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Q1 What initially sparked your interest in neurology, leading you to a research career focusing on sleep and neurodegeneration, and what has motivated you to continue researching?

Neurology is a fascinating field, as the nervous system is complex, and most brain functions are still not fully understood. So, for researchers in neurology and in neuroscience, there are still many important questions to be answered, making this area of research very stimulating, challenging, and fascinating. Among the complex brain functions to be disentangled, sleep is particularly captivating. We spend one-third of our life sleeping, and we are only starting to disentangle sleep functions more and more. The link between sleep and neurodegeneration is strong in particular for what concerns isolated rapid eye movement (REM) sleep behaviour disorder as prodromal synucleinopathy, and for what concerns the role of sleep in maintaining brain health, partly through the glymphatic system. The possibility to be able in the future to detect and treat neurodegeneration in the prodromal or even preclinical phase using sleep as a window into the future of the brain, and to help prevent or modulate neurodegeneration through sleep improvement, is a powerful motivation for me to continue research in this field.

Q2 Do you think there are any misconceptions about your speciality?

I do think there are some misconceptions about neurological sleep medicine. Sometimes sleep problems are regarded as a luxury of wealthy people and not considered as a relevant field in neurology. However, sleep disorders are present as comorbidities in several neurological (and non-neurological) diseases and contribute to worse prognosis and/or worse quality of life in these patients. Moreover, it has become increasingly clear that sleep has a vital function in maintaining brain health, and a healthy sleep is as essential as, e.g., a healthy diet and exercise, for healthy brain aging and prevention of neurological diseases. In particular, a growing amount of data is unravelling more and more about the bidirectional relationship between sleep and neurodegenerative diseases. Healthy sleep is fundamental also when addressing health disparities, as for example indigent people can less frequently get a healthy sleep due to environmental and social factors, among others. Thus, the view that health sleep is a problem of wealthy people or wealthy societies is fundamentally wrong. Hopefully, the current misconception will disappear in the near future.

Q3 What are the most significant breakthroughs you have seen in the field of sleep medicine since starting your career as researcher in 2013?

There have been a few breakthroughs in the sleep medicine field in the past 10 years. For what concerns my main area of research, one is the establishment of isolated REM sleep behaviour disorder as early α-synucleinopathy, based on long-term follow-up data, on the investigation of long-standing non convertors (i.e., those patients with still isolated REM sleep behaviour disorder 10 years or more after diagnosis) and on the demonstration of pathologic α-synuclein aggregates in these patients. Additionally, evidence has started

to disentangle the close relationship between sleep and neurodegeneration, also through the study of the glymphatic system. Another important breakthrough is the improvement in understanding of narcolepsy pathophysiology, with demonstration of the long-hypothesised role of autoimmunity in this condition. Moreover, a completely new class of drugs acting on orexin receptors have been developed or are currently under development: dual orexin-receptor antagonists for the treatment of insomnia, and orexin agonists for the treatment of narcolepsy. Besides these advancements, the technological developments with use of wearables and nearables, as well as the application of artificial intelligence in the sleep medicine field need to be mentioned, as these will likely lead to a revolution in how we assess and manage sleep disorders in the coming years.

Q4 You currently more than 120 publications to your name for your research on sleep. What do you believe to be the current gaps in literature?

This is a relatively recent field of research, so there are still gaps in the literature. First of all, long-term follow-up studies are needed, to prospectively confirm that disturbed sleep increases the risk of neurodegeneration. Moreover, basic science data and translational research further elucidating this bidirectional relationship will be critical and will improve knowledge on how specific changes in sleep are linked to specific neurodegeneration pathways. Further, long-term, prospective, randomised controlled trials with interventions to improve sleep longitudinally assessing biomarkers of neurodegeneration will fill a gap in understanding how to promote brain health and prevent or modulate neurodegeneration through sleep enhancement.

Q5 You have specialised in REM sleep behaviour disorders. What topics do you believe require greater attention?

When focusing on the REM sleep behaviour disorder area, I believe that isolated REM sleep without atonia, i.e., prodromal REM sleep behaviour disorder, requires greater attention as it possibly allows identification of α-synuclein

related neurodegeneration more than a decade (maybe two or even more) before manifestations of the classical motor or cognitive symptoms. However, this consideration leads to another topic urgently requiring more attention: qualified communication and counselling when diagnosing a prodromal or preclinical neurodegenerative disease (e.g., REM sleep behaviour disorder or REM sleep without atonia). From a scientific point of view, diagnosing neurodegeneration in a prodromal or even preclinical phase is a great opportunity to study the underlying processes leading to the overt clinical manifestations of disease. But it is fundamental to keep in mind that for people diagnosed with these conditions, the diagnosis is a cause of stress and anxiety without a concrete possibility of acting against this sword of Damocles, at least at the present moment. Therefore, assessing patients' preferences regarding disclosure, shared decision-making, individually tailored communication, and availability to answer all potential questions are essential.

