Recent developments and future perspectives of neuropathology

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Abstract

This brief statement describes some recent achievements of neuropathological research, with the focus on Alzheimer's and other age-related diseases, neurodegenerative disorders (tauopathies, synucleinopathies), multimorbidity of the aged brain, multiple sclerosis (MS), and other neuroinflammatory disorders, including central nervous system involvement by coronavirus disease 2019 (COVID-19), as well as new developments in neurovascular diseases, neurooncology, and myopathies. Although neuropathology, using modern technologies, such as cryo-electron microscopy, proteomic and experimental methods, has helped to increase diagnostic accuracy and provided insight into the pathogenesis of many neurological disorders, future studies in co-operation with clinical and other neurosciences should overcome the challenges of disease-influencing therapeutic approaches.

Keywords

Neuropathology, a special field of both pathology and neurosciences, is aimed to study the diseases of the nervous and muscular systems in order to detect pathological developments and disorders trying to validate the clinical diagnosis and detect the etiology and pathogenesis of these disorders as a basis for specific and successful treatment strategies. Neuropathology began to develop in the 19th century in Vienna, when Carl von Rokitansky (1804–1878), a renowned pathologist and founder of modern medicine based on morphological findings, Heinrich Obersteiner (1847–1922), founder of the first brain research institute in the world, and Ludwig Edinger (1855–1918), an influential anatomist and neurologist, co-founder of the Frankfurt University, developed modern methods of morphology and pathology of the nervous system. At the same time, fundamental principles of neuroscience, such as the lesions of multiple sclerosis (MS) described by Jean-Martin Charcot (1825–1893) or degeneration and regeneration, were enunciated by Ramón y Cajal (1852–1934) and the histologist Camillo Golgi (1843–1926) that culminated in studies of the cellular architecture of the central nervous system (CNS). Since that time modern diagnostic, experimental and scientific neuropathology have developed rapidly together with other medicobiological sciences, using

modern techniques, like immunohistochemistry, molecular, proteomic, genetic, imaging, ultrastructural, and other methods, gradually abandoning superstitions, arbitrary hypothesis, and speculations—to replace them with scientific approach and experimental investigations. By turning the focus of its rapidly reinforced light toward the future, neuropathology aims to penetrate depths hitherto unexplored. Thus, an attempt will be made to briefly summarize some recent breaking developments in the field of neuropathology.

In addition to recent brain-computational models that mimic brain information processing and brain charts identifying previously unexpected neuroanatomical milestones [1], or substrates of cell-specific markers in schizophrenia and other psychiatric disorders [2], a number of breaking new results about various brain diseases have been achieved. Modern single cell techniques are providing valuable information on cell states and, together with genetic methods, are helping to depict the degree of heterogeneity that was so far overlooked by conventional neuropathology [3]. Whether the new in-depth knowledge will translate into valuable concepts and new therapeutic approaches remains to be established.

Alzheimer's disease (AD), the most common neurodegenerative dementia, is morphologically featured by deposits of pathological proteins (β-amyloid and tau) in the brain tissue inducing neuronal loss and brain atrophy. Increased iron content, activated microglia, and pro-inflammatory lesions contribute to oxidative damage of the AD brain. New highly specific biomarkers in blood and cerebrospinal fluid, including specific proteins, markers of synaptic dysfunction and inflammation have enabled an early diagnosis of this "plague of our century" [4]. These new methods will change our understanding of the brain and many hitherto incompletely diagnosed neurological disorders and may result in new treatment possibilities. However, AD, usually defined as a clinicopathological entity, is a heterogenous, multifactorial proteinopathy, currently referred to as the Alzheimer's continuum, that, in addition to "typical" AD, includes various subtypes with characteristic regional patterns of tau pathology, biomarker levels, and patterns of key network destructions responsible for distinct clinical features [5]. Recent clinical and neuropathological studies have identified traumatic brain injury as a risk factor for all-cause dementias, Parkinson's disease (PD) and other neurodegenerative disorders, axonal injury, and disrupted transport influencing molecular mechanisms inducing the formation of pathological proteins leading to neuronal death [6].

Intracellular accumulation of abnormal proteins with conformational changes is the defining neuropathological feature of neurodegenerative diseases. The pathogenic proteins that accumulate in the brain adopt an amyloid-like fibrous structure and exhibit various ultrastructural and biochemical features. Analyses of postmortem brains have revealed structural polymorphisms (strains) and prion-like properties of essential pathogenic proteins [tau, α-synuclein (αSyn), amyloid, and TAR DNA-binding protein of 43 kDa (TDP-43)] [7]. Notably, recent cryo-electron microscopy (cryo-EM) studies have determined the ultrastructure of amyloid-β 42 and tau filaments from patients' brains, providing direct evidence of strain formation [8, 9]. The distribution of these two deleterious proteins in the brain detected by modern positron emission tomography (PET) methods *in vivo* can predict the short-term cognitive decline in unimpaired individuals [10], which, together with specific liquid markers, appears of high clinical relevance. Cryo-EM studies also described the ultrastructure of prion proteins [11]. Although recent studies in animal models demonstrate that certain misfolded proteins associated with neurodegenerative diseases can propagate across neuronal systems and therefore have some of the properties of classical prion diseases like Creutzfeldt-Jakob disease, there is currently no evidence for a risk of transmissibility or a direct infectious etiology for the human neurodegenerative disorders [12]. However, despite advances in knowledge of the essential cellular and molecular mechanisms in AD and other neurodegenerative disorders, we are still unable to block or slow down the basic pathological processes.

