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Original

Benign paroxysmal torticollis is a sensorimotor trigeminocervical convergence mechanism? Experimental evidence

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Abstract

Introduction

Benign paroxysmal torticollis (BPT) is likely an age-sensitive, childhood periodic syndrome that is commonly precursor of migraine, with atypical postural behavior (torticollis) to start early and self-limited, of unknown etiology.

Objective

To prove the existence of forms of sensorimotor convergence between the trigeminal nerve and upper cervical roots.

Methods

Ninety-five Norvegicus rats were submitted to infraorbital nerve blockade using botulinum neurotoxin type A (BoNT/A) (n=48) controlled by isotonic saline solution animals (ISS) (n=47). After 84 days, the animals were evaluated on their motor functions using open field test and postural behavior.

Results

Of the 48 animals in the BoNT/A group, one animal showed the torticollis ipsilateral to BoNT/A injection. The macroscopic analysis showed fasciculations on the clavotrapezius muscle. The biopsy with optical and electronic microscopy of this muscle showed changes suggestive of denervation secondary to BoNT/A.

Conclusion

We suggested the existence of a pathway sensorimotor probably in the brainstem involves the trigeminal system and cervical motoneurons.

Keywords:
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Precursors of migraine
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Introduction

Benign paroxysmal torticollis (BPT) of infancy is considered a migraine variant. Semiologic aspects include recurrent episodes of an abnormal rotation and inclination of the head to one side.[1] The torticollis lasted from a few hours to a few days; the frequency of the episodes initially ranged from once every two days to once every 45 days.[1] Associated symptoms include: pallor, sweating and vomiting, hypotonia of the homolateral lower limb and upward-diverted gaze, photophobia, sleepiness, asthenia, and headache.[1]

The International Headache Society included the BPT as one of the childhood periodic syndromes that are commonly precursors of migraine. Several factors can justify this statament: migraine familial history, associated symptoms during the BPT, recurrence and duration of the episodes, and the outcome of these patients who progress to a typical migraine.

The trigemino-cervical convergence mechanisms have been widely identified in human experiments[2], in pharmacological[3] and no pharmacological treatments[4] for migraine patients. Recently, patients with chronic migraine have been handled with greater occipital nerve neurostimulation with good results.[5] Besides, pain in the neck is common during migraine attacks.[6] The trigeminal and cervical systems are interrelated to other excitatory and/or inhibitory according to the stimulus´s intensity, duration and location.[7]

To support the hypothesis that BPT occurs as a result of trigeminal nociceptive activation on cervical motoneurons (trigeminocervical convergence motor sensory mechanisms), we carried out a preclinical study where we tried to determine the modulatory nociceptive influence on cervical motoneurons through nociceptive and motor inhibition using botulinum neurotoxin type A.

Methods

Subjects: Male rats (*Rattus-norvegicus*) (n=95), weight from 240-340 grams, were housed in standard plastic cages (4 per cage) with sawdust bedding in a temperature-controlled room (23+10C) and maintained on a 12 hours light-dark cycle. Animals were allowed to have free access to food pellets and water. The trial was conducted at the Neurology Research Laboratory of the Universidade Federal do Parana, Brazil. Animals were randomized double-blind to receive either isotonic 0.9% saline solution (ISS) as a control group or neurotoxin botulinum type-A (BoNT/A) as an active drug.

Phases of the study: All animals were submitted two treatments (day 0 and day 42), one open field test, and one posture behavior (84 days after the beginning of the treatment, "day 0").

Drugs and treatment: The animals were divided into two groups: one group used ISS, and the other used BoNT/A. For the experimental group, BoNT/A (Botox®, Allergan, Inc, Irvine, CA) was reconstituted in 2 ml of ISS, and, for the Control Group, only ISS was used. All the doses of BoNT/A and ISS used were administered as a 40 μl bolus into the right upper lip, just lateral to the nose using a 0.5 ml syringe with a 29-gauge needle. The dose of BoNT/A was 12 units per kilogram.

