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Letter to the Editor

Electrophysiological evidence of spino-cortical proprioceptive tracts dysfunction in hereditary spastic paraplegia with thin corpus callosum

1. Introduction

Hereditary spastic paraplegias (HSP) are rare genetic neurodegenerative diseases. Pathology discloses spinal axonal degeneration, maximal in the terminal portions of the longest descending (corticospinal tracts) and ascending spino-cortical tracts of spinal dorsal column. Clinically, patients present with leg spasticity and lower limb pyramidal weakness leading to progressive gait impairment. Often considered subclinical, involvement of the posterior spinal column and somatosensory impairments, mostly lower discrimination thresholds, are seen in the majority of patients when specifically sought for (Schady and Sheard, 1990). Such somatosensory processing alterations contribute to the daily life disabilities of HSP patients by worsening gait difficulties and upper-limb clumsiness associated to upper motor neuron axonal degeneration.

The integrity of spino-cortical proprioceptive tracts can be objectively quantified electrophysiologically by the corticokinematic coherence (CKC) that measures with high test-retest reliability the coupling between movement kinematics and primary sensorimotor (SM1) cortex activity (Naeije et al., 2020). In this magnetoencephalography (MEG) study, we investigated if upper-limb CKC was impaired in a population of clinically homogeneous HSP patients with thin corpus callosum (HSP-TCC) and could reflect spino-cortical proprioceptive tracts impairment missed by clinical testing.

2. Subjects and methods

Six patients with HSP-TCC (age: 22 ± 5 yrs, 2 females), were included between October 2018 and June 2019. Four patients had a *SPG11* mutations and 2 patients a *TUBβ4A* mutation (Monteiro et al., 2019). Neurological deficits were quantified by the Spastic Paraplegia Rating Scale (SPRS, Mean ± SD: 25 ± 20) and the Scale for the Assessment and Rating of Ataxia (SARA, Mean ± SD: 15 ± 14). Of notice, one patient had impairment of pallesthesia and superficial tactile perception on bedside testing. Six healthy subjects matched for age and sex were also recruited for comparison. This study was approved by the CUB Hopital Erasme Ethics Committee.

3. MEG data acquisition

The methods used in the present study are described in (Naeije et al., 2020). Upper-limbs were chosen over lower-limbs due to SPG feet deformations, amyotrophy, spasticity rendering passive movements difficult and the impossibility for most patients to perform toe or ankle repetitive movements. CKC was derived from whole-scalp MEG recordings (Triux, MEGIN, Helsinki, Finland) from all participants performing self-paced active right index finger–thumb opposition movements. MEG signal processing and CKC computation was realized as in (Naeije et al., 2020). Coherence maps at movement frequency (F0) and its first harmonic (F1) were computed at the group-level. Statistical differences between healthy subjects and HSP patients were assessed with a nonparametric permutation (Naeije et al., 2020). Movement frequency and regularity parameters were compared between the two groups with a two-tailed independent sample t-test.

4. Results

Patients with HSP-TCC displayed lower movement frequency (1.2 ± 0.6 Hz vs 1.7 ± 0.6 Hz, $p = 0.04$) and tended to have less regularity in movement frequency (33.4 ± 16% vs 22.9 ± 9%, $p = 0.07$) than healthy subjects.

Fig. 1 illustrates the CKC results. At the group-level, in both healthy subjects and patients, significant CKC values were found at F0 and F1 above contralateral SM1 cortex. CKC at F0 was significantly lower in HSP-TCC patients than in healthy subjects at contralateral SM1 cortex (0.12 vs 0.36, $p = 0.017$) while CKC values at F1 tended to be lower in HSP-TCC at contralateral SM1 cortex (0.10 vs 0.23, $p = 0.08$).

Of notice, sensory and motor nerve conduction studies (NCS) were performed in all 6 patients and within normal limits.

5. Discussion

This study shows that upper-limb CKC values are significantly lower in HSP-TCC patients than in healthy subjects demonstrating spino-cortical proprioceptive tracts impairment in HSP-TCC.

Clinically, the mean SPRS of our cohort is in line with SPRS values described in HSP-TCC while SARA scores were surprisingly high, a fact partly explained by the relative weight of the gait items (8 points /42) in the SARA score. However, our patients also displayed impairment in tests typically failed in ataxia such as finger-chase/finger-nose/heel-to-shin tests. This finding underlines the difficulty in the clinical evaluation of ataxia and in differentiating the relative contribution of corticospinal, cerebellar and spinal posterior columns impairments. Indeed, both corticospinal and cerebellar dysfunction lead to bradykinesia, hypokinesia and arythmokinesia (Shimoyama et al., 1990). Moreover, both weakness due to pyramidal tract dysfunctions and proprioceptive afference impairments are well-known causes of dysmetria. In that context, the low CKC values found in HSP-TCC patients argue for a possible role of spino-cortical proprioceptive tracts dysfunction in the development of ataxic symptoms in HSP-TCC. Indeed, in this study,

