Brainstem Reflexes in Idiopathic Cervical Dystonia: Does Medullary Dysfunction Play a Role?

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ABSTRACT: Background: Neurophysiological markers in dystonia have so far not been systematically applied in clinical practice due to limited reproducibility of results and low correlations with clinical findings. Exceptions might be represented by the blink reflex (BR), including its recovery cycle (BRRC) and the trigemino-cervical reflex (TCR) which, compared to other neurophysiological methods, have shown more consistent alterations in cervical dystonia (CD). However, a comparison between the two techniques, and their possible correlation with disease symptoms, have not been thoroughly investigated.

Objectives: To assess the role of BR, BRRC and TCR in the pathophysiology of idiopathic cervical dystonia.

Methods: Fourteen patients and 14 age-matched healthy controls (HC) were recruited. Neurophysiological outcome measures included latency of R1 and R2 components of the BR, R2 amplitude, BRRC, latency and amplitude of P19/N31 complex of TCR. Clinical and demographic features of patients were also collected, including age at disease onset, disease duration, presence of tremor, sensory trick and pain. The Toronto Western Spasmodic Torticollis Rating Scale was used to characterize dystonia.

Results: Compared to HC, CD patients showed increased latency of the BR R2 and decreased suppression of the BRRC. They also showed increased latency of the P19 and decreased amplitude of P19/N31 complex of TCR. The latency of P19 component of TCR was positively correlated with disease duration.

Conclusions: We propose that the increased latency of R2 and P19 observed here might be reflective of brainstem dysfunction, mediated either by local interneuronal excitability changes or by subtle structural damage.

Dystonia is a pathological condition of the central nervous system characterized by sustained or intermittent involuntary activity of muscles, which determines abnormal movements and postures.1 A number of electrophysiological abnormalities have been demonstrated in dystonia, the most common being loss of inhibition, alterations of synaptic plasticity and sensory dysfunction.2–5 However, limited reproducibility of these results has led some researchers to question their role as markers of dystonia.6,7 Additionally, due to the fact that correlations between neurophysiological and clinical findings have rarely been confirmed, the pathophysiology of dystonia is still debated.

Previous studies about electrophysiological features in cervical dystonia (CD) found controversial results. Excessive cortical plasticity was related to greater severity of motor symptoms in one study,8 whereas others showed that abnormal cortical plasticity occurs also in cortical motor areas that are not related to body parts affected by dystonia.9–11 Similarly, the majority of studies investigating cortical inhibitory circuits with transcranial magnetic stimulation (TMS) showed altered cortical excitability, irrespective of the clinical manifestations of dystonia,12–14 whereas some authors found a degree of lateralization corresponding to the direction of head deviation.15 Other markers, such as somatosensory temporal discrimination...
threshold (STDT), thought to reflect inhibition in the primary somatosensory cortex, and spatial discrimination threshold (SDT), have been found to be abnormal in patients with CD, again irrespective of the distribution and severity of motor symptoms.

Differently, some electrophysiological techniques assessing brainstem circuitry gave possibly more informative results. Several studies demonstrated a lack of paired-pulse inhibition of the R2 component of the blink reflex and abnormal trigemino-cervical responses (TCR) in CD, but not in focal hand dystonia. Therefore, unlike derangements in cortical plasticity and inhibition, these markers showed abnormalities related only to the body part affected by dystonia. However, a comparison between the two techniques, and their possible correlation with disease symptoms, including side, duration and severity of dystonia, have not been systematically investigated. Further investigation in this regard would be important also in the light of recent imaging and neuropathological data suggesting a direct involvement of the brainstem in the pathophysiology of cervical dystonia.

The present study aimed to revisit the role of brainstem circuitry in CD by assessing the blink reflex, its recovery cycle (BRRC) and the TCR bilaterally in the same group of patients with CD, as well as in matched healthy control (HC). Additionally, possible correlations between neurophysiological and clinical data were investigated.

