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Letter to the Editor

Cortical GABAergic dysfunction underlying abnormal hand movements in *ARX* mutation

The aristaless-related homeobox protein (ARX) is essential for GABAergic neuron development. *ARX* mutations frequently present with X-linked intellectual disability and infantile-onset hand movement abnormalities reported as limb-kinetic apraxia and/or dystonia with pathognomonic grip (Curie et al., 2014, 2018; Friocourt and Parnavelas, 2010). We present electrophysiological studies performed in a previously-reported boy with genetically-confirmed *ARX* mutation who is now 15-years-old and is left-handed (Breen et al., 2018). We aimed to clarify mechanisms underlying abnormal hand movements in patients with *ARX* mutations.

Upper extremity multi-channel surface electromyography (EMG) recorded activities from selected muscles including first dorsal interosseous (FDI) and abductor digiti minimi (ADM) (Fig. 1). At rest, there were spontaneous, distally-predominant, prolonged bursts (2–12 s) including agonist-antagonist co-contractions. These episodes were longer and of higher amplitude in the ADMs than other recorded muscles and were associated with finger posturing. During unsuccessful hand motor tasks, the EMG activities seen at rest had increased duration, amplitude and greater co-contraction and overflow but were not time-locked to commands. Resting ADM activity inappropriately increased and there were smaller and inadequately modulated increases in tonic FDI activity, even during thumb-to-index finger tapping attempts. During left-handed eating with a device to hold a fork, proximally-predominant, largely alternating contractions were followed by the episodes described above including inappropriate ADM and delayed FDI activation during gripping (Fig. 1, Supplementary Video 1). Remarkably, he has learned to use his chin rather than his hand to operate a computer mouse (Supplementary Video 1).

Transcranial magnetic stimulation was delivered using a figure-of-eight coil to the primary motor cortical representation (M1) of the FDI muscles (Supplementary Table 1). Left-M1 GABAergic circuits were dysfunctional as evidenced by absence of short and long-interval intracortical inhibition with normal cortical silent period (CSP). Left-M1 cholinergic circuits (short-latency afferent inhibition) were normal. Right-M1 CSP was short, possibly indicating GABAergic dysfunction. Lack of left hand relaxation precluded motor threshold assessment and further right-M1 assessments. Right-to-left-M1 interhemispheric inhibition (IHI) was absent. Left-to-right-M1transcallosal connectivity was demonstrated by IHI and ipsilateral silent period when stimulating left-M1.

Kinematic analyses during reaching-and-grasping were reported in 13*ARX* patients using infrared light-emitting diodes taped to the dominant hand (Curie et al., 2014). Similar to our patient, hand movements were characterized as loss of index preference, annular dexterity impairment and lack of pronation. A mixture of motor features was reported including upper limb

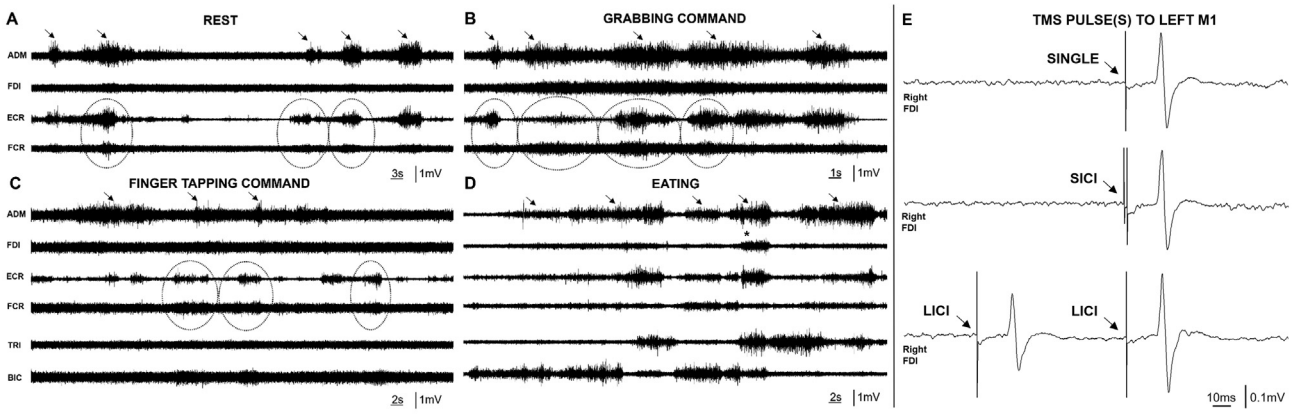

Fig. 1. Selected multichannel surface electromyography (EMG) and transcranial magnetic stimulation (TMS) studies. EMG from selected left upper limb muscles shows co-contraction (dashed circles), overflow and activation at rest and during unsuccessful hand motor tasks. (A) Prolonged ADM (arrows) without significant FDI contractions are present at rest. After (B) grabbing and (C) thumb-to-index finger tapping commands, resting ADM activity inappropriately increases in amplitude and duration (arrows), and there is a smaller and inadequately modulated increase in tonic FDI activity. (D) During spontaneous motor task execution (eating), alternating EMG patterns appear with less co-contraction but persistent ADM (arrows) and delayed FDI activation (asterisk). (E) Right FDI recordings during TMS delivered to left M1 show absent SICI and LICI. Surface EMG signals were amplified, bandpass filtered between 20 Hz and 2.5 kHz, and digitized at 5 kHz. See Supplementary Table 1 for technical details regarding TMS studies. ADM = abductor digiti minimi, FDI = first dorsal interosseous, ECR = extensor carpi radialis, FCR = flexor carpi radialis, TRI = triceps brachialis, BIC = biceps brachialis, M1 = primary motor cortical representation, SICI = short-interval intracortical inhibition, LICI = long-interval intracortical inhibition.

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distal motor apraxia with pathognomonic hand-grip with severity ranging from atypical handling to severe dystonia. The term limb-kinetic apraxia was used given the absent distal movement coordination and loss of independent digital dexterity (Curie et al., 2014).

Our electrophysiological findings are consistent with motor cortical GABAergic and transcallosal disturbances manifesting as distally-predominant inability to learn, initiate and maintain appropriate motor sequences since birth (Kolasinski et al., 2019). Although similar electrophysiological studies are lacking in apraxia, this concept is defined by the loss of previously learned motor patterns. The co-contraction and overflow of muscle activities are consistent with but not specific to dystonia. Moreover, proximal alternating EMG patterns during self-initiated movements suggest some non-dystonic periods during execution of learned motor programs. In conclusion, impaired GABAergic-mediated cortical inhibition might explain the lack of FDI activity and inappropriate ADM activation during gripping in this patient (Friocourt and Parnavelas, 2010; Kolasinski et al., 2019).

Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2019.07.003.

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