

Letter to the Editor

Neurophysiologic characterization of motor and sensory projections in Joubert syndrome



Joubert syndrome (JS) is a rare inherited form of ataxia characterized by episodic hyperpnea/apnea, oculomotor apraxia, mental retardation, and cerebellar vermis hypoplasia [1,2]. The hallmark

radiographic ‘molar-tooth sign’ (MTS) in axial sections of the brainstem isthmus [4] is thought to reflect the absence of the pyramidal decussation [5]. Here, we report neurophysiologic evidence of strong ipsilateral motor projections and predominantly contralateral sensory projections in JS.

All procedures were approved by the Institutional Review Board at Beth Israel Deaconess Medical Center. Two affected male

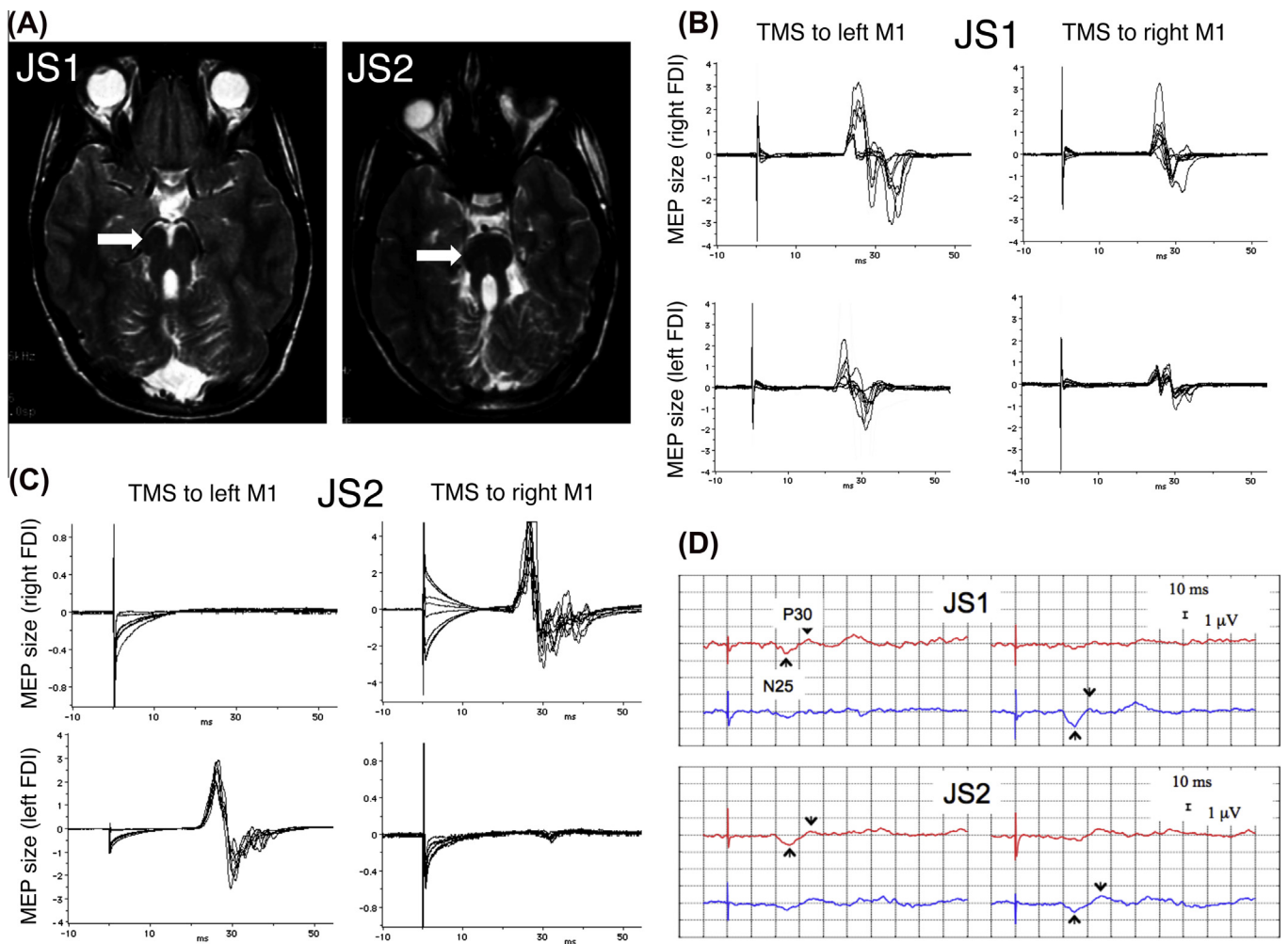


Fig. 1. (A). Axial MRI sections at the level of the brainstem showing MTS (arrows). (B). TMS-induced MEPs in patient JS1 showing bilateral projections to the FDI. Ipsilateral MEPs occurred on average 0.77 ms sooner than contralateral MEPs, suggesting a primary, uncrossed projection with branching, possibly at a transcallosal or spinal level, giving rise to slightly later contralateral responses. (C). TMS-induced MEPs in patient JS2 showing an ipsilateral projection to the FDI. (D) Somatosensory evoked potentials in patients JS1 and JS2 with stimulation of the median nerve. Blue tracing represents left-sided electrical stimulation, and red tracing represents right-sided electrical stimulation. Left panels: left hemisphere, right panels: right hemisphere. Contrary to the CST, sensory afferents are predominantly contralateral. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