Many neurodegenerative diseases are caused by tau protein (tauopathies, including cognitive and movement disorders) or deposition of misfolded αSyn either in neurons (Lewy bodies) or (oligodendro)glia (glial cytoplasmic inclusions, multiple system atrophy). They are associated with the "prion-like" propagation and association of toxic proteins that show complex interaction mechanisms [13]. Tauopathies have been classified by modern methods [14], and a robust and reliable system for assessing Lewy body pathology was proposed [15]. A specific form associated with human aging is primary age-related tauopathy (PART) which is

characterized by tau neurofibrillary tangles in the medial temporal lobe in the absence of amyloid-β plaques. It involves people over age 80 and is clinically similar to AD but shows essential differences [16]. Both disorders show increased cognitive decline due to the limbic-predominant age-related TDP-43 encephalopathy (LATE) that frequently co-exists with AD neuropathology [17, 18]. The complexity of mixed pathologies in aging and neurodegenerative diseases should be emphasized since up to 100% of AD cases show between one and six co-pathologies, including LATE, cerebral amyloid angiopathy, Lewy body disease (LBD), hippocampal sclerosis, etc. This is due to the interaction of pathogenic proteins and vascular processes, and can be responsible for difficulties in clinical diagnosis and treatment [19]. Recent studies have demonstrated the importance of cerebral amyloid angiopathy for interacting with neuritic plaques to promote tau burden and cognitive decline in aged individuals [20] and together with other co-morbidities in LBD, thus distinguishing PD-dementia from the recently described Lewy body dementia that often shows additional AD co-pathology [21].

In PD, the most frequent neurodegenerative movement disorder caused by degeneration of the dopaminergic (striatonigral) and other nervous systems due to accumulation of misfolded αSyn, with the formation of intracellular inclusions (Lewy bodies), recent experimental studies demonstrated synaptic energy failure and autophagic decline due to deregulated proteins as the earliest events preceding structural changes and cell death [22]. *In vivo* diagnosis of PD can be increased by both liquid (plasma and cerebrospinal fluid) markers and peripheral nerve or intestinal biopsies [23]. The essential pathogenic factors of PD are monoaminergic imbalance and disruption of multiple brain networks related to degeneration of the relevant systems due to aggregation of toxic misfolded αSyn, mitochondrial dysfunction, impairment of protein clearance, neuroinflammatory mechanisms, and oxidative stress [24]. In addition, there is increasing evidence for the highly complex relationship between the gut and the brain in PD [25, 26].

For the less frequent but more aggressive multiple system atrophy, α-synucleinopathy with glioneuronal degeneration, new consensus criteria may improve diagnostic accuracy [27], which is difficult because of its heterogeneity [28]. This is due to the wide heterogeneity of αSyn seeding [29] that is spreading in a "prion-like" matter [30]. Recent studies have identified multicellular mechanisms with defunct trophic and anti-inflammatory intercellular communications and impaired autophagy causing early neuronal decline and resulting in multisystem degeneration [31]. Recently, neurodevelopmental alterations due to abnormalities in neuronal migration have been observed in Huntington's disease, a hyperkinetic movement disorder caused by polyglutamine (polyQ) repeat expansion.

Another important goal of neuropathology is to decipher molecular pathological mechanisms in MS. In addition to its contribution to the diagnosis of the disease, it includes analysis of the three-dimensional distribution of brain damage, the temporal sequence of lesion involution, and the basic molecular mechanisms offering the potential to decipher disease, as well as to discriminate MS from other inflammatory autoimmune or demyelinating processes, such as the neuromyelitis optica spectrum disorders (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Neuropathology of MOGAD more closely resembles acute or relapsing disseminated encephalomyelitis or transverse myelitis than classical MS [32]. Mechanisms of demyelination may change at different stages of lesion development, suggesting different disease entities hiding behind a common clinical and pathological phenotype, or the lesions may change at different stages of the disease course. The only way to resolve these questions is to analyze initial demyelinating lesions at early disease stages, although suitable material, brain biopsies taken in early disease stages or autopsy material from acute MS, is rare and only available by international co-operation. In these patients, active demyelination developed on the background of an inflammatory reaction, dominated by T-lymphocytes and B-cells, having an essential role in both the inflammatory and neurodegenerative components of the disease process [33].

