The "Glymphatic-Lymphatic System Pathology" and a New Categorization of Neurodegenerative Disorders

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INTRODUCTION

Neurodegeneration is the ultimate manifestation of various neurodegenerative, neurovascular, and neuroinflammatory diseases, brain traumatisms, and aging. However, viewing neurodegeneration as the pathological/clinical epiphenomenon of numerous specific pathogenetic mechanisms has not provided a unitary neurodegenerative model nor a cure.

It is emerging that neurodegeneration is related to failure of the glymphatic-lymphatic system(G-Ls) (Nedergaard and Goldman, 2020). This system represents a functionally integrated unit regulating solute trafficking and immune-surveillance in the CNS (Louveau et al., 2018; Nedergaard and Goldman, 2020). The G-Ls sub-serves CSF's flow from the subarachnoid spaces into the perivascular spaces and subsequently into the interstitium, and the aquaporin-4 water channels drive it. The cerebrospinal-interstitial fluid then passes to the venous perivascular and perineural spaces, lastly draining toxic molecules and immune cells from the brain into meninges and deep lymph nodes.

If we think of G-Ls dysfunction as the common final pathway to neurodegeneration (Nedergaard and Goldman, 2020), we can no longer consider the heterogeneous clinical cases where neurodegeneration manifests distinctively as diseases *per se,* but pathologies of G-Ls where *noxae* and symptoms are centered on a unique physiopathology. We propose a systematic vision of the events leading to the "G-Ls pathology" and, according to the relevant G-Ls dysfunctions, introduce a new categorization of diseases manifesting with neurodegeneration.

OPINION

Primary or secondary *noxae* may affect the G-Ls. Primary *noxae* are the genetic aquaporin-4 channelopathies (Rainey-Smith et al., 2018) or auto-antibodies that directly damage aquaporin-4 (Papadopoulos and Verkman, 2013). Secondary *noxae* are the derangements of the intra-extra cranial hydrodynamic at various levels leading to CSF circulation alterations (Wilson, 2016; Tuovinen et al., 2020; Rajna et al., 2021). CSF flow waves, hemodynamic, and neuronal electrical activity oscillations connect in sleep (Fultz et al., 2019). CSF flow failure follows a reduction of arterial pulsatility (Mestre et al., 2018; Daversin-Catty et al., 2020) and an increase in intracranial venous pressure due to the restriction of intracranial veins or increased extracranial venous pressure transmitted to the brain (Wilson, 2016). CSF flow suppress during breath-holding (Dreha-Kulaczewski et al., 2015, 2017). Moreover, debris in the CSF spaces or their obstruction for congenital, inflammatory, infectious, haemorrhagic, neoplastic, and traumatic processes impairs

CSF circulation, see Table 2 in Williams et al. (2019).

Failure of the CSF dynamic interacts with G-Ls flow processes and triggers the "G-Ls pathology." If CSF does not flow efficiently, it stagnates and accumulates in the perivascular spaces, expanding and becoming visible at imaging, as observed in neurodegeneration conditions (Wardlaw et al., 2020). Also, minor changes in CSF pressure, tissue pressure, or vascular function may alter the shape of perivascular spaces, leading to an altered flow dynamic in perivascular spaces and secondary flow impairment (Wardlaw et al., 2020). Arteriolar hypopulsatility also hampers perivascular CSF outflow (Mestre et al., 2018), as hypothesized when global CSF circulation stops (Gallina et al., 2019a). Experimental evidence supports this mechanism, since decreasing plasma osmolality, functionally simulating perivascular spaces congestion, leads to slowed G-Ls inflow (Plog et al., 2018). Furthermore, impairment of respiratory motion might reduce perivascular spaces flushing (Wardlaw et al., 2020) and failure of the perivascular CSF outflow leads to "perivascular spaces damage."

Perivenular involvement may also occur (Wilson, 2016). Therefore, cerebrospinal-interstitial fluid might also stagnate in the interstitium due to the rise of resistance on the venous side of perivascular spaces from decreased fluid efflux (Jiang et al., 2017). The interstitial spaces are then engulfed, interstitial bulk flow blocked, and interstitial and likely intracranial pressures increase (Lenck et al., 2018). Disturbances at the interstitium level may, in addition, damage the perivascular astrocyte endfeet, with injury of aquaporin-4 water channels, a further slowing down of interstitial fluid flow, and self-sustained interstitial congestion (Simon and Iliff, 2016). The events at the level of interstitial spaces configure the "interstitial damage." Neuroinflammation and reactive gliosis perpetuate the *noxa*e by reverberating the above-mentioned pathological steps in a vicious circle.