Open Field Test (OFT): This test assesses motor skills, including animals´ integrity and spontaneous exploratory behavior. As described, the OFT is a behavioral test that depends upon other cortical functions, such as the integrity of the motor circuitry of the animal. During the OFT, the animals were deprived of food and water. The parameters evaluated were: 1- latency to movement onset; 2- rearing frequencies (number of times the animals stood on their hind legs); 3- numbers of the square (numbers of the time that the animal entered a new square with all four paws); 4- immobility time (number of seconds of lack of movement during testing), and 5- abnormal posture during the test. After five minutes of the test, the animals were removed from the OFT arena and transferred to a second room. The OFT apparatus was washed with 5% ethanol before testing to eliminate possible bias due to odors left by previous mice.

Posture Behavior: The test was performed during the open field test. The evaluation was purely semiological, trying to identify anomalous cervical postures. Animals that showed postural abnormalities underwent cervical dissection of neck muscles and visualization of ectopic cervical muscles. Anomalies such as muscle atrophy or fasciculations and muscles changes were considered to be investigated.

Muscle Biopsy: For this procedure, all animals were anesthetized utilizing intraperitoneal ketamine 50 mg/kg and 10 mg/kg xylazine. The muscle was undergoing optical microscope analysis and electronic scanning.

Regulatory aspects: All the experiments adhered to the guidelines of the Committee for Research and Ethical Issues of IASP (Pain 1983). The experimental procedures

were reviewed and approved by the regulatory committee of the Universidade Federal do Paraná, Health and Animal Sciences Sector.

Statistical analysis: The t-test was used for comparisons between paired subgroups. For comparisons between unpaired subgroups, the Mann-Whitney test was used. For all tests, only "p" values smaller than 0.05 were considered significant.

Results

In this study, 48 animals were subjected to treatment with BoNT/A, and 47 animals used ISS.

Open field test: The results showed that there was no difference between all the parameters studied between the groups: 1- latency to movement onset; 2- rearing frequencies; 3- numbers of the square; 4- immobility time; and 5- abnormal posture during the test.

Posture behavior: Of the 48 animals subjected to treatment with BoNT/A, only one animal showed postural abnormalities behavior. The animal showed turning of the head to left side "torticollis" (Figure 1). Animals treated with ISS showed no changes in postural behavior.

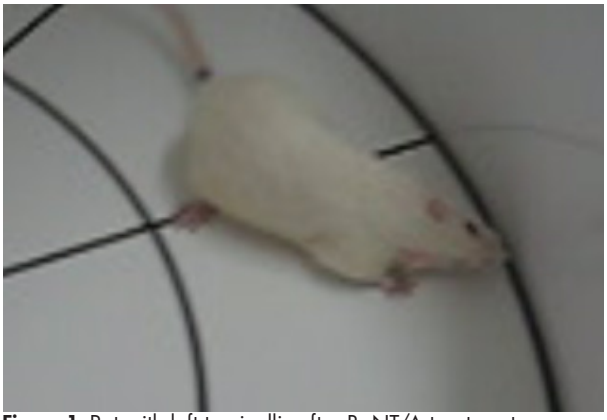

Figure 1. Rat with left torcicollis after BoNT/A treatment.

Muscle biopsy: During the muscle biopsy, the anesthetized animal was assessed macroscopically, which showed the presence of fasciculations on clavotrapezius muscle ipsilateral to the site of nerve block infraorbital with BoNT/A. Motoneurons supplying the clavotrapezius showed a rostrocaudal somatotopic distribution in the spinal accessory nucleus and in column-5. Column-5 consists of the motoneurons passing through the central nervous system extending longitudinally from C3 to C5.[8] This muscle was resected and underwent biopsy using optical microscopy techniques and electronics. Optical microscopy showed space between cells and formed round or triangular suggested atrophy of the myofibres (Figure 2 panels A and B). Eletromicrography of the muscle in scanning electron microscopy showed spacing between the muscle bundles (Figure 2 panels C and D). Eletromicrography of muscle in transmission electron microscopy, showed the absence of mitochondrial cristae, and there little glycogen scattered throughout the cytoplasm also suggested muscle atrophy (Figure 2 panels E and F).