Materials and Methods

Subjects

Fourteen patients (9 female and 5 male, 61.0 ± 8.5 years old, range 45–71) and 14 sex- and age-matched HC (9 female and 5 male, 56.0 ± 11.2 years old, range 42–81) participated in the study. All patients were enrolled in the Movement Disorders outpatient’s clinic of the University Hospital of Verona, and presented with idiopathic CD; the diagnosis was made according to the international classification of dystonia. Standard magnetic resonance imaging investigation ruled out causes of secondary dystonia. All patients were not on any medication for their dystonia, except for botulinum toxin injections; their neurophysiological and clinical assessment was performed just before treatment, to exclude any carry-over effects from previous treatments. The study protocol was approved by the local ethics committee and all subjects gave their written informed consent prior to testing.

Clinical Evaluation

Patients’ and disease characteristics, including age at onset, disease duration, presence of tremor and sensory trick were collected. Pain was investigated by the pain visual analogue scale (VAS) and dystonia was assessed by means of the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS). Results are shown in Table 1.

### Table 1 Clinical and demographic characteristics of the subjects recruited

| Variables                  | Patients | Healthy Controls |
|----------------------------|----------|------------------|
| Age (y)                    | 61 (± 8.48) | 56 (± 11.19)     |
| Gender (M:F)               | 5:9      | 5:9              |
| Duration (y)               | 13.21 (± 7.58) | –              |
| Age at onset (y)           | 47.07 (± 9.15) | –              |
| TWSTRS (mean)              | 18.88 (± 11.46) | –              |
| Clinical presentation      | Torticollis (100%) | –              |
|                           | Laterocollis (64%) | –              |
|                           | Anterocollis (35%) | –              |
|                           | Retrocollis (14%)  | –              |
| Pain intensity (VAS)       | 2.29 (± 3.31) | –               |
| Sensory trick (%)          | 71%      | –               |
| Head tremor (%)            | 58%      | –               |

Neurophysiological Investigations

Both patients and controls underwent recording of BRRC and TCR in a single experimental session. All recordings were performed in a silent room. For BRRC recording participants were comfortably seated on a chair with supports for neck, head and arms. During TCR recording, subjects were lying on a bed and were asked to hold their head slightly raised, in middle position, to activate the sternocleidomastoid (SCM) bilaterally. Electromyography (EMG) was recorded using a NeMus amplifier (EBNeuro, Florence, Italy), through 9-mm-diameter Ag–AgCl surface cup electrodes. Signals were amplified (gain 10000X), filtered (bandpass 3–2000 Hz) and digitally sampled (5 kHz).

To record the BRRC, the left supraorbital nerve was stimulated with square wave pulses of 200 μs duration at three times the motor threshold, defined as the lowest intensity able to evoke at least five R2 responses in 10 consecutive trials. Single or double pulses were given randomly at interstimulus intervals (ISI) of 100, 200, 300 and 500 ms and at an inter-trial interval of 30 ± 10 s to minimize habituation. Ten trials for each ISI were collected. EMG activity was recorded from the right and left orbicularis oculi muscles, with the active electrode placed over the lower lid, the reference electrode 2 cm lateral to the outer canthus and the ground electrode over the forehead. Recorded activity was DC-corrected, rectified, and averaged. The latency of the early ipsilateral (R1) and late bilateral (ipsilateral, iR2, and contralateral, cR2) component, as well as the area of R2 component were measured. The recovery cycle was defined by the R2 area ratio (R2 area of the conditioned response divided by the R2 area of the unconditioned response) for each ISI.