DISCUSSION

Considering how G-Ls functions (Louveau et al., 2018; Nedergaard and Goldman, 2020), its chronic failure may lead to dysregulation of brain waste molecule clearance, intra-extracellular water, ion homeostasis, and CNS immune response alterations. Moreover, since aquaporin-4 is involved in ependymal development and physiology (Kahle et al., 2016), G-Ls damage may disrupt the anatomy and function of CSF spaces.

We categorize disorders culminating in neurodegeneration with a new path: (1) proteinopathies; (2) interstitial/cellular water accumulation and neural hyperexcitation pathologies; (3) autoimmune brain pathologies; and (4) CSF resorption and flow disturbances.

In the "G-Ls pathology" model, therapies to prevent neurodegeneration should target aquaporin-4 polymorphisms

and alterations; therapies aimed at preventing aquaporin-4-specific IgG binding are under investigation (Papadopoulos and Verkman, 2013). Moreover, the prevention of hydrodynamic disturbances related to arterial circulation can follow treatment indications for cerebrovascular disease (Smith et al., 2017). The efficiency of systemic arterial flow may avoid CSF stagnation at the perivascular spaces, while implantable pump methods can regulate the CSF pulsatility by volume changes in low blood flow situations in the canine (Luciano et al., 2017). On the venous side, the search and correction of possible causes of intracranial venous hypertension (Wilson, 2016), including hepatic (Gallina et al., 2019b; Hadjihambi et al., 2019) and pulmonary dysfunctions (Gallina et al., 2020; Kananen et al., 2020; Russ et al., 2020; Tuovinen et al., 2020), may prevent or restore a reduction of the blood brain flow and facilitate CSF circulation. Moreover, CSF drainage may reverse venous hypertension, restoring interstitial fluid circulation (Wilson, 2016). Yet, CSF cleaning by shunting can minimize the alteration of the anatomy of subarachnoid spaces at the time of the injury (Abolfazli et al., 2016). At the same time, endothelial growth factor treatments promise to correct meningeal lymphatic vessel dysfunctions (Da Mesquita et al., 2018). Overall, interventions at the intra-extracranial hydrodynamic system level may prevent CSF circulation failure and "perivascular space damage." In parallel, intervening on the CSF circulation dynamic by shunting can target "interstitial damage," creating more room for the interstitial space (Graff-Radford, 2014). The quality of night's sleep guards neurotoxic proteins' clearance, and therapies targeting molecular mechanisms might promote G-Ls repair (Boland et al., 2018). Finally, since inflammation plays a role at all of the proposed cascade levels, anti-inflammatory treatment might be helpful in various steps of the process. It would be crucial to understand the time-course of the sequence of events in the "G-Ls pathology" and the threshold of possible reversibility in any of its steps to plot new therapeutic strategies. To this end, the possibility of using dynamic magnetic resonance imaging to track G-Ls, in small laboratory animals (Xue et al., 2020) and humans (Rajna et al., 2021), at various steps, might prove instrumental in achieving this goal.

CONCLUSION

In our opinion, neurodegeneration is no longer the result of several heterogeneous brain diseases but the ultimate clinical/pathological expression of the unique "G-Ls pathology," as the consequence of multiple factors classifiable in the frame of cerebral hydrodynamic disturbances.

AUTHOR CONTRIBUTIONS

PG and FL conceived the study, acquired the data, and wrote the paper. AS and CN revised the paper critically for important intellectual content. All authors gave final approval of the version to be published.

