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REDUCED SLEEP SPINDLE ACTIVITY IN RETT SYNDROME: A POLYSOMNOGRAPHIC CASE-CONTROL STUDY

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INTRODUCTION AND OBJECTIVE

- Rett syndrome (RTT) is a rare and severe neurological disorder primarily affecting females, mainly associated with MECP2 gene mutations.
- Key clinical features include psychomotor regression, loss of spoken language, stereotypic hand movements, gait abnormalities, epilepsy, autonomic dysfunction, and sleep disturbances[1].
- Although sleep disturbances are reported in up to 80% of individuals with RTT[2], few polysomnographic studies have been performed and the electroencephalographic (EEG) biomarkers underlying sleep dysfunction are poorly understood.
- A single study by Pretl et al showed a significant paucity of sleep spindles per minute in the fronto-central region of patients with RTT (six patients)[3].
- Evidence from animal models suggested that dendrito-synaptogenic and other brain construction errors underpin RTT syndrome pathophysiology[4].

OBJECTIVE: To investigate sleep structure and spindle density in patients with RTT compared to an age-matched healthy control group (HG).

RESULTS

SLEEP MACROSTRUCTURE

- Increased representation of N1 (p=0.009) and reduced representation of REM sleep stage (p=0.003) (TST=Total Sleep Time).
- Higher values of Wake After Sleep Onset (WASO) and nocturnal awakenings (n AWN) (p<0.001; p<0.001).
- Positive correlation between age of patients and WASO, n. awakenings, and the N1 representation. No correlations with disease severity.

SPINDLE DENSITY

- Patients with RTT presented very few spindles, ranging from none to a maximum of 15 throughout the whole night (mean – 4 spindles, frontal channels).
- The RTT group showed a remarkable spindle density decrease compared to control group in both frontal, central and occipital derivations (p<0.001; p<0.001; p<0.005).
- Spindle density seemed not to correlate with age in RTT group.

Rett syndrome (RTT)

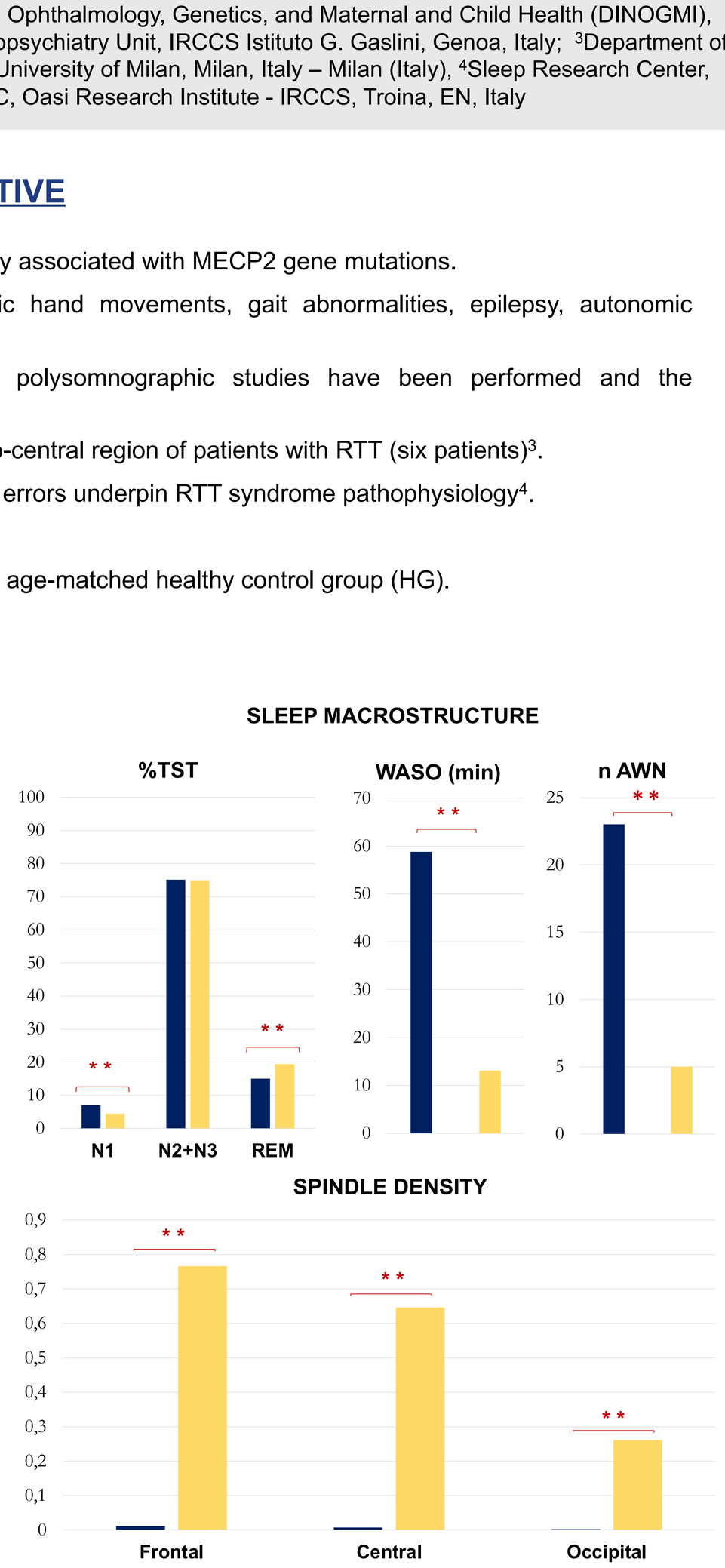
Healthy controls (HC)

Patients with RTT (n=17)

- Typical Rett syndrome
- Females
- Age 3-39 years, mean 14.2

Control group (n=17)

- Healthy subjects
- Females
- Age 4-39 years, mean 13.8



DISCUSSION AND CONCLUSION

The RTT group showed a great impairment in sleep macrostructural parameters with a more significant sleep structure fragmentation, as well as a decrease in sleep spindle density compared to control group. These sleep abnormalities could have a multifactorial origin, as in other genetic neuropsychiatric diseases.

Interestingly, EEG biomarkers have proven to be a valuable tool to understand the pathophysiology of brain dysfunction in many disorders. Consistently, the identification of reduced spindle parameters could suggest deficits in thalamo-cortical circuits. Intriguingly, Lee et al showed that, in Mecp2-deficient mice, at the morphological level, the thalamocortical axon arbors fail to develop.[5]

Relying on the same strategy, the analysis of other EEG biomarkers (e.g., the power and slope of slow waves and aperiodic activity) is in progress, with special focus on abnormal synaptic plasticity. Indeed, multiple lines of evidence from animal models support the notion that the disorder targets synapses and synaptic plasticity and has been shown to disrupt the balance between glutamate excitatory synapses and GABAergic inhibitory synapses.[4]

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