The TCR was performed according to the protocol used by Di Lazzaro and colleagues. Twenty-five 120 square wave pulses (100 μs duration, 3 Hz frequency) were applied to the infraorbital notch to stimulate the maxillary nerve bilaterally in two different blocks. The intensity of the stimulation was set at three times the somatosensory threshold. EMG activity was recorded from both SCM muscles with the active electrode placed on the muscle belly, roughly 8 cm above the reference electrode, which was put on the clavicle, close to the insertion point of the sternocleidomastoid muscle; the ground electrode was placed on

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the sternum. Recordings were performed during a tonic contraction of the SCM, during flexion of the head at 30°. The latency of the p19 and n31 components, as well as the peak-to-peak amplitude of P19/N31 complex, were measured and entered the statistical analysis.

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS software version 24.0 (Chicago, IL). Results are expressed as mean ± standard deviation. Age and gender were compared between CD and HC by means of an unpaired t-test and a chi-square test, respectively. The Shapiro–Wilk test was used to assess normality of distribution of electrophysiological variables. Since it yielded negative results, analysis of variance (ANOVA) or covariance (ANCOVA) were performed, compound symmetry was assessed by testing sphericity with the Mauchly’s test. The Greenhouse–Geisser correction was used to compensate for non-spherical data. A one-way between-group ANOVA with factor “group” (CD, HC) was performed to evaluate the difference of the latency of the R1 component of the BR. Electrophysiological variables related to the BR, BRRC and TCR were analyzed by means of ANCOVAs, using the presence of sensory trick and tremor as covariates. The former was investigated since an association between sensory trick and BRRC suppression had been suggested, whereas the role of the latter was assessed since recent evidence supported the existence of different sub-phenotypes of CD, based on characteristics of involuntary movements (slow/tonic vs. tremulous). Therefore, to evaluate possible differences in the latency and area of the BR R2 following single pulse stimulation, two mixed ANCOVAs with factors “group” (CD, HC) and “recording side” (iR2, cR2), and the presence of sensory trick and tremor as covariates, were performed. Two separate mixed ANCOVAs (one for each recording side) with factors “group” (CD, HC) and “ISI” (100, 200, 300 and 500 ms), and the presence of sensory trick and tremor as covariates, were used to test differences between groups on R2 ratio. To investigate possible differences in the latency of P19 and N31 components of TCR, as well as the peak-to-peak amplitude of P19/N31 complex, three separate mixed ANCOVA with “group” (CD, HC), “recording side” (ipsilateral, contralateral) and “stimulation side” (left, right) as factors of analysis, and the presence of sensory trick and tremor as covariates, were performed. In case the ANCOVAs did not show

![Example traces from representative subjects. Panel A: BR from a CD patient. Panel B: BR from a HC. Panel C: TCR from a CD patient. Panel D: TCR from a HC.](image-url)
any significant effects of “recording side” and “stimulation side” all
responses were grouped together as single distributions and under-
went similar ANCOVAs, this time using only the factor “group” and the mentioned covariates. The rationale for pooling responses
was based on the observation that the TCR is little influenced by
stimulation or recording side.27,33,37 For post hoc comparisons a
t-test with Bonferroni correction was used. Correlation analysis
between clinical and neurophysiological variables was performed by
using the Pearson’s correlation coefficient or the point-biserial cor-
relation coefficient when binary variables were used. Given the
large number of comparisons, p values of correlations were
corrected with the false discovery rate (FDR) method. P-values
equal or lower than 0.05 were considered significant.

**Results**

The two groups of participants were not significantly different in
terms of age and gender. Clinical and demographic characteristics
are summarized in Table 1. Example traces from representative
subjects are shown in Fig. 1.

