropathol. 133 (5) (2017) 751–765.
[35] E.H. Bigio, TDP-43 variants of frontotemporal lobar degeneration, J. Mol. Neurosci. 45 (3) (2011) 390–401.
[36] I.R. Mackenzie, M. Neumann, A. Baborie, D.M. Sampathu, D. Du Plessis, E. Jaros, et al., A harmonized classification system for FTLD-TDP pathology, Acta Neuropathol. 122 (1) (2011) 111–113.
[37] J.L. González De Aguilar, Lipid biomarkers for amyotrophic lateral sclerosis, Front. Neurol. 10 (2019) 284.
[38] K. Otake, H. Kamiguchi, Y. Hirozane, Identification of biomarkers for amyotrophic lateral sclerosis by comprehensive analysis of exosomal mRNAs in human cerebrospinal fluid, BMC Med. Genet. 12 (1) (2019) 7.
[39] P. Steinacker, C. Hendrich, A.D. Sperfeld, S. Jesse, S. Lehnert, A. Pabst, et al., Concentrations of beta-amyloid precursor protein processing products in cerebrospinal fluid of patients with amyotrophic lateral sclerosis and frontotemporal lobar degeneration, J. Neural Transm. 116 (9) (2009) 1169–1178.
[40] E. Feneberg, E. Gray, O. Ansorge, K. Talbot, M.R. Turner, Towards a TDP-43-based biomarker for ALS and FTLD, Mol. Neurobiol. 55 (10) (2018) 7789–77801.
[41] R.W. Paterson, C.F. Slattery, T. Poole, J.M. Nicholas, N.K. Magdalinou, J. Toombs, et al., Cerebrospinal fluid in the differential diagnosis of Alzheimer's disease: clinical utility of an extended panel of biomarkers in a specialist cognitive clinic, Alzheimers Res. Ther. 10 (2018) 32.
[42] L. Gaetani, K. Blennow, P. Calabresi, M. Di Filippo, L. Parnetti, H. Zetterberg, Neurofilament light chain as a biomarker in neurological disorders, journal of neurology, Neurosurg. Psychiatry. 90 (8) (2019) 870–881.
[43] T.T. Robey, P.K. Panegyres, Cerebrospinal fluid biomarkers in neurodegenerative disorders, Future Neurol. 14 (1) (2019) FNL6.
[44] F. Fazekas, J.B. Chawluk, A. Alavi, MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging, AJR 149 (2) (1987) 351–356.
[45] Y. Gu, J. Gutierrez, I.B. Meier, V.A. Guzman, J.J. Manly, N. Schupf, et al., Circulating inflammatory biomarkers are related to cerebrovascular disease in older adults, Neurol. Neuroimmunol. Neuroinflammation. 6 (1) (2019) e521.
[46] B.N. Dugger, C.H. Adler, H.A. Shill, J. Caviness, S. Jacobson, E. Driver-Dunckley, et al., Concomitant pathologies among a spectrum of parkinsonian disorders, Parkinsonism Relat. Disord. 20 (5) (2014) 525–529.
[47] G.G. Kovacs, I. Milenkovic, A. Wöhrer, R. Höftberger, E. Gelpi, C. Haberler, et al., Non-Alzheimer neurodegenerative pathologies and their combinations are more frequent than commonly believed in the elderly brain: a community-based autopsy series, Acta Neuropathol. 126 (3) (2013) 365–384.
[48] J. Rahimi, G.G. Kovacs, Prevalence of mixed pathologies in the aging brain, Alzheimers Res. Ther. 6 (9) (2014) 82.
[49] S.E. Marsh, M. Blurton-Jones, Examining the mechanisms that link beta-amyloid and alpha-synuclein pathologies, Alzheimers Res. Ther. 4 (2) (2012) 11.
[50] R. Savica, T.G. Beach, J.G. Hentz, M.N. Sabbagh, G.E. Serrano, L.I. Sue, et al., Lewy body pathology in Alzheimer's disease: a clinicopathological prospective study, Acta Neurol. Scand. 139 (1) (2019) 76–81.
[51] W.R. Galpern, A.E. Lang, Interface between tauopathies and synucleinopathies: a tale of two proteins, Ann. Neurol. 59 (3) (2006) 449–458.
