A Case of Congenital Hypoplasia of the Left Cerebellar Hemisphere and Ipsilateral Cortical Myoclonus

We describe a case of a 32-year-old woman presenting with intermittent jerks, limited to the left upper limb, starting at age 15. After some years the jerks became constant, present at rest and worse during action and spread to the left leg. They remained stable after age 21. The patient had normal birth and reached all developmental milestones on target. She tended to walk pigeon-toed, and she was clumsy as a child; despite this, she used to play netball at school. Her family history was unremarkable. On examination she had distal, positive, arrhythmic jerks involving the left upper and lower limbs, present intermittently at rest and exacerbated by action and tactile stimuli. Our clinical impression was that of unilateral cortical myoclonus (CM). There was no personal and family history suggesting secondary causes of CM. The electroencephalogram was normal, and brain magnetic resonance imaging was compatible with congenital hypoplasia of the left cerebellar hemisphere, including mild dysplastic features. The magnetic resonance imaging appearance has not changed in 10 years. A combination of clonazepam (1 mg/day) and valproate (600 mg/day) was effective in controlling the jerks, with subjective improvement of 60%.

The most likely cause of unilateral cerebellar hypoplasia and focal dysplasia is a prenatally acquired injury (such as haemorrhage),[1] and we hypothesized that the left hypoplasic cerebellar hemisphere had led to abnormal function in the right sensorimotor cortex, and hence CM, as previously proposed.[2] To investigate this, we tested measures commonly used to confirm the cortical origin of myoclonus, such as somatosensory-evoked potentials (SEP) and long-latency reflexes. We were not able to perform jerk-locked back averaging because of the high frequency of jerks and difficulties in estimating their onset. By using transcranial magnetic stimulation, we assessed the excitability of the primary motor cortex (M1) by measuring short-interval intracortical inhibition (SICI), long intracortical inhibition (LICI) and intracortical facilitation (ICF), sensorimotor interaction using short-latency afferent inhibition, and cerebellar-brain inhibition to test functional connectivity between the cerebellum and contralateral M1. All measures were obtained bilaterally, with the prediction that if any of them were causally linked to the observed myoclonus, they would show an asymmetry. Clinical examination, methods, and results are detailed in the Supporting Information.

The results are summarized in Figure 1. We found bilaterally enlarged SEP and clear peaks in the long-latency reflexes (I and III) recorded from the left abductor pollicis brevis, both indicating a cortical origin of the myoclonus.[3] Interestingly, the increase in SEP was bilateral, suggesting that the jerks were not a necessary consequence of S1 hyperexcitability. The situation is similar to that in dystonia, where changes in S1 excitability can be found by stimulating afferent nerve fibers from unaffected body parts.[4] A likely possibility is that myoclonus arises because this somatosensory abnormality is coupled with decreased SICI, LICI, and short-latency afferent inhibition and increased ICF, all found in the right M1 only. Short-latency afferent inhibition reflects the inhibition that a somatosensory afferent volley exerts on motor-evoked potentials, whereas SICI, LICI, and ICF are thought to represent the function of different systems of neurotransmitters and receptors, that is, GABA-A, GABA-B, and NMDA, respectively.[5] This evidence considered, it is likely that the myoclonus is the result of a global breakdown of inhibitory intracortical mechanisms and an abnormal increase in glutamatergic neurotransmission coupled with a hyperexcitable S1. Moreover, the observation that cerebellar brain inhibition was absent when tested between the left, hypoplasic, cerebellar hemisphere, and the right M1 suggests that a lack of cerebellar inhibitory control over contralateral sensorimotor areas is involved in the pathophysiology of CM. This is consistent with a previously formulated hypothesis based on clinical, pathological, and neuroimaging findings.[2] For instance, cerebellar ataxia is associated with CM in several conditions, such as Ramsay-Hunt syndrome and celiac disease, where pathological findings are mainly located in the cerebellum.[2,6] However, this leaves us with two puzzles: Why did the myoclonus only develop at age 15, and why are the SEP bilaterally enlarged? One possibility is that increased SEP are unrelated to the cerebellar damage. If so, the presence of a hyperexcitable S1 prior to age 15 may have posed no problems because compensatory mechanisms prevented the occurrence of the myoclonus. One source of compensation might be input from cerebellum. Indeed, in healthy subjects, phasic activation of the cerebello-thalamo-cortical pathway using transcranial magnetic stimulation has inhibitory effects on M1 and its interneurons (ie, cerebellar brain inhibition).[7] The delay in the onset of myoclonus suggests that absent input from the left hypoplasic cerebellum could be compensated by other networks until the teenage years. However, during final maturation of cortical circuits, this could no longer be sustained within the right sensorimotor cortex and myoclonus ensued on the left side.

