Abnormalities of Eye–Hand Coordination in Patients with Writer’s Cramp: Possible Role of the Cerebellum

Ketan Jhunjhunwala 1,2, Raviteja Kotikalapudi 2, Abhishek Lenka 1,2, Kandavel Thennarassu 3, Ravi Yadav 1, Jitender Saini 4 & Pramod Kumar Pal 2*

1 Department of Clinical Neurosciences, National Institute of Mental Health & Neurosciences, Bangalore, Karnataka, India, 2 Department of Neurology, National Institute of Mental Health & Neurosciences, Bangalore, Karnataka, India, 3 Department of Neurobiotics, National Institute of Mental Health & Neurosciences, Bangalore, Karnataka, India, 4 Department of Neuroimaging & Interventional Radiology, National Institute of Mental Health & Neurosciences, Bangalore, Karnataka, India

Abstract

Background: Writer’s cramp (WC) is one of the commonly observed focal dystonias. The pathophysiology of WC has not been fully understood. The role of the cerebellum is crucial for maintaining accurate eye–hand coordination (EHC), its role in the pathogenesis of WC can be investigated by studying the EHC in patients with WC.

Methods: Fifteen patients with WC (women:men, 3:12) and 15 age- and gender-matched controls performed oculomotor and EHC tasks. A visually guided stimulus (VGS) task was first performed with eye-only condition (EOC) and then with EHC.

Results: A significant interaction between the groups (controls and patients) and tasks (EOC and EHC) with age as a covariate confirmed that the two groups reacted differently to the tasks in saccadic latency (F(1,27)=4.8; p=0.039) and average saccade acceleration (F(1,27)=10.6; p=0.003). The curvature index of acceleration of the hand was significantly more in patients compared to controls (patients vs. controls, 2.4±0.4 vs. 1.8±0.2, p=0.01). While performing the EHC task, there was a significant correlation of the Writer’s Cramp Rating Score with the average saccadic speed (−0.61, p=0.016), peak saccadic deceleration (0.59, p=0.019) and average saccadic acceleration (−0.63, p=0.012).

Discussion: Saccadic acceleration and latency are abnormal while performing EHC tasks in patients with WC. Our study gives further insights into the possible role of the cerebellum in the pathogenesis of WC.

Keywords: Writer’s cramp, focal dystonia, eye–hand coordination, cerebellum

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* To whom correspondence should be addressed. E-mail: palpramod@hotmail.com

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Introduction

Dystonias are a heterogeneous group of disorders characterized by sustained or intermittent muscle contractions that result in involuntary posturing or repetitive movements.1 Focal dystonia (FD), such as writer’s cramp (WC), is one of the most frequently observed dystonias. WC is defined as involuntary muscular contractions when the patient writes, resulting in occasional pain and difficulty in controlling the pen.2 The pathophysiology of dystonia has been attributed to the basal ganglia and its connections, especially to the supplementary motor area (SMA).3 Although the evidence pointing towards the basal ganglia as a cause of dystonia has been robust, the cerebellum has also been implicated as one of the important structures in its causation.4 Filip et al. in their recent study in patients with cervical dystonia, which is a type of FD, have shown a miscommunication between the basal ganglia and cerebellar loops as the cause of dystonia.5 Evidence from animal6 and human studies based on the analysis of gait7 and eye blink8 suggest that FDs may have a cerebellar pathophysiology.

Eye–hand coordination (EHC) refers to the ability to produce goal-oriented hand actions that are guided by visual information from the eyes.9
A number of studies have highlighted the role of the cerebellum in maintaining the EHC. Miall and Reckess\textsuperscript{10,11} highlighted the role of the cerebellum in coordinated movements through functional imaging, lesion studies, and electrophysiological recordings. A limited number of studies have explored eye movement abnormalities in patients with dystonia. In a study using a saccade adaptation task, Hubsch et al.\textsuperscript{12} had reported impaired saccadic adaptation in patients with DYT1 dystonia. Another study by Shaikh and colleagues\textsuperscript{13} on patients with cervical dystonia revealed longer voluntary head saccades. To the best of our knowledge, currently there are no studies in WC demonstrating the abnormalities in the EHC. As the cerebellum is crucial for accurate EHC, studying EHC in patients with focal dystonias such as WC may help in assessing the involvement of the cerebellum in the pathogenesis of WC.