**Blink Reflex**

The ANOVA on R1 latency showed a non-significant difference
between groups (F1,26 = 1.739, p = 0.199; CD: 11.19 ± 0.75 ms;
HC: 10.84 ± 0.67 ms) (Fig. 2). The ANCOVA on R2 latency
showed a significant main effect of “group” (F1,26 = 19.694,
p < 0.001), a non-significant effect of “recording side”
(F1,26 = 3.542, p = 0.071) and a non-significant interaction
among factors (F1,26 = 2.537, p = 0.123). There were no effects
of “sensory trick” (F1,11 = 2.511, p = 0.141) and “tremor”
(F1,11 = 0.223, p = 0.646) as covariates. Post-hoc analyses
showed that CD patients had a longer-latency BR R2, when
considering responses ipsilateral (CD: 38.06 ± 4.96 ms; HC:
32.87 ± 2.65 ms; p = 0.002) and contralateral (CD: 40.24 ± 4.66 ms; HC: 33.05 ± 3.49 ms; p < 0.001) to the stimu-
lation side (Fig. 2).
The ANCOVA on R2 area showed a non-significant effect of “group” \((F_{1,26} = 0.065, p = 0.801)\), “recording side” \((F_{1,26} = 3.110, p = 0.091)\) and a non-significant interaction among factors \((F_{1,26} = 1.900, p = 0.181)\), indicating that the test R2 BR elicited by single electrical pulses were of comparable area between groups and sides. There were no effects of “sensory trick” \((F_{1,11} = 0.278, p = 0.608)\) and “tremor” \((F_{1,11} = 0.004, p = 0.952)\) as covariates.

The ANCOVA on ipsilateral BRRC showed a non-significant effect of “group” \((F_{1,26} = 2.562, p = 0.122)\), a significant effect of “ISI” \((F_{3,78} = 4.358, p = 0.007)\) and a non-significant “group × ISI” interaction \((F_{3,78} = 1.439, p = 0.238)\). There were no effects of “sensory trick” \((F_{1,11} = 0.356, p = 0.563)\) and “tremor” \((F_{1,11} = 0.529, p = 0.482)\) as covariates. Post-hoc comparisons showed that inhibition at 100 and 200 ms ISIs were significantly lower in CD than HC \((p = 0.032\) and \(p = 0.039\), respectively). Although less inhibition in CD was found also in other ISIs, this did not reach statistical significance \((p \text{ values} \geq 0.05)\) (Fig. 3).

The ANCOVA on contralateral BRRC showed a significant effect of “group” \((F_{1,26} = 4.442, p = 0.045)\), a significant effect of “ISI” \((F_{3,78} = 10.601, p < 0.001)\) and a non-significant “group × ISI” interaction \((F_{3,78} = 0.141, p = 0.935)\). There were no effects of “sensory trick” \((F_{1,11} = 0.079, p = 0.784)\) and “tremor” \((F_{1,11} = 0.107, p = 0.750)\) as covariates. Post-hoc comparisons showed that inhibition at 100 and 200 ms ISIs was significantly lower in CD than HC \((p = 0.09\) and \(p = 0.031\), respectively). Although less inhibition in CD was found also in other ISIs, this did not reach statistical significance \((p \text{ values} \geq 0.05)\) (Fig. 3).

## Trigemino-Cervical Reflex

The three-way ANCOVA on P19 latency showed non-significant effects of “group” \((F_{1,26} = 2.098, p = 0.159)\), “stimulation side” \((F_{1,26} = 0.77, p = 0.784)\), “recording side” \((F_{1,26} = 0.430, p = 0.518)\) and non-significant “group × stimulation side” \((F_{1,26} = 0.581, p = 0.453)\), “group × recording side” \((F_{1,26} = 0.934, p = 0.343)\) and “group × stimulation side × recording side” \((F_{1,26} = 0.230, p = 0.632)\).
The three-way ANCOVA on N31 latency showed non-significant effects of “group” (F(1,26) = 0.198, p = 0.665) as covariates. When grouping responses as single distributions, the one way between-group ANCOVA showed significantly longer P19 latency values for CD compared to HC (F(1,110) = 7.118, p = 0.009). Again, no effects of “sensory trick” (F(1,110) = 0.222, p = 0.884) and “tremor” (F(1,110) = 0.198, p = 0.665) as covariates were observed (Fig. 4).