In conclusion, we propose that a decreased cerebellar drive from left cerebellum causes abnormalities in the mechanisms that regulate transmission within the right M1 and that these, combined with abnormal somatosensory transmission, result in CM. Overall, our single case provided a unique opportunity to investigate the pathophysiology of CM. Although no causal evidence is provided, the present findings suggest that

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Relevant conflicts of interests/financial disclosures: Nothing to report.

Received: 17 June 2019; **Revised:** 3 September 2019; **Accepted:** 9 September 2019

Published online 14 October 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27881

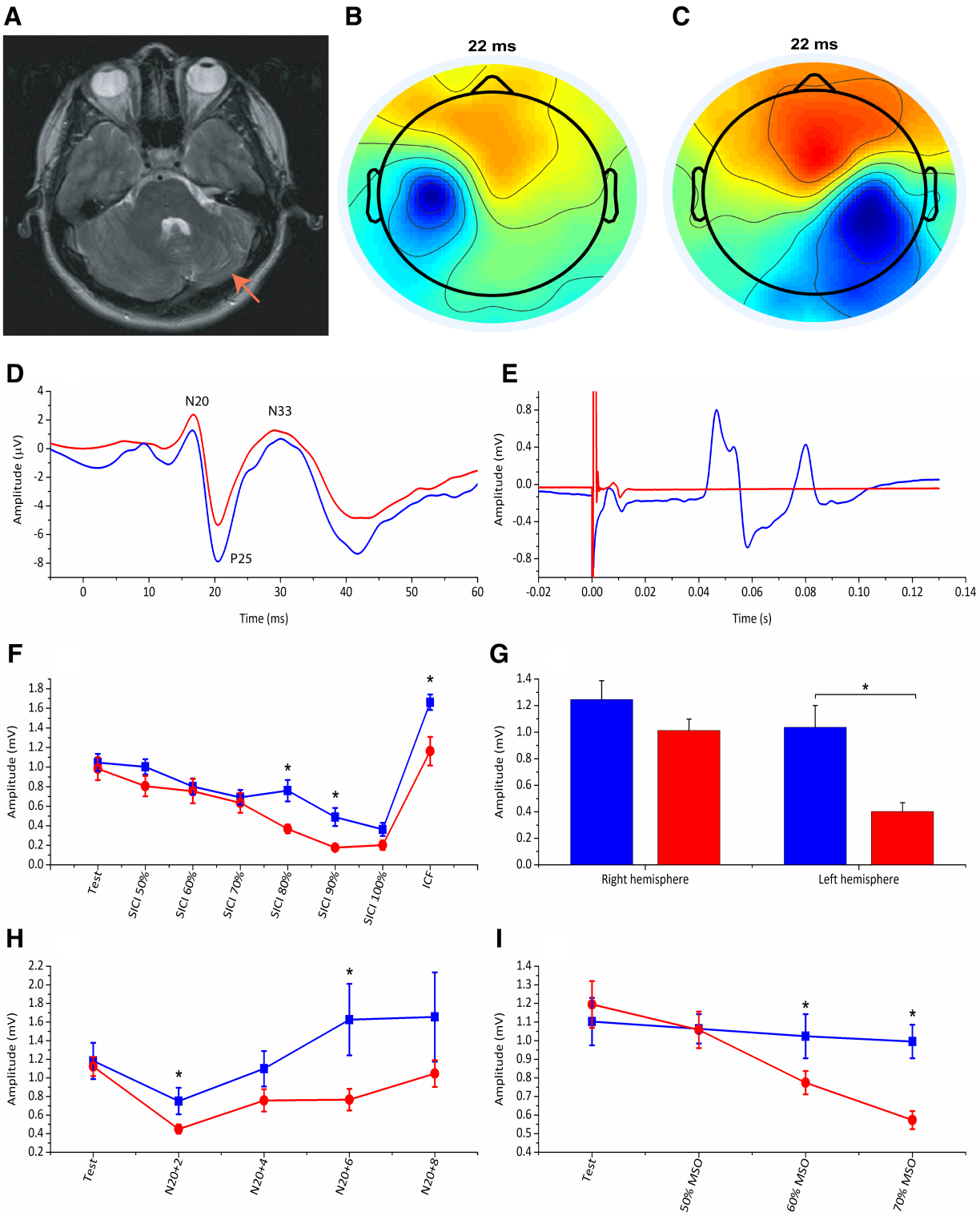

FIG. 1. (**A**) Magnetic resonance imaging section in the transverse plane showing a small left cerebellar hemisphere (red arrow) with an abnormal fissural pattern and a concomitant small left brachium pontis and bony posterior fossa. (**B** and **C**) Topography of the P25 component of somatosensory evoked-potentials at its peak latency (22 ms). The color blue indicates positivity, whereas red indicates negativity. (**D**) Somatosensory-evoked potential traces obtained from the right (electrode CP4, blue line) and left (CP3 electrode, red line) cerebral hemispheres. (**E**) Long-latency reflexes recorded from the left (blue line) and right (red line) abductor pollicis brevis muscles. (**F**) SICI and ICF obtained by stimulation of the right (blue line) and left (red line) cerebral hemispheres. (**G**) LICI. Blue bars indicate test MEP amplitude, and red bars indicate amplitude of conditioned motor-evoked potentials. (**H**) Short-latency afferent inhibition obtained by stimulation of the right (blue line) and left (red line) cerebral hemispheres. (**I**) Cerebellar-brain inhibition obtained by stimulation of the right (blue line) and left (red line) cerebellar hemispheres. ICF, intracortical facilitation; SICI, short-interval intracortical inhibition; MSO, maximal stimulator output. [Color figure can be viewed at wileyonlinelibrary.com]

multiple nodes of a network, including the cerebellum, are involved in the pathophysiology of CM.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Long-Term Safety and Efficacy of 24-Hour Levodopa-Carbidopa Intestinal Gel in Parkinson's Disease

Levodopa/carbidopa intestinal gel (LCIG) 16-hour infusion is safe and improves quality of life, motor, and nonmotor symptoms in Parkinson's disease (PD).[1,2] There are few studies reporting the outcomes of 24-hour LCIG infusion.[3-5] We report 24-hour LCIG infusion safety and efficacy data in a single-center cohort.

Safety outcomes were retrospectively reviewed in all patients treated with 24-hour LCIG infusion from January 2012 to January 2019. The incidence of drug-related adverse events (AEs) was calculated and divided into the 16- and 24-hour LCIG infusion phases of treatment. The efficacy analysis of 24-hour infusion was performed using prospectively collected data in 14 patients (Supporting Information). We used SPSS software (version 23.0; SPSS, Inc., Chicago, IL) and the Wilcoxon signed-rank test to compare continuous variables and the chi-squared test to compare AE frequencies between the two infusion periods. A Bonferroni correction was used to account for multiple comparisons.