To explore the subclinical cerebellar dysfunction in FD, we evaluated patients with WC and performed experiments on eye movements and combined EHC. In the current study, visually guided stimulus (VGS) and EHC paradigms are used to explore the existence of saccadic abnormalities in patients with WC, if any, and to identify kinematic changes in visually guided hand pointing tasks.

Methods

Clinical evaluation

The study was conducted on 15 patients with WC (women: men, 3:12) in the Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, and 15 age- and gender-matched healthy controls. WC was diagnosed by a single movement disorder specialist (P.K.P.) based on history, neurological examinations, and detailed observation of writing. Dystonia was specifically looked for in all the fingers, outstretched hands, wrist, elbow, shoulder, and trunk. In addition, it was evaluated when the patients performed the finger–nose test. Each patient and control was evaluated while writing first with the dominant hand and later with the non-dominant hand. Observation for the presence of mirror dystonia was made when the patients wrote with the non-dominant hand. As anti-dystonic medications may have an effect on eye movements,\textsuperscript{14} these medications were stopped in all patients 1 week prior to their appointment for the experiments. Controls were included in the study after confirming that there was no family history of tremor, writing problems, dystonia, and Parkinson’s disease. Handedness was assessed using the Edinburgh Handedness Inventory (EHI) scale. All the subjects provided written informed consent for participation in this study and the institute Ethics Committee approved the study.

Evaluation of writing

Assessment of writing was done by observing the patients writing on plain white paper using a pen. Each patient was instructed to write alphabets, numbers, and a sentence, first in their mother tongue and then in English. Later, the patients were asked to write with the non-dominant hand. Severity of writing difficulty and dystonia were also assessed in all patients using the Writer’s Cramp Rating Scale (WCRS).\textsuperscript{15}

Experimental paradigms

The experiment was designed using the Experiment Center Software (SensoMotoric Instruments GmbH, Teltow, Germany). Stimuli were presented on a 21-inch LCD monitor (DELL Ltd., Round Rock, TX, USA). Each patient sat on a chair approximately 50 cm in front of a screen with his or her head fixed comfortably on a chinrest. An IVIEW X HI-SPEED eye tracker (SensoMotoric Instruments GmbH) was used to record the patient’s eye movements while he/she performed the tasks. The sampling rate was set at 1250 Hz with the accuracy rate less than 1 degree and the spatial resolution about 0.01 degree. The task was a visually guided stimuli (VGS) task in which a single circle about 1 degree (0.94°) in sight was randomly displayed in the background with a maximum horizontal amplitude of 17 degrees from the central fixation. The position of the dot was randomized and the duration of the dot’s display was also randomized between 1000 ms and 2000 ms with no intervals between two dots. The patient was told to fixate on the black dots, leading to guided saccades as the positions of the dots changed.

At first, the patients’ data were recorded with “eye-only condition” (EOC), i.e. subjects performed only the eye task. Later, eye and hand data were recorded when the subjects were performing the eye movements along with the hand movements of touching the target, i.e. the EHC task. There were 10 practice trials and 100 formal trials (the practice trials were not included in the analyses). Saccade duration was detected with a velocity threshold of 40 degrees per second (°/second) and recorded automatically by the BeGaze software (SensoMotoric Instruments GmbH, Germany) (Figure 1).

Hand movements were recorded with the Zebris system (Zebris Medizintechnik, Isny, Germany) at a sampling rate of 500 Hz. The system helps to determine the position (specified by three values, \( r = (x, y, z) \)) of an ultrasound-emitting marker relative to an array of three receivers. The calibration and the subsequent analysis of the hand data were done using a program written using the Matlab programming language (Mathworks Matlab R2013a).

