Sleep and Neurodegeneration: novel biomarkers for new challenges

There is convergence that sleep and neurodegeneration are closely associated in a causal rather than casual relationship. Two the possible scenarios to decode this intriguing interaction: i) sleep disorders cause/accelerate neurodegenerative disorders according to a novel model of a common neurodegeneration; ii) a common etiology impairs both sleep systems and centres target of neurodegeneration, but in a different time: sleep disorders precede the clinical onset of neurological disorders.

Consistent evidence links Alzheimer's disease (AD) to obstructive sleep apnea (OSA), a sleep-related breathing disorder characterized by repeated episodes of upper airway obstruction during sleep, chronic intermittent hypoxia and sleep fragmentation. A possible explanation is related to the neurobiological link between OSA and AD: sleep fragmentation, slow wave sleep disruption and intermittent hypoxia could cause an increase of the $\beta$-secretase activity resulting in a significant increase of $\beta$-amyloid (A$\beta$) deposition in the brain. In collaboration with the Neurology-Sleep Disorder Center of IRCCS San Raffaele of Milan, Italy and the John Hunter Hospital-University of Newcastle, Australia, we investigated whether brain regions and networks involved in OSA may be considered areas or targets vulnerable for the development of AD neuropathology. We demonstrated that OSA and AD share common areas of neurodegeneration and neuropathology in the brain and provided a new model of a neurodegeneration so called OSA-AD neurodegeneration. Sex-related changes in specific limbic structures, in particular hippocampus may be considered neuroimaging biomarkers for this novel condition.

As research future agenda, given the greater risk of AD for females compared to males, we aimed to investigate the longitudinal changes in brain regions vulnerable to AD neuropathology with a focus on OSA females. To assess whether the brain OSA damage can revert after specific treatment as continuous positive airway pressure (CPAP), we also have collected neuroimaging and neuropsychological data from severe OSA patients in collaboration with Neurology-Sleep Disorder Center of IRCCS San Raffaele, IBFM-Catanzaro and Cognitive Neuroscience Laboratory, Istituti Clinici Scientifci Maugeriri ICSS, Pavia. After CPAP-treatment, we preliminarily found a recovery of OSA brain damage related to the improvement of neurocognitive profile emphasizing the importance of an early diagnosis of OSA. Neurophysiological biomarkers might be also useful in early detection of OSA. Cardiac autonomic dysfunctions may occur in these patients as result of prolonged hypoxia during sleep and impaired arousal response. We previously identified a cardiac autonomic index, in particular cardiac parasympathetic index (CPI) strictly associated to the circadian autonomic fluctuations occurring in OSA patients. Moreover, in collaboration with IBFM-Catanzaro and Neurology-Sleep Disorder Center of IRCCS San Raffaele, we recently demonstrated that CPI was normalized after a single-night of CPAP therapy thus confirming that CPI may be a specific marker of OSA pathology. We will collect additional data in larger cohort of OSA patients to validate the usefulness of CPI in clinical practice.

REM sleep behaviour disorder (RBD) is a parasomnia characterized by dream enacting behaviors during sleep and can precede the onset of synucleinopathies as Parkinson Disease (PD) and Dementia with Lewy Body (DLB) by several decades. RBD is really in the middle of a pathogenetic process in which many neuropathological alterations have already begun and others may occur, in absence of clinical manifest motor features of PD/DLB. Facial mimic impairment is considered a strong biomarker of early motor dysfunction in PD. As Co-Principal Investigator of “Facial expressivity Automatic Classifier for Early detection of Parkinson's Disease: FACE-PD project”, funded by the Michael J Fox Foundation for Parkinson’s research, we are developing an innovative method for early detection of facial expression in PD. In collaboration with IBFM-Catanzaro and Neurology-Sleep Disorder Center of IRCCS San Raffaele, we are starting to collect FACE-PD data in PD and RBD patients respectively. It can be a great measure to improve the early PD recognition in at high-risk subjects such as those with RBD.
In conclusion, emphasis should be placed on the early identification of sleep disorders as a bridge to neurodegeneration, for the opportunity that this creates for a timely treatment. In the precious pre-clinical window between what has happened and what is yet, the development of novel biomarkers able to capture the conversion into neurodegeneration represents the most important challenge.

References:

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