Q6 You are on the teaching course sub-committee for the European Academy of Neurology (EAN) 2023. How is the EAN using its position to educate surgeons, nurses, and trainees about the field of neurology?

The EAN aims to foster and support the development of neurological excellence, leading to better patient care and outcomes, and promotes quality in neurology. To achieve this aim, the EAN educates not only neurologists but also related scientists, thus including interested surgeons and nurses. Trainees are a key target group of EAN's activities, as reflected in the manifold events organised specifically for trainees, such as the Spring and Autumn Schools, the most recently started Science School, fellowship grants, a mentoring programme, and the leadership programme. Accordingly, one of the EAN priorities is education, which is reflected in activities like the European Training Requirements for Neurology, the very comprehensive E-learning platform 'eanCampus', and podcast updates through the 'eanCast: Weekly Neurology'. EAN is going even further and working on a pre-graduate neurology curriculum, which can be used afterwards as a recommendation and guidance paper to many neurological member societies and medical

universities when looking at teaching in neurology and to harmonise neurology education even before the beginning of neurology training.

Q7 What is one of the biggest challenges for the EAN in their goal to advance high-quality patient care and to reduce the burden of neurological diseases?

Being a European Academy, one of the biggest challenges is certainly to overcome differences among countries, avoiding having situations where only basic care is possible, coexisting with excellence centres where high-quality patient care is provided, but instead increasing the level in all Europe to high-quality neurological care. So many factors are involved, from education in different countries to cultural and economic issues, making this a huge challenge. On the other hand, reducing the burden of neurological diseases is key, and it becomes more and more clear that the only way to really lower this burden is a shift towards detection of early stages of neurological diseases (i.e., preclinical and prodromal stages, for diseases like neurodegenerative conditions) and towards prevention, acting on risk factors. This is a huge challenge. Raising awareness on brain health is the obvious starting point, and the EAN is doing a great job on this, as can be seen online.[1]

Q8 Are there any innovations on the horizon in the field of sleep disorders that you think are particularly noteworthy?

I expect several innovations and changes in the sleep medicine field in the upcoming years. In my opinion two innovations are particularly noteworthy. As mentioned before, there is a massively increasing use of wearable devices, nearables, and other digital health technologies, which at least in part use artificial intelligence-based methods to analyse and interpret collected data. I believe that these instruments will revolutionise the way we assess and manage sleep and sleep disorders, although a lot still needs to be done to achieve a common framework for assessment and application of digital health technologies. This is already clearly visible on the horizon, whereas more far away and more blurred on the horizon is the other substantial innovation: sleep becoming a

constitutive part of the brain health pillars, and sleep improvement as a strategy to prevent neurodegeneration. More work is certainly needed to further clarify the general role of sleep in brain health, as well as the role of specific sleep changes in different neurological disorders, but I am excited about the idea that in the near future we will have instruments to improve sleep, and use them to reduce the risk of neurodegenerative diseases or even prevent them.

Q9 Since your appointment as researcher at the Innsbruck Medical University, Austria, what has been your proudest achievement?

I started my career as researcher at the Sleep Disorders Clinic, Department of Neurology, of the Medical University Innsbruck, Austria, 10 years ago. This time was not fully dedicated to research, as it included my residency in Neurology, besides my PhD in neuroscience. My achievements have been possible thanks to the constant support of my mentor, Professor Birgit Högl, Head of the Sleep Disorders Clinic. If I have to pick one thing as my proudest achievement, I would select the study I planned and coordinated on analysis of olfactory mucosa for pathologic α-synuclein using real-time quaking-induced conversion in isolated REM sleep behaviour disorder, at the Department of Neurology in Innsbruck, Austria, and in collaboration with Professor Gianluigi Zanusso's group from Verona Medical University, Italy, and with Professor Alex Iranzos group from the Hospital Clinic de Barcelona, Spain. Another important achievement I would like to mention was being awarded the Max Kade Fellowship, which supports my current research on REM sleep behaviour disorder with Professor Aleksandar Videnovic at the Neurological Clinical Research Institute, Massachusetts General Hospital, in Boston, USA. ●

References

1. European Academy of Neurology (EAN). Brain Health Strategy. Available at: https://www.ean.org/ean/advocacy/brain-health/brain-health-strategy. Last accessed: 23 May 2023