The following parameters were recorded during each saccade for both EOC and EHC:

1) saccadic latency calculated in ms
2) saccadic gain calculated as
   \[
   \text{amplitude of the first saccade to the target} \\
   \text{actual distance in degree from the point of fixation to the actual target}
   \]
3) peak velocity calculated as \( \text{°/second} \)
4) average speed calculated as \( \text{°/second} \)
5) peak acceleration calculated as \( \text{°/second}^2 \)
6) peak speed calculated as 
   \[
   \text{time taken to reach the peak speed while performing the paradigm}
   \text{time taken to complete the paradigm}
   \]
7) Asymmetric Acceleration Index (AAI) calculated as 
   \[
   \frac{|\text{peak acceleration} - |\text{peak deceleration}|}{|\text{peak acceleration} + |\text{peak deceleration}|}
   \]
The following parameters were analyzed for the hand movements:
1) maximum velocity calculated in meters/second
2) maximum velocity time calculated as time taken to reach maximum velocity in ms
3) acceleration time calculated as time taken to reach maximum acceleration in ms
4) deceleration time as time taken to reach maximum deceleration in ms
5) ballistic period – acceleration time + deceleration time
6) curvature index of acceleration and deceleration was derived as described by Deuschl et al.16

Statistics

SPSS Version 21 was used for analysis, with the t test being used for continuous variables and the chi square test for categorical variables. The statistical level of significance was set at p<0.05. Correlation analysis was done using the two-tailed Pearson’s correlation test.

The parameters were analyzed with repeated-measures analysis of variance for the between-subjects factors (patients vs. controls) and tasks (EOC vs. EHC).

Results

The subjects included 15 patients with WC (women:men, 3:12) and 15 gender- and age-matched controls. All the patients and controls were right handed. The mean age of the patients and controls did not differ significantly (38.6 ± 11.2 years vs. 35.6 ± 9.2 years, p=0.09). The mean duration of illness was 7.9 ± 5.5 years.

Clinical features

Difficulty while writing was the chief presenting symptom in all patients. Other symptoms included pain during writing in 10 (66.6%) and twisting of hand in four (26.6%). The mean WCRS score was 14.1 ± 3.4. Details of the profiles of occupation were carefully recorded for all patients. Writing was an essential part of the professional life of the majority of the patients, which comprised three (20%) students, three (20%) teachers, and six (40%) government officers and clerks. One patient had a family history of WC and one of cervical dystonia.

Medication details

In our cohort, four patients (26.6%) were not on any treatment for WC. Among those on treatment, trihexyphenidyl alone was the most commonly used drug (four patients, 26.6%) followed by trihexyphenidyl in combination with baclofen (two patients, 13.3%), and propranolol alone (two patients, 13.3%). Other patients were on tetrabenazine alone (one patient, 6.7%), a combination of trihexyphenidyl and clonazepam (one patient, 6.7%), and a combination of trihexyphenidyl and prazosin (one patient, 6.7%). All patients were counseled for behavioral therapy and botulinum toxin injections. Two patients (13.3%) opted for the botulinum toxin injection after counseling.
Pattern of dystonia while writing

While writing, the following abnormalities were noted:

1) wrist involvement: 10 patients (66.6%)
   a) extension: six patients (60%)
      • only extension: three patients
      • extension with ulnar deviation: two patients
      • extension with radial deviation: one patient
   b) flexion: four patients (40%)
      • only flexion: one patient
      • flexion with ulnar deviation: one patient
      • flexion with radial deviation: two patients
2) thumb involvement: 10 patients (66.6%)
   • excessive flexion: eight patients
   • excessive extension: two patients
3) index finger involvement: five patients (33.3%)
   • excessive flexion: three patients
   • excessive extension: two patients
4) middle finger involvement: two patients
5) shoulder, ipsilateral shoulder elevation: four patients (26.6%)
6) elbow involvement
   • normal: 11 patients (73.3%)
   • extension: three patients (20%)
   • flexion: one patients (6.7%)

Mirror dystonia of the dominant hand while writing with the non-dominant hand was seen in eight patients (53.3%).

Eye tracking tasks

Saccadic latency. The saccadic parameters are summarized in Table 1. In the control group, the mean saccadic latency while performing the EHC task was significantly shorter than that when performing the EOC task (173.4 ± 15.4 vs. 232.8 ± 77.1 ms, p = 0.008). In the patient group, the mean saccadic latencies during these two tasks were not different (EHC, 293.8 ± 51.7; EOC, 295.8 ± 43.4 ms, p = 0.79) (Figure 2A). There was a significant interaction between the groups (controls and patients) and the effectors (EOC and EHC) (F(1,28) = 9.3; p = 0.005). This interaction effect further confirms the fact that the saccadic latencies of the controls reacted differently to the two tasks (EOC and EHC), while the same was not seen with the patients.