Discussion

The features of our study showed the existence of a convergence mechanism between the trigeminal sensory system and cervical motoneurons. The semiology of this animal demonstrated a shift in posture characterized as torticollis. The semiology features are similar to those found in BPT.

First described by Snyder in 1969, benign paroxysmal torticollis (BPT) is characterized by abnormal postural head behavior, sometimes accompanied by vomiting, pallor, agitation, vomiting, nystagmus, abnormal trunk posture, apathetic, unsteadiness of gait, and ataxia which duration is limited from one hour to 14 days.[9,10] The frequency is most variable from one per month to several times per month.[10] Symptoms begin very early, like within two months, and the duration can reach up to eight years; most patients have a family history of migraine (mother), and many of these patients will develop migraine.[10] Additional tests, such as EEG and neuroimaging (CT or MRI), are normal.[1,9,10]

Having demonstrated that, Snyder reported that "ice water applied to the ear canal failed to produce nystagmus" in 9 of his 12 patients, and Sanner and Bergstrom[11] "normal vestibular responses with electronystagmography control both between attacks and during the BPT", many papers have suggested that BPT probably was a compensatory torticollis for a functional vestibular disturbance.[9,10] The hypothesis is based on clinical manifestations during the paroxysms, especially since these patients develop in the evolution the benign paroxysmal vertigo of childhood, a precursor form of migraine.[12]

A vascular disruption in the brainstem territory, as in basilar migraine, might be responsible for BPT.[11,13] Although, torticollis has not been reported in cases of basilar migraine in children.[11] Four new cases were described with the unusual syndrome of BPT showed evidence that it may be considered as a childhood migraine equivalent and may be associated with a calcium channelopathy.[14]