brothers ages sixteen (JS1) and twenty years (JS2), were studied. These patients had each of the defining clinical hallmarks of JS, a history of hyperpnea/apnea in the newborn period, oculomotor apraxia, ataxia and mental retardation. MRI examination revealed the presence of a 'molar tooth sign' [4] in patients JS1 and JS2, identified by the presence of elongated and reoriented superior cerebellar peduncles and deep interpeduncular fossa in the isthmus of the brain stem (Fig. 1A). Corticospinal tract (CST) and somatosensory projection wiring was tested using transcranial magnetic stimulation (TMS) and somatosensory evoked potentials (SEP). Single TMS pulses were applied over each hemisphere at intensities of up to 100% maximum stimulator output (MSO) using a focal, 8-shaped coil. Motor evoked responses were recorded using surface EMG electrodes from both first dorsal interossei (FDI) muscles. In both parents of JS1 and JS2, stimulation produced exclusively contralateral FDI motor evoked potentials (MEPs) of 1.5–4 mV amplitude with latencies of approximately 20.8 ms (mother) and 22.7 ms (father) from stimulation of either hemisphere as expected [3]. In JS1 MEPs were recorded bilaterally and were more variable in amplitude (Fig. 1B). The latency of the ipsilateral MEPs matched what might be expected for normal, crossed CST projections (21.4 ms) and was 0.77 ± 0.18 ms shorter than the latency of contralateral MEPs. In JS2, MEPs were exclusively ipsilateral at a normal latency (20.8 ms), amplitude and configuration, suggesting absence of decussation of fast conducting, ipsilateral projections (Fig. 1C). To investigate sensory wiring, JS1 and JS2 were studied using short-latency SEPs. SEPs were obtained from two post-central scalp EEG electrodes placed contra- and ipsilaterally to the peripheral stimulation side, respectively. Two EEG electrodes were placed 3 cm posterior to the electrode positions C3 and C4 of the international 10–20 electrode system. A midfrontal electrode (Fz) served as the reference. Both JS1 and JS2 showed predominantly contralateral potentials with an initial negative deflection around 25 ms (N25) followed by a positive deflection with a latency of 30–35 ms (P30) (Fig. 1D), most likely corresponding to the cortical SEP-components N20 and P25 that can be recorded in healthy controls. In JS1, SEPs were almost exclusively contralateral, while JS2 showed some bilateral representation, with N25/P30 amplitudes approximately twice as high on the contralateral side. The presence of uncrossed CST projections in JS was confirmed in a third, 16 year-old patient (JS3), unrelated to patients JS1 and JS2 (Supplementary Figure S1). As in the two other patients, MTS was located at the pontomesencephalic junction. TMS applied over the right hemisphere at 100% MSO resulted in no MEP in either hands whereas TMS over the left hemisphere at 100% MSO produced bilateral MEPs with smaller amplitudes on the ipsilateral side. When TMS was applied during maximal isometric contraction of the hand contralateral to stimulation, left hemisphere stimulation resulted in predominantly ipsilateral, desynchronized, and irregular MEPs. Right hemisphere TMS was associated with bilateral MEPs and cortical silent periods of similar amplitude and duration, respectively. MEP latencies for the contracted muscles at 100% MSO were between 15 and 16 ms in both hands.

The present findings provide for the first time a neurophysiological confirmation of neuropathological [4,5] data showing abnormalities of the pyramidal decussation at the medullary level

in patients with JS. Neurophysiological data show that individuals with JS display strong ipsilateral CST projections but predominantly contralateral sensory projections, indicating that each cortical hemisphere receives sensory input from one side of the body but projects motor output to the other half. These wiring defects result in a striking mismatch between target of motor output and source of sensory information in each cerebral hemisphere that may have functional and behavioral correlates.

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2. Conflict of interest

Dr. Pascual-Leone serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience, Allied Mind, Neosync, and Novavision, and is an inventor on patents and patent applications related to noninvasive brain stimulation and real-time integration of TMS with EEG and fMRI.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.clinph.2013.06.006>.

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