The three-way ANCOVA on P19/N31 amplitude showed non-significant effects of “group” (F(1,26) = 6.663, p = 0.016), “stimulation side” (F(1,26) = 2.122, p = 0.135) and non-significant “group × stimulation side” (F(1,26) = 0.048, p = 0.829) as covariates. When grouping responses as single distributions, the one way ANCOVA did not show any between-group differences (F(1,110) = 0.533, p = 0.467). No effects of “sensory trick” (F(1,110) = 2.753, p = 0.125) and “tremor” (F(1,110) = 0.135, p = 0.720) as covariates were observed (Fig. 4).

Correlations

The only statistically significant result, after correction for multiple comparisons, was a positive correlation between the latency of the P19 component of the TCR and disease duration (r = 0.773, p = 0.001) (Fig. 5). To further investigate whether this correlation was influenced by deranged pain processing in CD, a partial correlation controlling for pain VAS scores was performed. The result (r = 0.751, p = 0.003) was very similar to the zero-order correlation, indicating that pain processing has little influence in controlling for the described association between disease duration and P19 latency.

Discussion

The present study examined brainstem circuitry, assessed by means of the BR, BRRC and TCR, in CD patients. We found that, compared to HC, patients with CD have increased latency of the R2 component of the BR and decreased paired-pulse suppression of the BRRC. Patients also showed an increase in latency and decreased amplitude of the P19/N31 complex of TCR. Overall, these data points to an involvement of brainstem circuitry in the pathophysiology of CD, independently from additional clinical features, such as sensory trick and head tremor.

Interestingly, the latency of P19 component of TCR was positively correlated to disease duration; it is thus possible that the circuitry underlying TCR is more closely linked to CD than that involved in BR. In line with previous work, we found no significant difference in the latency of R1 component of blink reflex between HC and CD patients.25,26 We also confirmed previous findings of a reduced suppression of the R2 response of the BR, that normally follows a conditioning stimulus,31 albeit the present effect was statistically significant only for short ISI. This could be due to the fact that the BRC sensitivity in discriminating HC from patients is usually higher in the left part of the recovery curve, where inhibition is stronger.39,40 The altered BRRC in dystonia is usually interpreted as a dysfunction of brainstem inhibitory interneurons.31,32 A novel finding is the longer latency of the R2 component of the BR in CD patients. This was not found in previous studies, possibly due to the fact that small samples of patients were tested. The R2 BR response is generated by a complex bilateral polysynaptic circuit in the lateral reticular formation of the lower brainstem, connecting the descending spinal fifth nerve nucleus to the ipsilateral and contralateral facial nucleus.41 Since R2 and R1 share primary afferent fibers and motoneurons, the difference in R2 latency between CD patients and HC cannot be explained by excitability differences in the facial motor nucleus or by damage to trigeminal afferents. Thus, this result is likely ascribable to delayed conduction in the interneuronal chain giving rise to the reflex, similar to that observed with damage to lateral medulla.42,43

Another finding is the reduced amplitude of the P19/31 complex and the longer latency of P19 component shown by CD patients, compared to HC. This result is in line with previous work showing abnormal TCR in patients with CD.27,44 The input of the TCR travels across trigeminal fibers to the rostral portion of the spinal trigeminal nucleus; efferent axons from the spinal nuclei of the accessory nerve project then to the SCM bilaterally. Previous evidence in humans, showing an altered TCR in isolated lesions in the medulla oblongata, led to hypothesize that the reflex is probably generated via an oligosynaptic neuronal chain in the lower brainstem.37 TCR has classically been interpreted as part of a head withdrawal reflex to noxious stimulus33,45 and, according to previous studies, is reflective of inhibition of ongoing activity in the SCM and is sensitive in detecting lesions at the medullary level.37