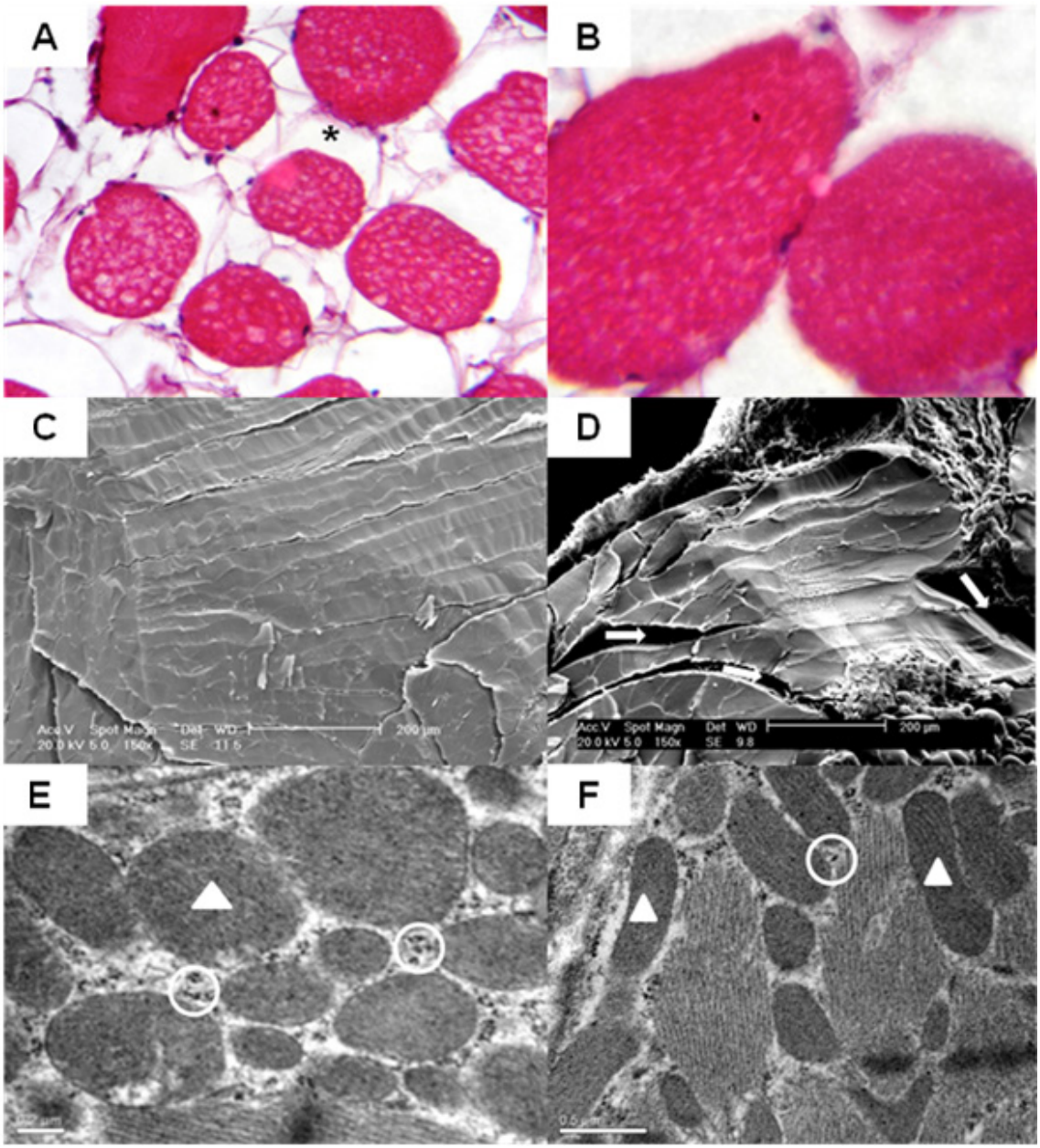

Figure 2. A- Atrophy of the myofibras (Picrosírius 40x) (*) Presence of space between cells and form round or triangular and of the same; B- Immersion (Picrosírius) round form clearer; C- Electromicrography of muscle in scanning electron microscopy of the ISS rat, muscle tissue in longitudinal view of the ISS rat; D- Electromicrography of muscle in scanning electron microscopy of the BoNT/A rat, muscle tissue in longitudinal view of the BoNT/A rat areas with a spacing between the muscles bundles (arrows); E- Electromicrography of muscle in transmission electron microscopy, mitochondria dispersed throughout the cell cytoplasm (arrow head) among the mitochondria to see if the material deposition electron rosettes of glycogen (circle) animal of the ISS group; F BoNT/A group in this group did not observe the mitochondrial cristae, and there is little glycogen scattered throughout the cytoplasm.

Recently was suggested that BPT is commonly accompanied by delayed motor development; this study showed gross motor delays in 50% of the children (5/10) with additional fine motor delays in 3/5 children.[15]

In this study we suggested a connection between the trigeminal sensory and motor system (motoneurons) in the neck. BoNT/A was administered in the second branch of the trigeminal nerve traffic until the fifth column of the rats producing denervation of the motoneurons of C3 through C5 paralyzing and atrophying the cervical muscles (specifically the clavotrapezius). The paralysis of this muscle produced a very similar behavior semiological (torticollis) in rats, similar to BPT in humans.

We can suggest that, in patients with BPT, stimulation of the trigeminal nerve roots that converge to promote activation of cervical motoneurons and induce contractions (dystonia) can generate transient torticollis. This hypothesis can be acceptable in patients with headaches associated with BPT; however, we know that many patients do not show this association. Many forms of periodic precursors of migraine also do not present headaches at earlier ages, presenting migraine many years later, during adult age.