REFERENCES

Abolfazli, E., Fatouraee, N., and Seddighi, A. S. (2016). Effects of lumbar drainage on CSF dynamics in subarachnoid hemorrhage condition: a computational study. *Comput. Biol. Med.* 77, 49–58. doi: 10.1016/j.compbiomed.2016.08.003

Boland, B., Yu, W. H., Corti, O., Mollereau, B., Henriques, A., Bezard, E., et al. (2018). Promoting the clearance of neurotoxic proteins in neurodegenerative disorders of ageing. *Nat. Rev. Drug Discov.* 17, 660–688. doi: 10.1038/nrd.2018.109

Da Mesquita, S., Louveau, A., Vaccari, A., Smirnov, I., Cornelison, R. C., Kingsmore, K. M., et al. (2018). Functional aspects of meningeal lymphatics in ageing and Alzheimer's disease. *Nature* 560, 185–191. doi: 10.1038/s41586-018-0368-8

Daversin-Catty, C., Vinje, V., Mardal, K. A., and Rognes, M. E. (2020). The mechanisms behind perivascular fluid flow. *PLoS ONE* 15:e0244442. doi: 10.1371/journal.pone.0244442

Dreha-Kulaczewski, S., Joseph, A. A., Merboldt, K. D., Ludwig, H. C., Gärtner, J., and Frahm, J. (2015). Inspiration is the major regulator of human CSF flow. *J. Neurosci.* 35, 2485–2491. doi: 10.1523/JNEUROSCI.3246-14.2015

Dreha-Kulaczewski, S., Joseph, A. A., Merboldt, K. D., Ludwig, H. C., Gärtner, J., and Frahm, J. (2017). Identification of the upward movement of human CSF. *J. Neurosci.* 37, 2395–2402. doi: 10.1523/JNEUROSCI.2754-16.2017

Fultz, N. E., Bonmassar, G., Setsompop, K., Stickgold, R. A., Rosen, B. R., Polimeni, J. R., et al. (2019). Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. *Science* 366, 628–631. doi: 10.1126/science.aax5440

Gallina, P., Boschi, A., Angelini, L., and Lastrucci, G. (2020). The possible link between poor pulmonary function and dementia. *Chest* 158, 833–834. doi: 10.1016/j.chest.2020.02.082

Gallina, P., Gallo, O., Nicoletti, C., and Romanelli, R. G. (2019b). A hydrodynamic hypothesis for the pathogenesis of glymphatic system impairment in hepatic encephalopathy. *J. Hepatol.* 71, 228–229. doi: 10.1016/j.jhep.2019.02.010

Gallina, P., Scollato, A., Nicoletti, C., and Lolli, F. (2019a). Letter to the Editor. Cerebrospinal fluid circulation failure in the pathogenesis of post-craniectomy glymphatic flow impairment. *J. Neurosurg* 133:267–271. doi: 10.3171/2019.6.JNS191758

Graff-Radford, N. R. (2014). Alzheimer CSF biomarkers may be misleading in normal-pressure hydrocephalus. *Neurology* 83, 1573–1575. doi: 10.1212/WNL.0000000000000916

Hadjihambi, A., Harrison, I. F., Costas-Rodríguez, M., Vanhaecke, F., Arias, N., Gallego-Durán, R., et al. (2019). Impaired brain glymphatic flow in experimental hepatic encephalopathy. *J. Hepatol.* 70, 40–49. doi: 10.1016/j.jhep.2018.08.021

Jiang, Q., Zhang, L., Ding, G., Davoodi-Bojd, E., Li, Q., Li, L., et al. (2017). Impairment of the glymphatic system after diabetes. *J. Cereb. Blood Flow Metab.* 37, 1326–1337. doi: 10.1177/0271678X16654702

Kahle, K. T., Kulkarni, A. V., Limbrick, D. D., and Warf, B. C. (2016). Hydrocephalus in children. *Lancet* 387, 788–799. doi: 10.1016/S0140-6736(15)60694-8

Kananen, J., Helakari, H., Korhonen, V., Huotari, N., Järvelä, M., Raitamaa, L., et al. (2020). Respiratory-related brain pulsations are increased in epilepsy-a two-centre functional MRI study. *Brain Commun.* 2:fcaa076. doi: 10.1093/braincomms/fcaa076

Lenck, S., Radovanovic, I., Nicholson, P., Hodaie, M., Krings, T., and and, V., Mendes-Pereira (2018). Idiopathic intracranial hypertension: the veno glymphatic connections. *Neurology* 91, 515–522. doi: 10.1212/WNL.0000000000006166

Louveau, A., Herz, J., Alme, M. N., Salvador, A. F., Dong, M. Q., Viar, K. E., et al. (2018). CNS lymphatic drainage and neuroinflammation are regulated by meningeal lymphatic vasculature. *Nat. Neurosci.* 21, 1380–1391. doi: 10.1038/s41593-018-0227-9