Average saccadic acceleration. In the control group, the mean of the average saccadic acceleration while performing the EHC task was significantly higher than that when performing the EOC task (13441.4 ± 2330.8 vs. 10995.6 ± 3069 ˚/s², p = 0.008). However, in the patient group, the means of the average saccadic acceleration during these two tasks were not significantly different (EHC, 9434.3 ± 31273.6; EOC, 9016.1 ± 2734.6 ˚/s², p = 0.12) (Figure 2B). There was a significant interaction between the groups (controls and patients) and the effectors (EOC and EHC), implying that the two groups reacted differently to the tasks (F(1,28) = 17.8; p < 0.0001). There was no significant main effect or interaction for other saccadic parameters such as amplitude, accuracy rate, peak velocity, peak acceleration and peak deceleration.

Hand kinematics results

The results on the hand kinematic task are given in Table 2. The curvature index of acceleration was significantly more in patients than in controls (patients vs. controls, 2.3 ± 0.8 vs. 1.9 ± 0.3, p = 0.02).

Correlations

There was a significant correlation between the WCRS and the following saccadic parameters on the EHC task:

1) WCRS and average saccade speed (−0.61, p = 0.016)
2) WCRS and peak saccade deceleration (0.59, p = 0.019)
3) WCRS and average saccade acceleration (−0.63, p = 0.012)

There was no significant correlation between the WCRS and the saccadic parameters on the EOC task and between WCRS and the hand parameters on the EHC task.

Discussion

In this study, we have demonstrated abnormalities in the EHC, which is presumably fine-tuned by the cerebellum in patients with WC. The pathophysiology of focal hand dystonia (FHD) has been explained as abnormal patterns of activity at multiple levels within the sensorimotor network. The important mechanisms identified in the pathogenesis of FHD are deficient inhibition, abnormal sensation and sensorimotor processing, and maladaptive plasticity.17 According to various functional and structural neuroimaging studies, the pathophysiology of FHD has been attributed to various basal ganglia structures.18,19 The role of the cerebellum in the pathophysiology of dystonia is highlighted by Filip et al.4 in a comprehensive review. Structural neuroimaging studies in WC have also shown the involvement of the cerebellum.20 Functional neuroimaging studies have shown abnormal cerebellar activation in WC patients observed during writing21 and a taping task.22 Prudente et al.23 in their post-mortem study of four patients with cervical dystonia reported a patchy loss of Purkinje cells with reduced density, areas of focal gliosis, and torpedo bodies in the cerebellum.

EHC refers to the ability to produce goal-oriented hand actions that are guided by visual information from the eyes. Various studies have highlighted the role of the cerebellum in EHC. Vercher et al.24 in their study on baboons highlighted the role of the cerebellum in the EHC. Later, Miall et al.10 in a functional magnetic resonance imaging study on humans reported an increase in the activity of the cerebellum during the EHC task as well as independent eye and hand coordination tasks. In their study, Miall and colleagues reported a positive interaction between EHC tasks and independent eye and hand tracking tasks in the bilateral lateral cerebellum (lobule V and VI), bilateral precuneus, right prefrontal area, and Brodmann areas 32 and 18. Their results suggested a separate EHC network or involvement of more areas in the EHC task. Miall and Reckess11 later highlighted the role of the cerebellum in coordinated movements through functional...
imaging, lesion studies, and electrophysiological recordings. In our study, we have used VGS and visually guided hand movement paradigms to explore the role of the cerebellum in patients with WC.

The neurophysiological role of the cerebellum in FD has been previously explored. Teo et al. 8 by performing eye blink conditioning (EBC) in 12 patients with FD (seven cervical dystonias, five FHD), and eight healthy controls provided neurophysiological evidence of cerebellar involvement in patients with FHD. Sadnicka et al. 25 performed classical EBC response in patients with DYT1 and DYT6 genetic mutations. In their study, patients with DYT1 and DYT6 had normal ability to acquire conditioned responses, but blink reflex recovery was enhanced in patients with DYT1. Their observations in patients with DYT6 mutations were contrary to the EBC responses in other FDs, suggesting that the cerebellum may have a distinct role only in different subsets of dystonia. Kojovic et al. 26 in a study between primary and secondary dystonias explored the neurophysiological changes using the eye blink conditioning paradigm. Patients with secondary dystonia had a normal EBC, whereas patients with primary dystonia had reduced EBC compared with controls. The above findings suggest dystonia to be a motor symptom, reflecting different pathophysiological states triggered by a variety of insults.

