Epilepsy and Frontotemporal Theta Activity in C9orf72 Repeat Expansion

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BACKGROUND: Janssen et al. recently described one patient harbouring the C9orf72 repeat expansion with young onset cognitive decline, who showed slowed background activity and photoparoxysmal response at EEG recording. They suggest that these electroencephalographic abnormalities represent a previously unrecognized feature of the C9orf72 phenotype (1).

OBJECTIVES: To report clinical and electrophysiological findings in C9orf72-mutated patients identified in our Clinic during the last four years and for whom EEG recording was available as a part of the diagnostic work-up.

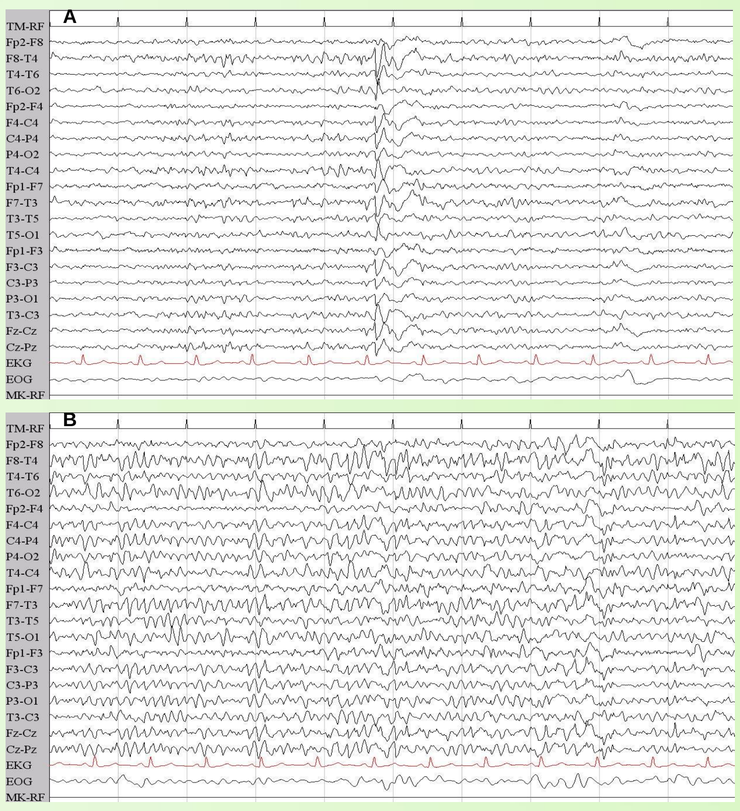

Figure 1. EEG recording: 7uV\mm, TC1 0.1sec, HF1 30Hz.
A: single spike-wave complex on bilateral fronto-temporal channels (3-4Hz, 130uV).
B: slow theta polymorphic activity on bilateral fronto-temporal channels (6-7Hz, 70-90uV).

CASE SERIES: We found five patients (four women). All had amyotrophic lateral sclerosis (ALS), with bulbar-onset in four cases, associated with frontotemporal cognitive decline and family history of ALS or early-onset dementia.
One woman, who developed progressive bulbar dysfunction at the age of 61, also presented with recurrent brief episodes characterized by unresponsiveness, staring eyes and purposeless movements, consistently with complex partial seizures. Brain and spinal MRI was unremarkable. **EEG recording showed polispikes/waves on the right frontotemporal channel and sustained frontotemporal bilateral theta activity** (Fig 1A). Following the introduction of levetiracetam, seizures were not yet observed, despite the persistence of epileptic abnormalities at EEG. ALS rapidly progressed to tetraplegia and respiratory failure, and she died 18 months after onset.
Another woman was also affected with Moskowitz Syndrome complicated by a left temporo-parieto-occipital ischemic stroke with minimal residual language dysfunction, at the age of 34. Eight years later she developed tonic-clonic generalized epilepsy. She was on levetiracetam 2000 mg/day at the time of ALS onset, at the age of 49. In this case, EEG showed left posterior temporal theta of 6-7 Hz and low amplitude incremented by hyperventilation, consistent with a lesional abnormality.
Two other patients, with no co-morbidities and normal brain MRI, presented with **sustained fronto-temporal bilateral theta activity** (Fig 1B) without epileptiform abnormalities. In the remainder patient EEG was normal. Photoparoxysmal response was not observed in any case.

DISCUSSION: Standard EEG is generally normal during the course of frontotemporal dementia (FTD). Recently, epilepsy has been reported in few FTD patients carrying heterozygous MAPT mutations or homozygous TREM2 mutations (2-3).
Now, the report by Janssen and coauthors and our findings suggest that **slowing of EEG background activity and epilepsy, associated or not to photosensitivity, may constitute uncommon features of the C9orf72 phenotype.**
We hypothesize that this reflects neuronal loss in the frontotemporal area, imbalance in intracortical neurotransmitters and/or intrinsic alterations of neuronal properties leading to cortical hyperexcitability.

Of note, in patients with frontotemporal dementia and/or ALS, complex partial seizures and other kinds of non motor seizures may escape observation due to advanced cognitive decline, speech impairment and weakness, which may all mask the expression of seizures semiology or prevent the communication of symptoms. Definite evidence may only come from targeted studies in large cohorts.

References:
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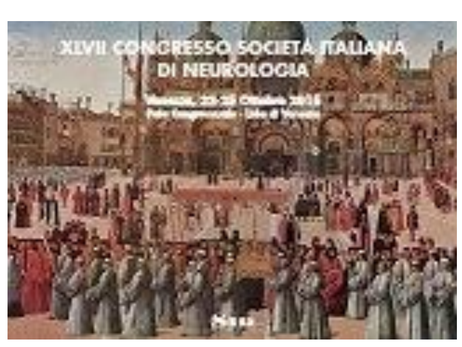

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