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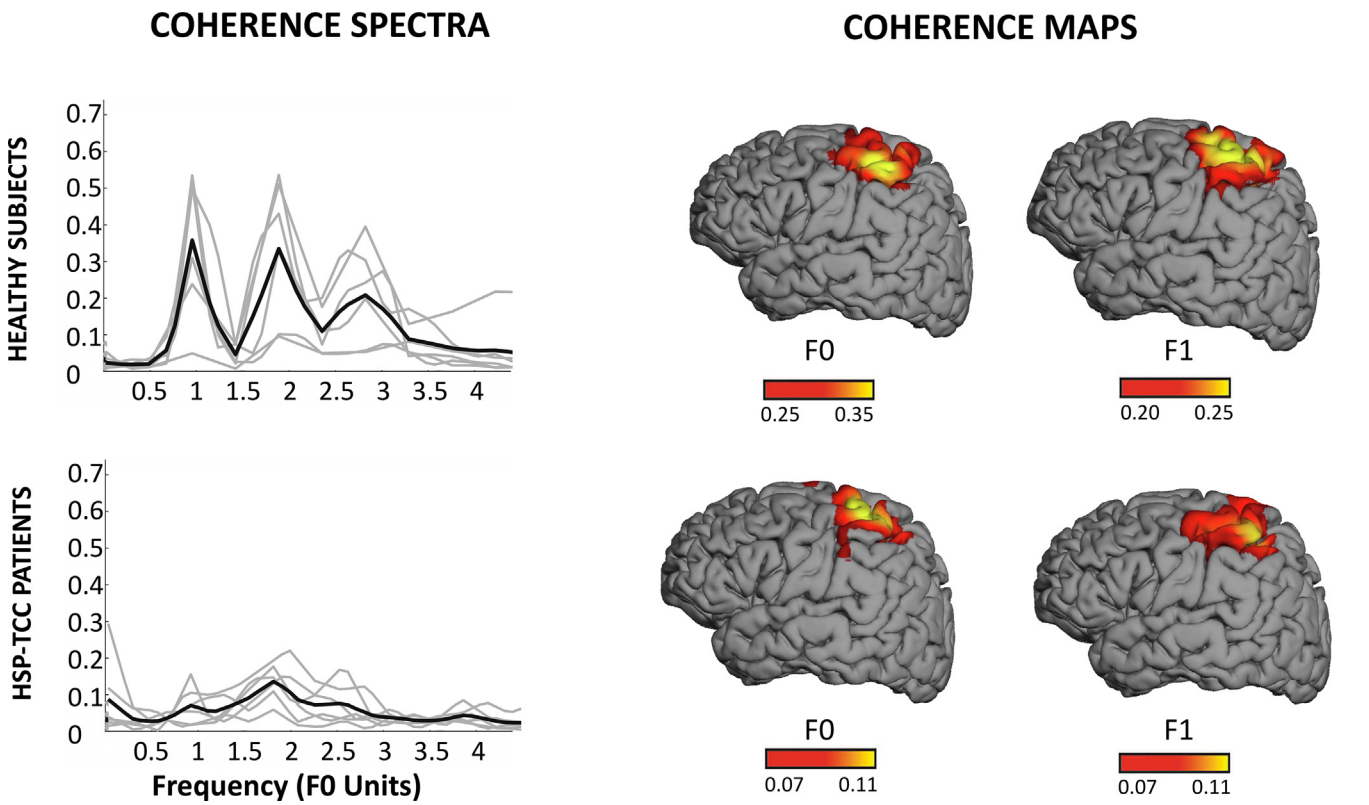

Fig. 1. Left. Individual corticokinematic coherence spectra for each participant for healthy subjects (Top) and hereditary spastic paraplegia with thin corpus callosum (HSP-TCC) patients (bottom). Each gray trace represents the coherence between MEG and accelerometer signals of right hand index finger-thumb opposition movements for a single individual. The coherence value displayed is the maximum coherence across the MEG sensors covering the left rolandic MEG sensors. Black traces correspond to the group-level average. Frequencies are expressed in movement frequency (F0) units (i.e., 1 corresponds to the individual F0, 2 to its first harmonics (F1), etc.). **Right.** Group-level corticokinematic coherence maps superimposed on left-hemisphere brain surface rendering. The brain is viewed from the left. Group-level coherence maps for healthy subjects (Top) and HSP-TCC patients (bottom) at F0 (Left) and F1 (Right). Note the different scaling of the color bars between healthy subjects and HSP-TCC patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the mean CKC level at F0 was about a third of that in matched healthy subjects and similar to those previously observed in Friedreich Ataxia where posterior columns are affected beyond doubts (Naeije et al., 2020). CKC alterations parallel the posterior columns anomalies on HSP pathology and reflect the length-dependent central axonopathy that occurs in proprioceptive tracts. That only one of our patients had impaired sensory findings on classical neurological testing may seem surprising. However, posterior column dysfunctions are not well apprehended by routine neurological examinations and seminal reports showed that when the information normally supplied by posterior columns is severed, by surgery for instance, light touch and pressure are not lost and only somatosensory discrimination is disturbed (Nathan et al., 1986). Testing for somatosensory discriminative thresholds requires specific equipment and has unknown test-retest reliability (Schady and Sheard, 1990). Despite those limitations, when somatosensory thresholds are tested in HSP, they are impaired in at least one modality (vibration, discrimination, temperature or pain) in almost all HSP patients. Somatosensory discrimination threshold impairments are not trivial and lead to severe disturbances in daily life activities when electively injured and worsens significantly impairments due corticospinal tract dysfunctions. This study suggests that in HSP and potentially other spinal diseases, posterior column dysfunction should be investigated and that CKC, in that context, could stand as objective electrophysiological marker to detect and monitor spino-cortical ascending tracts degeneration with a good test-retest reliability (Naeije et al., 2020).

Routine CKC testing in a larger cohort of HSP could help refine its yield and potential use as a non-invasive marker of disease progression.

6. Conclusion

Electrophysiological assessment of spino-cortical proprioceptive tracts function by CKC in HSP-TCC showed significant reduction of upper-limbs CKC levels suggesting a non-trivial alteration of proprioceptive functions, likely to contribute to and worsen patients' disability.

Declaration of Competing Interest

No author discloses conflicts of interest.

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