As described above, the most recent studies suggest that patients with BPT present delayed motor development[15], probably making these motoneurons more sensitive to noxious stimulation during this phase of human development. This would explain why the BPT does not occur in adulthood in patients with migraine, and why patients during migraine attacks can show symptoms in the cervical spine.[6] Additionally, a semiological aspect of migraine related to this hypothesis is that many pediatric and adult patients can experience symptoms like neck pain and stiff neck (2.91% of the patients) as premonitory migraine symptoms.[16]

Here we suggested the existence of a pathway trigeminocervical sensory-motor type (Figure 3). The relationship of this pathway with the BPT cannot be wholly confirmed; new studies will be necessary to prove but is a new hypothesis on the pathophysiology of the BPT.

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Conflict of interest: The authors deny any conflict of interest.

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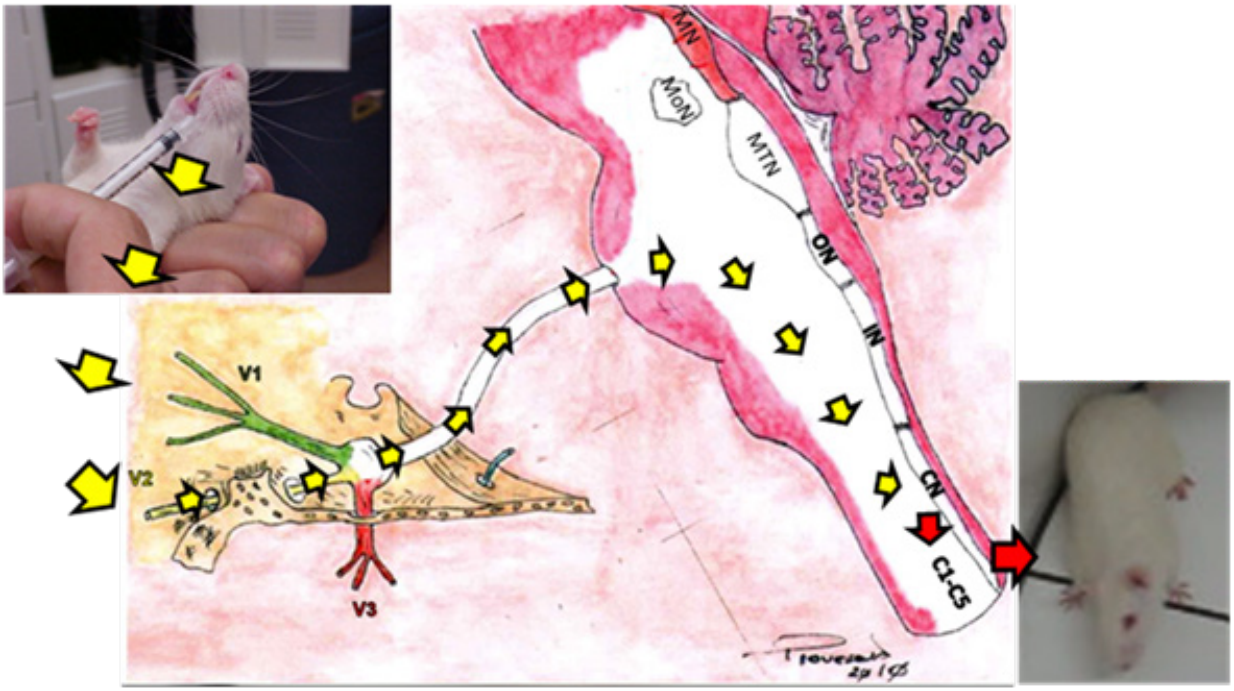

Figure 3. Convergence mechanism. CN, Caudalis nucleus; IN, Inerpolaris nucleus; ON, Oral nucleus; MTN, Mean trigeminal nucleus; MN, Motor nucleus; C1-C5, Cervical roots.