The normal functioning of the medio-posterior cerebellum (MPC) is required for accurately orienting the gaze toward a visual target. 27,28

| Table 1. Summary of Saccadic Parameters between Patients and Controls |
|---------------------------------------------------------------|
| **Saccadic Parameters**                                      | **Patients** | **Controls** |
| Peak speed (°/second)                                         |              |              |
| Eye only                                                      | 396.4±126.4  | 364.6±59.3   |
| Eye-hand                                                      | 454.8±122.4  | 475.7±74.6   |
| Peak speed at                                                 |              |              |
| Eye only                                                      | 0.41±0.17    | 0.42±0.09    |
| Eye-hand                                                      | 0.42±0.13    | 0.36±0.08    |
| Average speed (°/second)                                      |              |              |
| Eye only                                                      | 217.1±33.1   | 220.6±38.3   |
| Eye-hand                                                      | 253.7±53.9   | 245.9±55.9   |
| Peak acceleration (°/second²)                                 |              |              |
| Eye only                                                      | 16320.4±4339 | 16477±4099.4 |
| Eye-hand                                                      | 19554.6±5792.3 | 21852.8±2497.7 |
| Peak deceleration (°/second²)                                 |              |              |
| Eye only                                                      | –14873±6201  | –12935.2±2227.5 |
| Eye-hand                                                      | –16477.8±5372.6 | –17107±3738.8 |
| Average acceleration (°/second²)                              |              |              |
| Eye only                                                      | 9016.1±2734.6 | 10995.6±3069  |
| Eye-hand                                                      | 9434.3±31273.6 | 13441.4±2330.8 |
| Asymmetric Acceleration Index                                 |              |              |
| Eye only                                                      | 1831.5±6990.4 | 3416.6±3116.6 |
| Eye-hand                                                      | 2999.7±4637.3 | 4746.7±2742.4 |
| Saccadic gain                                                 |              |              |
| Eye only                                                      | 0.76±0.11    | 0.83±0.40    |
| Eye-hand                                                      | 0.82±0.15    | 0.80±0.14    |
| Saccadic latency (ms)                                         |              |              |
| Eye only                                                      | 293.8±51.7   | 232.8±77.1   |
| Eye-hand                                                      | 295.8±43.4   | 173.4±15.4   |

Abbreviations: ms, Milliseconds.

1Significant interaction between the groups (controls and patients) and the effectors (EOC and EHC) with age as covariate, F(1,27)=10.6; p=0.003.
2Significant interaction between the groups and the effectors with age as covariate, F(1,27)=4.8; p=0.039.
oculomotor vermis that are located in the vermal lobules VIc–VII and the two caudal fastigial nuclei (cFNs). The cFNs are the output areas by which the MPC influence the accuracy of a visual target. Quinet and Goffart in their latest study on head-restrained monkeys proved the role of the cerebellum in controlling saccadic parameters such as latency, velocity, and acceleration by its fastigial projections towards the pontomedullary reticular formation. In our patients with WC, VGS were normal when performed without hand movements. There was a significant interaction in the saccadic latency in patients while performing the EOC and EHC tasks. In controls, while performing the EHC task, the saccadic latency significantly reduced. This reduction in saccadic latency is in agreement with the normal findings reported in human subjects. In our study, WC patients did not have a reduction in the saccadic latency while performing the EHC task. It is well known that there is a coupling of the eye and hand movements when pointing to, aiming at, or reaching a peripheral target. However, since we did not calculate the latency of the hand movements from the display of the visual target, it is not possible to determine whether this increased latency is a result of a delay in initiating the saccade or a delay in initiating the hand movement or both. Gopal and Murthy in their study on latency of the saccades and hand motor system have documented the existence of a dedicated circuit for the EHC. Since there was a failure in reduction of saccadic latency in patients with WC during EHC, we propose that there may be an involvement of this circuit in WC patients.