Thus, taken together, our results about BR R2, BRRC and TCR are likely ascribable to a dysfunction in the activity of inhibitory interneurons in the lower brainstem. Further supporting this hypothesis, we found a positive correlation between P19 latency and disease duration, which apparently was not due to defective pain processing described in CD.38 This was not the case for R2 latency, which is not entirely surprising, given the fact that central pathways generating the TCR are...
probably independent from those involved in the BR R2. The correlation between P19 latency and disease duration is not easy to interpret. One possibility is a closer link between TCR and diseases’ manifestation in CD, possibly due to the specific involvement of neck muscles, which are tested by TCR. However, this association might be subtle, given the absence of correlation with the TWSTRS. Another explanation might be that the circuitry underlying the TCR is longer, and thus more susceptible to conduction abnormalities. Overall, our hypothesis is that the abnormality of TCR in CD reflects inhibitory interneurons dysfunction at medullary level, presumably involving projections to motoneurons destined to neck muscles.

The present findings leave us with one puzzle though: are the observed electrophysiological abnormalities causative of deranged activity in brainstem circuitry, or consequental to them? It is well known that abnormalities in basal ganglia activity occur in CD. These are thought to produce a cascade of changes in neuronal function that occurs throughout the pallido-thalamocortical motor circuits and possibly throughout basal ganglia to brainstem pathways. Therefore, changes in neuronal activity at the pallidum level may account for the observed alteration in brainstem reflexes. This is in line with several works which demonstrated an improved in clinical manifestation of CD after pallidotomy and or pallidal deep brain stimulation. Therefore, the hypothesis of a dysfunction of the basal ganglia leading causative of hyperexcitability in brainstem circuitry is plausible and could justify the decreased suppression of BRRC and the decreased amplitude of the TCR found here. However, such a hypothesis would be more difficult to reconcile with the finding of increased latency of the R2 component of the BR and of the P19 wave of TCR. One possibility is that, due to excitability changes in brainstem circuitry, post-synaptic potentials giving rise to the BR R2 response and the P19/N31 complex of TCR occur less synchronously than normal; this increased jitter would lead to ineffective summation and, consequently, to an increase in the latency of the recorded potentials. However, increased latency of evoked responses can be generally found with damage to the central nervous system in delayed conduction, as with denervation, or in case of loss of fast-conducting nerve fibers. Therefore, an alternative hypothesis would be that CD patients have a degree of damage to the medulla oblongata, where pathways mediating the BR and the TCR reside.

There is controversy about the presence of central nervous system damage in idiopathic dystonias. In contrast to the classical notion that no obvious structural defects are found, a substantial amount of literature has reported abnormalities in several brain regions in CD. Human neuroimaging studies using fractional anisotropy and voxel based morphometry have demonstrated abnormalities in both white and gray matter in the basal ganglia, the corpus callosum, thalamus, cerebellum and brainstem. Additionally, structural changes in the cerebellum and brainstem were confirmed by neuropathological investigations. The functional impact of the mentioned abnormalities has yet to be assessed but, considered the previous literature, it is not excluded that the increase in latency of R2 and P19 observed here might reflect subtle brainstem damage in CD. Several limitations of the present study need to be acknowledged, such as its exploratory nature, the small sample of patients examined, and the limited correlation found between neurophysiological and clinical variables. Additionally, we only performed a standard neuroimaging investigation, so a relation between the neurophysiological abnormalities and a possible, subtle brainstem damage, cannot be established with certainty. However, the present results may suggest a direct involvement of the brainstem in CD and should prompt more detailed investigations in this regard.

Author Roles

(1) Research Project: A: Conception, B: Organization, C: Execution; (2) Statistical Analysis: A: Design, B: Execution, C: Review and Critique; (3) Manuscript Preparation: A: Writing of the First Draft, B: Review and Critique.

N.M.: 1A, 2A, 3A, 3B
P.T.: 1A, 1B, 1C, 2A, 3B
F.G.: 1A, 2A, 2B, 2C, 3A, 3B
L.B.: 1A, 1B, 2A, 3B
L.R.: 1A, 2A, 2B, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: The study has been approved by the ethics committee of the University of Verona. Patients signed a written informed consent prior to the experimental procedure. All authors confirm that they have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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