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References

1. Drigo P, Carli G and Laverda AM. **Benign paroxysmal torticollis of infancy**. *Brain Dev* 2000;22(3):169-172 Doi:10.1016/s0387-7604(00)00099-1
2. Piovesan EJ, Kowacs PA, Tatsui CE, Lange MC, Ribas LC and Werneck LC. **Referred pain after painful stimulation of the greater occipital nerve in humans: evidence of convergence of cervical afferences on trigeminal nuclei**. *Cephalalgia* 2001;21(2):107-109 Doi:10.1046/j.1468-2982.2001.00166.x
3. Piovesan EJ, Werneck LC, Kowacs PA, Tatsui CE, Lange MC and Vincent M. **Anesthetic blockade of the greater occipital nerve in migraine prophylaxis**. *Arq Neuropsiquiatr* 2001;59(3-a):545-551
4. Piovesan EJ, Di Stani F, Kowacs PA, Mulinari RA, Radunz VH, Utiumi M, . . . Werneck LC. **Massaging over the greater occipital nerve reduces the intensity of migraine attacks: evidence for inhibitory trigemino-cervical convergence mechanisms**. *Arq Neuropsiquiatr* 2007;65(3a):599-604 Doi:10.1590/s0004-282x2007000400010
5. Saper JR, Dodick DW, Silberstein SD, McCarville S, Sun M and Goadsby PJ. **Occipital nerve stimulation for the treatment of intractable chronic migraine headache: ONSTIM feasibility study**. *Cephalalgia* 2011;31(3):271-285 Doi:10.1177/0333102410381142
6. Calhoun AH, Ford S, Millen C, Finkel AG, Truong Y and Nie Y. **The prevalence of neck pain in migraine**. *Headache* 2010;50(8):1273-1277 Doi:10.1111/j.1526-4610.2009.01608.x
7. Piovesan EJ, Kowacs PA and Oshinsky ML. **Convergence of cervical and trigeminal sensory afferents**. *Curr Pain Headache Rep* 2003;7(5):377-383 Doi:10.1007/s11916-003-0037-x
8. Kitamura S and Sakai A. **A study on the localization of the sternocleidomastoid and trapezius motoneurons in the rat by means of the HRP method**. *Anat Rec* 1982;202(4):527-536 Doi:10.1002/ar.1092020412
9. Snyder CH. **Paroxysmal torticollis in infancy. A possible form of labyrinthitis**. *Am J Dis Child* 1969;117(4):458-460 Doi:10.1001/archpedi.1969.02100030460013
10. Deonna T and Martin D. **Benign paroxysmal torticollis in infancy**. *Arch Dis Child* 1981;56(12):956-959 Doi:10.1136/adc.56.12.956
11. Sanner G and Bergström B. **Benign paroxysmal torticollis in infancy**. *Acta Paediatr Scand* 1979;68(2):219-223 Doi:10.1111/j.1651-2227.1979.tb04992.x
12. Dunn DW and Snyder CH. **Benign paroxysmal vertigo of childhood**. *Am J Dis Child* 1976;130(10):1099-1100 Doi:10.1001/archpedi.1976.02120110061008
13. Deonna T. **Neurologic problems of abdominal migraine in children. Clinical study of 15 cases and review of the literature**. *Pediatrie* 1977;32(2):119-127
14. Giffin NJ, Benton S and Goadsby PJ. **Benign paroxysmal torticollis of infancy: four new cases and linkage to CACNA1A mutation**. *Dev Med Child Neurol* 2002;44(7):490-493 Doi:10.1017/s0012162201002407
15. Rosman NP, Douglass LM, Sharif UM and Paolini J. **The neurology of benign paroxysmal torticollis of infancy: report of 10 new cases and review of the literature**. *J Child Neurol* 2009;24(2):155-160 Doi:10.1177/0883073808322338
16. Cuvellier JC, Mars A and Vallée L. **The prevalence of premonitory symptoms in paediatric migraine: a questionnaire study in 103 children and adolescents**. *Cephalalgia* 2009;29(11):1197-1201 Doi:10.1111/j.1468-2982.2009.01854.x