While performing VGS with hand movements, the average saccade acceleration was less in WC patients with a significant interaction between and EOC and EHC tasks. The role of the cerebellum (vermal lobules VIc–VII) in controlling the acceleration of the saccades has been well documented by Quinet and Goffart. In a recent meta-analysis on the functional topography of the cerebellum, Stoodley and Schmahmann have reported the role of lobule VI of the cerebellum in performing spatial tasks such as EHC. Delmaire et al. in their voxel-based morphometry study in WC reported lobule VI of the cerebellum to be atrophied compared with controls. Our finding is in agreement with the structural imaging study in WC, further suggesting the involvement of the cerebellum through neurophysiological techniques.

The cerebellum is known to be involved in the coordination of multi-joint movements as it regulates the activation of different muscles involved in movement. The curvature index is known to increase in conditions affecting the cerebellum. We noted that the curvature index of acceleration was more in WC patients than in controls, implying that the path taken by the patients to reach the maximum velocity was significantly more than controls.

In our study, the patients with WC while performing the EHC task had a significant negative correlation of their WCRS scores with 1) the average saccadic acceleration, and 2) the speed of the saccades. These results suggest the involvement of EHC circuits, which govern the saccadic acceleration and velocity (bilater al lateral cerebellum (lobule VI)) to be impaired in patients with WC and determine the severity of the disease.

![Figure 2. Graphical Presentation of the Marginal Means of Saccadic Latency and Saccadic Acceleration while Performing the Tasks Related to the Experimental Paradigms.](image)

(A) Graph showing the estimated marginal means of the latency of the saccades of patients with writer’s cramp and healthy controls while performing eye only condition (EOC) and eye–hand condition (EHC). Error bar, ±1 standard error of mean (SEM).

(B) Graph showing the estimated marginal means of the average saccadic acceleration of the saccades of writer’s cramp patients and healthy controls while performing EOC and EHC. Error bar, ±1 SEM.

Table 2. Summary of the Hand Kinematics between Patients and Controls

| Hand Parameters          | Patients       | Controls       | p   |
|--------------------------|----------------|----------------|-----|
| Maximum velocity (m/sec) | 0.78±0.22      | 0.72±0.16      | 0.38|
| Maximum velocity time (ms)| 4625±1157.3    | 8020±9027.35   | 0.075|
| Acceleration time (ms)   | 203.33±115.7   | 130.83±50.2    | 0.078|
| Deceleration time (ms)   | 300.8±94.9     | 235.8±65.7     | 0.336|
| Ballistic period (ms)    | 504.1±167.4    | 366.7±44.2     | 0.071|
| CI of acceleration¹      | 2.3±0.8        | 1.9±0.3        | 0.021|
| CI of deceleration       | 15.6±4.4       | 14.7±3.6       | 0.536|

Abbreviations: CI, Curvature Index; ms, Milliseconds; m/sec, Meter/second.
Low-frequency repetitive transcranial magnetic stimulation over the premotor cortex is reported to have significant improvement in patients with FHD.54 Hiroka et al.55 reported that cerebellar Repetitive Transcranial Magnetic Stimulation (rTMS) evokes a long latency motor response during a VGS task. Through the preliminary findings in our study and previously published literature on the role of rTMS in focal dystonias, cerebellar rTMS as a therapeutic tool can be further studied in patients with WC.

We recognize a few limitations in this study. The small sample size of our study is one of the limitations because of which findings of this study cannot be generalized for all patients with WC. In addition, the patients with WC were of varied clinical phenotype due to involvement of different muscles while writing, further diluting our results. We could not calculate the latency of the hand movements from the display of the visual target because of technical limitations, which could have provided accurate insights into the EHC abnormalities in the patient cohort. The results in our study were not corrected for multiple comparisons for the various eye and hand parameters. Hence, future studies need to confirm our results in a larger cohort of WC patients.

**Conclusion**

To conclude, we have explored the pathophysiology of WC through evaluation of eye movements and EHC and found definite abnormalities in the latter. The expected reduction of saccadic latency and increase in average saccadic acceleration while performing the EHC task seen in healthy subjects was not observed in patients with WC. Although saccadic abnormalities in patients with WC cannot be exclusively attributed to cerebellar dysfunction, our study certainly provides preliminary evidence for the involvement of the cerebellum in the pathogenesis of this complex disorder. Nonetheless, future studies on a larger number of patients are needed to confirm our results.

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