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EDITORIAL

The multi-morbid old brain

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While it is well known that the "old" brain is characterised by the simultaneous presence of multiple neurodegenerative pathologies, rather than by the hallmark pathologies of one single age-associated neurodegenerative disease, comprehensive articles putting this multi-morbidity in context with clinical, neuropathological, genetic, and experimental data are lacking. Therefore, this issue of *Acta Neuropathologica* features two articles reviewing the various aspects and implications of age-associated cerebral multi-morbidity.

Spires-Jones and colleagues inform the reader about the current evidence for interactions between different pathological proteins and provide data from both human brain tissue and experimental models [8]. The interaction between amyloid-β (Aβ) and tau is clearly the best documented one; while the "amyloid-hypothesis" in its strict sense, i.e., Aβ "causes" tau pathology, has been disproven, not least by the fact that tau pathology can develop in the complete absence of any Aβ (i.e., primary age-associated tauopathy (PART) [3]), we also know from human studies that severe neocortical tau pathology as reflected by Braak stages V/VI has never been described in the absence of Aβ, which clearly indicates that Aβ has an aggravating effect on tau pathology (in particular pyroglutamylated Aβ [7]). However, evidence for similar interactions between α-synuclein (α-syn) and both Aβ and tau is emerging and TDP-43 likewise seems to aggravate AD pathology [2, 5].

It has often been suggested that the presence of additional pathologies, such as cerebrovascular pathology in Alzheimer's disease (AD), lowers the threshold for the amount of AD pathology necessary to cause clinical dementia [1]. Kapasi and colleagues now try to clarify this assumption and review data from large community-based cohorts to evaluate the influence of multiple pathologies on the clinical phenotype [6].

Despite recent advances in the development of biomarkers for neuropathological lesions, such as Aβ and tau by both imaging methods and cerebrospinal fluid assessment, cerebral multi-morbidity is not accurately reflected in clinical diagnoses. This has a detrimental impact on clinical cohort studies as cohorts are assumed to be homogenous, while they are in fact highly heterogenous; e.g., a clinical AD cohort will have patients with (i) Aβ and tau pathology only; (ii) Aβ, tau, and α-syn pathology (over 40%); and (iii) Aβ, tau, and TDP-43 pathology (over 50%). In addition, there will be a range of cerebrovascular pathologies present and likely combinations of (ii) and (iii). Therefore, the interpretation of clinical data will be highly biased and there is an urgent need for tools that allow for a more accurate cohort stratification based on the underlying pathologies. To date, this can only be achieved by neuropathological post-mortem examination as neuropathological data can be used to retrospectively stratify clinical cohorts and thereby facilitate the development of more accurate clinical biomarkers. The latter will in turn lead to an improvement in patients' diagnostics and therapy.

Age-associated cerebral multi-morbidity challenges our current concept of classifying age-associated neurodegenerative diseases, which categorises cases according to the main underlying pathology, e.g., AD equals Aβ and tau pathology and dementia with Lewy bodies (DLB) equals α-syn pathology. Such a concept is actually based on the rather whimsical assumption that these diseases are mutually exclusive. However, it should not come as a surprise

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that age-associated neurodegenerative diseases are not mutually exclusive as this would imply that the presence of one disease protects the individual against the other. Indeed, quite the opposite is likely to be the case as different protein aggregates seem to aggravate each other [8]. Hence, it was not surprising when Irwin and colleagues recently reported that 30% of clinical dementia with Lewy bodies (DLB) cases showed full blown AD pathology in addition to DLB at post-mortem examination, as AD is by far the most common age-associated neurodegenerative disease [4].

Instead of categorising cases into one main disease with or without additional pathology, we should aim to establish a concept that is rather based on the quality, quantity, and topographical distribution of protein aggregates and takes cerebrovascular disease into account. Such an approach would not only be helpful in large clinico-pathological correlative studies as it may unravel subtle clinico-pathological phenotypes, but it would also provide a much clearer and less convoluted picture of neurodegeneration in general. Naturally, such a classification can currently only be pursued in neuropathological diagnostics as intra-vitam diagnosis relies on clinical symptoms, imaging, and biomarkers, of which none can currently predict all underlying pathologies. However, even if we still have to clinically categorise into AD, DLB, and vascular dementia (etc.), we should always be aware that the old brain is a multi-morbid organ which can simultaneously show a variety of neuropathological lesions of which Aβ and tau are just the most frequent, but by no means the only ones.

References

1. Attems J, Jellinger KA (2014) The overlap between vascular disease and Alzheimer's disease-lessons from pathology. BMC Med 12:206
2. Clinton LK, Blurton-Jones M, Myczek K, Trojanowski JQ, LaFerla FM (2010) Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. J Neurosci 30:7281–7289
3. Crary JF, Trojanowski JQ, Schneider JA, Abisambra JF, Abner EL, Alafuzoff I, Arnold SE, Attems J, Beach TG, Bigio EH, Cairns NJ, Dickson DW, Gearing M, Grinberg LT, Hof PR, Hyman BT, Jellinger K, Jicha GA, Kovacs GG, Knopman DS, Kofler J, Kukull WA, Mackenzie IR, Masliah E, McKee A, Montine TJ, Murray ME, Neltner JH, Santa-Maria I, Seeley WW, Serrano-Pozo A, Shelanski ML, Stein T, Takao M, Thal DR, Toledo JB, Troncoso JC, Vonsattel JP, White CL 3rd, Wisniewski T, Woltjer RL, Yamada M, Nelson PT (2014) Primary age-related tauopathy (PART): a common pathology associated with human aging. Acta Neuropathol 128:755–766
4. Irwin DJ, Grossman M, Weintraub D, Hurtig HI, Duda JE, Xie SX, Lee EB, Van Deerlin VM, Lopez OL, Kofler JK, Nelson PT, Jicha GA, Woltjer R, Quinn JF, Kaye J, Leverenz JB, Tsuang D, Longfellow K, Yearout D, Kukull W, Keene CD, Montine TJ, Zabetian CP, Trojanowski JQ (2017) Neuropathological and genetic correlates of survival and dementia onset in synucleinopathies: a retrospective analysis. Lancet Neurol 16:55–65
5. Josephs KA, Murray ME, Whitwell JL, Parisi JE, Petrucelli L, Jack CR, Petersen RC, Dickson DW (2014) Staging TDP-43 pathology in Alzheimer's disease. Acta Neuropathol 127:441–450
6. Kapasi A, DeCarli C, Schneider JA (2017) Impact of multiple pathologies on the threshold for clinically overt dementia. Acta Neuropathol. doi:10.1007/s00401-017-1717-7 **(in press)**
7. Mandler M, Walker L, Santic R, Hanson P, Upadhaya AR, Colloby SJ, Morris CM, Thal DR, Thomas AJ, Schneeberger A, Attems J (2014) Pyroglutamylated amyloid-beta is associated with hyperphosphorylated tau and severity of Alzheimer's disease. Acta Neuropathol 128:67–79
8. Spires-Jones TL, Attems J, Thal DR (2017) Interactions of pathological proteins in neurodegenerative diseases. Acta Neuropathol. doi:10.1007/s00401-017-1709-7 **(in press)**