[52] M. Colom-Cadena, E. Gelpi, S. Charif, O. Belbin, R. Blesa, M.J. Martí, et al., Confluence of α-synuclein, tau, and β-amyloid pathologies in dementia with Lewy bodies, J. Neuropathol. Exp. Neurol. 72 (12) (2013) 1203–1212.
[53] H. Uchikado, W.L. Lin, M.W. DeLucia, D.W. Dickson, Alzheimer disease with amygdala Lewy bodies: a distinct form of α-synucleinopathy, J. Neuropathol. Exp. Neurol. 65 (7) (2016) 685–697.
[54] D.R. Thal, C. Schultz, G. Botez, K. Del Tredici, R.E. Mrak, W.S.T. Griffin, et al., The impact of argyrophilic grain disease on the development of dementia and its relationship to concurrent Alzheimer's disease-related pathology, Neuropathol. Appl. Neurobiol. 31 (3) (2005) 270–279.
[55] Y. Compta, O. Ramos-Campoy, O. Grau-Rivera, M. Colom-Cadena, J. Clarimón, M.J. Martí, et al., Conjoint FTLD-FUS of the neuronal intermediate filament inclusion disease type, progressive supranuclear palsy and Alzheimer's pathology presenting as parkinsonism with early falls and late hallucinations, psychosis and dementia, Neuropathol. Appl. Neurobiol. 43 (4) (2017) 352–357.
[56] K.E. McAleese, L. Walker, D. Erskine, A.J. Thomas, I.G. McKeith, J. Attems, TDP-43 pathology in Alzheimer's disease, dementia with Lewy bodies and ageing, Brain Pathol. 27 (4) (2017) 472–479.
[57] X.L. Chang, M.S. Tan, L. Tan, J.T. Yu, The role of TDP-43 in Alzheimer's disease, Mol. Neurobiol. 53 (5) (2016) 3349–3359.
[58] T. Arai, I.R. Mackenzie, M. Hasegawa, T. Nonoka, K. Niizato, K. Tsuchiya, et al., Phosphorylated TDP-43 in Alzheimer's disease and dementia with Lewy bodies, Acta Neuropathol. 117 (2) (2009) 125–136.
[59] K.A. Josephs, M.E. Murray, J.L. Whitwell, J.E. Parisi, L. Petrucelli, C.R. Jack, et al., Staging TDP-43 pathology in Alzheimer's disease, Acta Neuropathol. 127 (3) (2014) 441–450.
[60] S. Higashi, E. Iseki, R. Yamamoto, M. Minegishi, H. Hino, K. Fujisawa, et al., Concurrence of TDP-43, tau and α-synuclein pathology in brains of Alzheimer's disease and dementia with Lewy bodies, Brain Res. 1184 (2007) 284–294.
[61] B.D. James, R.S. Wilson, P.A. Boyle, J.Q. Trojanowski, D.A. Bennett, J.A. Schneider, TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia, Brain. 139 (11) (2016) 2983–2993.
[62] K.A. Josephs, J.L. Whitwell, S.D. Weigand, M.E. Murray, N. Tosakulwong, A.M. Liesinger, et al., TDP-43 is a key player in the clinical features associated with Alzheimer's disease, Acta Neuropathol. 127 (6) (2014) 811–824.
[63] J. Attems, K.A. Jellinger, The overlap between vascular disease and Alzheimer's disease-lessons from pathology, BMC Med. 12 (1) (2014) 206.
[64] J.B. Toledo, S.E. Arnold, K. Raible, J. Brettschneider, S.X. Xie, M. Grossman, et al., Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's coordinating Centre, Brain. 136 (9) (2013) 2697–2706.
[65] S. Saito, M. Ihara, Interaction between cerebrovascular disease and Alzheimer pathology, Curr. Opin. Psychiatry. 29 (2) (2016) 168–173.
[66] Y. Hase, R. Ding, G. Harrison, E. Hawthorne, A. King, S. Gettings, et al., White matter capillaries in vascular and neurodegenerative dementias, Acta Neuropathol. Commun. 7 (2019) 16.
[67] G. Gold, P. Giannakopoulos, F.R. Herrmann, C. Bouras, E. Kövari, Identification of Alzheimer and vascular lesion thresholds for mixed dementia, Brain. 130 (11) (2007) 2830–2836.
[68] Z. Rohan, R. Matej, R. Rusina, Prekryvani neurodegenerativních demenci [Overlap of neurodegenerative dementias], Ceska a Slovenska Neurologie a Neurochirurgie, 78/111(6) (2015), pp. 641–648.