Of 99 patients treated with LCIG, 35 received a 24-hour LCIG infusion. Seventy-eight percent were male, and mean (standard deviation) age of PD onset was 52 ± 9 years, with a disease duration of 18 ± 7 years when 24-hour LCIG was commenced. Eighty percent of patients (n = 28) were initially treated with a 16-hour infusion, transitioning to 24-hour therapy after 24 ± 18 months. The remainder (n = 7) were initiated on 24-hour LCIG from oral dopaminergic and/or apomorphine therapy. The indications for a 24-hour infusion were: freezing of gait (FOG) unresponsive to 16-hour infusion (n = 15); nocturnal akinesia (n = 4); troublesome dyskinesias unresponsive to 16-hour infusion (n = 8); and combination of nocturnal akinesia and FOG with or without troublesome dyskinesias (n = 8). Troublesome dyskinesias could be diphasic and/or peak dose. Total L-dopa equivalent daily dose (LEDD) during 16-hour LCIG was 1,955.8 ± 631 mg. After 40 ± 25 months with a 24-hour infusion, total LEDD was 2,538.8 ± 733 mg with a daytime rate of 5.1 ± 1.4 mL/h and nocturnal rate of 3.2 ± 1.4 mL/h. The incidence of de novo AEs that developed during 40 ± 25 months of 24-hour treatment was not significantly different to the incidence of AEs that occurred during 24 ± 18 months of 16-hour therapy, except for the (lesser) incidence of neuropathy (Table 1). There was a significant reduction in total UPDRS Part 4 and complexity of motor fluctuations subscore after 11 ± 2 months of treatment with 24-hour compared with 16-hour infusion (Table 1).

In our study, 24-hour LCIG infusion was well tolerated, with AE rates comparable to a 16-hour infusion. Moreover, additional reduction of motor complications was obtained with a 24-hour infusion in patients transitioned from a 16-hour infusion. The similar risk of AEs may be attributed to our close biochemical and neurophysiological monitoring every 6 to 12 months during 16-hour infusion, which may help reduce further AE risk during 24-hour infusion, in particular neuropathy. Our main study limitation is the lack of blinding and randomization between 16- versus 24-hour LCIG groups to evaluate motor outcomes. In addition, scores for FOG and nocturnal akinesia

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Relevant conflicts of interest/financial disclosures: Nursing salaries for J.G. and D.G. are part funded by unrestricted grants to the Western Sydney Local Health District from AbbVie. V.F. has been on paid Advisory Boards for AbbVie. J.G. has received travel grants and speaking honoraria from AbbVie. Full financial disclosures and author roles may be found in the online version of this article.

Received: 26 June 2019; **Accepted:** 5 September 2019

Published online 11 October 2019 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.27883