Recently developed techniques, which examine a large battery of different molecules within single cells, have proven useful in experimental and human neuroinflammatory conditions. They have elucidated defects in activated microglia, which act in a stage- and context-dependent manner, with emphasis on the importance of synaptic vulnerability, providing a connection between neuroinflammation and neurodegeneration [33]. Molecular studies in pathologically defined micro-dissected MS lesions identified a cascade of oxidative injury,

mitochondrial damage, and energy failure as a major pathway of tissue injury in MS [34], similar pathogenic molecular pathways also being essential for the development of many neurodegenerative disorders. Other recent studies have identified early neurodegenerative pathways in progressive MS, featured by multicellular changes of trophic and anti-inflammatory changes in local microenvironments leading to neuronal death [31]. All hallmarks of neuronal and glial pathology present in acute MS lesions may be explained by a mechanism of virtual hypoxia, which is induced by microglia activation, oxidative injury, and/or mitochondrial damage.

After the involvement of the nervous system by infection with the human immunodeficiency virus (HIV), where neuropathology not only gave essential insight into the pathogenesis of CNS lesions, the mechanisms of neuronal damage underlying neurological complications, and HIV-related cognitive disorders (HIV dementia), many studies have shown the spectrum of neuropathology in patients who died from complications of a coronavirus disease 2019 (COVID-19) illness during the greatest public health crisis in the 21st century [35]. In addition to cerebral hemorrhages, brain infarcts, acute hypoxic-ischemic changes, microthrombi, acute necrotizing encephalopathy, and acute disseminated encephalomyelitis (ADEM)-like pathology, axonal injury, demyelination, microglial activation, and lymphatic inflammation have been described. Although these findings do not seem to be specific to COVID-19 infection, they are most likely due to systemic inflammation and coagulopathy caused by COVID-19, but further large-scale molecular investigations are warranted to clarify the neuropathological correlates of the frequent neuro-psychiatric complications of this pandemic [36–38]. Post-COVID-19 long-term conditions are due to virus-induced long-term ischemic and neuroinflammatory changes (microglial activity) causing chronic-progressive neurodegenerative processes [39].

Last but not least, neuropathologists and neurooncologists have provided the 5th edition of the World Health Organization (WHO) classification of tumors of the CNS, establishing new approaches to both tumor nomenclature and grading, and emphasizing the importance of integrated diagnosis, based not only on histology and immunohistochemistry but also on novel technologies such as DNA methylome profiling and new genetic approaches [40]. Modern neuropathology has also focused on neurovascular diseases, such as brain injuries from intracerebral hemorrhage and white matter repair after ischemic injury, depending on the cross-talk between innate and adaptive immunity, in which antibody secreting blood-derived B cells may be active. The contribution of immune cells to amyloid deposition as well as clearing of amyloid-β in the cerebral vessels in AD patients treated by immunotherapy is also a matter of current discussion. According to recent studies relating antemortem neuroimaging parameters of cerebrovascular disease (CVD) with postmortem neuropathological scales, diffuse white matter microstructural lesions measured by diffusion magnetic resonance imaging (MRI) may be a meaningful surrogate of neuropathological CVD scales, while AD neuropathological changes did not associate with neuropathological CVD scales. This appears important given the significance of CVD in aging and dementia [41], since it may be difficult to distinguish the underlying substrate (CVD *vs.* neurodegenerative disease caused by tau or TDP-43 pathology) for cognitive impairment in older adults [42]. Advances have also been achieved in neuromuscular diseases, such as autosomal recessive neuromuscular disease caused by von Willebrand factor A containing 1 (VWA1) protein mutation myopathy, myopathies with autophagic defects, transfer RNA (tRNA) synthetase-associated Charcot-Marie-Tooth disease, systemic sclerosis-associated myopathy, humoral immune endoneurial microvasculopathy, and other gene-related and immune-mediated myopathies that will be of significant interest for clinicians [43].

These and other results of neuropathology in this age of rapidly advancing research technologies have provided some essential scientific information about the pathogenesis and course of many neurological and psychiatric diseases, thus increasing diagnostic accuracy and signaling possible disease-influencing therapeutic options in highly prevalent diseases, such as stroke, MS, infectious diseases, and other diseases, whereas for the majority of neurodegenerative diseases, despite diagnostic advances due to modern biomarkers, no real disease-blocking or delaying treatment options are available. Despite these challenges, the cooperation of neuropathologists with clinicians, neuroimaging specialists, and other neuroscientists may overcome them and will provide further developments in preventive, diagnostic, and therapeutic options for at least some of the hitherto untreatable and fatal nervous diseases.

Abbreviations

AD: Alzheimer's disease

CNS: central nervous system

COVID-19: coronavirus disease 2019

CVD: cerebrovascular disease

HIV: human immunodeficiency virus

MS: multiple sclerosis

PD: Parkinson's disease

TDP-43: TAR DNA-binding protein of 43 kDa

αSyn: α-synuclein

Declarations

Author contributions

The author contributed solely to this work.

Conflicts of interest

The author declares that he has no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

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