Luciano, M. G., Dombrowski, S. M., Qvarlander, S., El-Khoury, S., Yang, J., Thyagaraj, S., et al. (2017). Novel method for dynamic control of intracranial pressure. *J. Neurosurg.* 126, 1629–1640. doi: 10.3171/2016.4.JNS15 2457

Mestre, H., Tithof, J., Du, T., Song, W., Peng, W., Sweeney, A. M., et al. (2018). Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. *Nat. Commun.* 9:4878. doi: 10.1038/s41467-018-07 318-3

Nedergaard, M., and Goldman, S. A. (2020). Glymphatic failure as a final common pathway to dementia. *Science* 370, 50–56. doi: 10.1126/science.abb8739

Papadopoulos, M. C., and Verkman, A. S. (2013). Aquaporin water channels in the nervous system. *Nat. Rev. Neurosci.* 14, 265–277. doi: 10.1038/nrn3468

Plog, B. A., Mestre, H., Olveda, G. E., Sweeney, A. M., Kenney, H. M., Cove, A., et al. (2018). Transcranial optical imaging reveals a pathway for optimizing the delivery of immunotherapeutics to the brain. *JCI Insight* 3:e120922. doi: 10.1172/jci.insight.120922

Rainey-Smith, S. R., Mazzucchelli, G. N., Villemagne, V. L., Brown, B. M., Porter, T., Weinborn, M., et al. (2018). Genetic variation in Aquaporin-4 moderates the relationship between sleep and brain Aβ-amyloid burden. *Transl. Psychiatry* 8:47. doi: 10.1038/s41398-018-0094-x

Rajna, Z., Mattila, H., Huotari, N., Tuovinen, T., Krüger, J., Holst, S. C., et al. (2021). Cardiovascular brain impulses in Alzheimer's disease. *Brain* awab144. doi: 10.1093/brain/awab144

Russ, T. C., Kivimäki, M., and Batty, G. D. (2020). Respiratory disease and lower pulmonary function as risk factors for dementia: a systematic review with meta-analysis. *Chest* 157, 1538–1558. doi: 10.1016/j.chest.2019.12.012

Simon, M. J., and Iliff, J. J. (2016). Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease. *Biochim. Biophys. Acta* 1862, 442–451. doi: 10.1016/j.bbadis.2015.10.014

Smith, E. E., Saposnik, G., Biessels, G. J., Doubal, F. N., Fornage, M., Gorelick, P. B., et al. (2017). prevention of stroke in patients with silent cerebrovascular disease: a scientific statement for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 48, e44–e71. doi: 10.1161/STR.0000000000000116

Tuovinen, T., Kananen, J., Rajna, Z., Lieslehto, J., Korhonen, V., Rytty, R., et al. (2020). The variability of functional MRI brain signal increases in Alzheimer's disease at cardiorespiratory frequencies. *Sci. Rep.* 10:21559. doi: 10.1038/s41598-020-77984-1

Wardlaw, J. M., Benveniste, H., Nedergaard, M., Zlokovic, B. V., Mestre, H., Lee, H., et al. (2020). Perivascular spaces in the brain: anatomy, physiology and pathology. *Nat. Rev. Neurol.* 16, 137–153. doi: 10.1038/s41582-020-0312-z

Williams, M. A., Nagel, S. J., Luciano, M. G., Relkin, N., Zwimpfer, T. J., Katzen, H., et al. (2019). The clinical spectrum of hydrocephalus in adults: report of the first 517 patients of the Adult Hydrocephalus Clinical Research Network registry. *J. Neurosurg.* 132, 1773–1784. doi: 10.3171/2019.2.JNS183538

Wilson, M. H. (2016). Monro-Kellie 2.0: the dynamic vascular and venous pathophysiological components of intracranial pressure. *J. Cereb. Blood Flow Metab.* 36, 1338–1350. doi: 10.1177/0271678X16648711

Xue, Y., Liu, N., Zhang, M., Ren, X., Tang, J., and Fu, J. (2020). Concomitant enlargement of perivascular spaces and decrease in glymphatic transport in an animal model of cerebral small vessel disease. *Brain Res. Bull.* 161, 78–83. doi: 10.1016/j.brainresbull.2020.04.008