Clinical Neurophysiology 126 (2015) 626–633

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Brainstem reflexes in patients with familial dysautonomia

Joel V. Gutiérrez [a], Lucy Norcliffe-Kaufmann [b], Horacio Kaufmann [c,*]

[a] Department of Clinical Neurophysiology, Cuban Institute of Neurology and Neurosurgery, La Habana, Cuba
[b] Department of Physiology and Neuroscience, New York University School of Medicine, New York, NY, USA
[c] Department of Neurology, New York University School of Medicine, New York, NY, USA

ARTICLE INFO

Article history:
Accepted 25 June 2014
Available online 3 July 2014

Keywords:
Familial dysautonomia
Blink reflex
Jaw jerk reflex
Afferent disorder
Hereditary sensory neuropathy
Hereditary sensory and autonomic neuropathy type III

HIGHLIGHTS

- Patients with familial dysautonomia (FD) have severe and widespread abnormalities in brainstem reflexes.
- Sensory afferent fibers are more affected than motor efferent fibers.
- These findings could explain some clinical features of patients with FD, such as slurred speech, dental trauma, chewing difficulties, dysphagia and dysarthria.

ABSTRACT

Objective: Several distinctive clinical features of patients with familial dysautonomia (FD) including dysarthria and dysphagia suggest a developmental defect in brainstem reflexes. Our aim was to characterize the neurophysiological profile of brainstem reflexes in these patients.
Methods: We studied the function of sensory and motor trigeminal tracts in 28 patients with FD. All were homozygous for the common mutation in the IKAP gene. Each underwent a battery of electrophysiological tests including; blink reflexes, jaw jerk reflex, masseter silent periods and direct stimulation of the facial nerve. Responses were compared with 25 age-matched healthy controls.
Results: All patients had significantly prolonged latencies and decreased amplitudes of all examined brainstem reflexes. Similar abnormalities were seen in the early and late components. In contrast, direct stimulation of the facial nerve revealed relative preservation of motor responses.
Conclusions: The brainstem reflex abnormalities in FD are best explained by impairment of the afferent and central pathways. A reduction in the number and/or excitability of trigeminal sensory axons is likely the main problem.
Significance: These findings add further evidence to the concept that congenital mutations of the elongator-1 protein (or IKAP) affect the development of afferent neurons including those carrying information for the brainstem reflex pathways.

1. Introduction

Familial dysautonomia (FD) is a congenital autosomal recessive neuropathy caused by mutations in the elongator-1/IKAP gene (Anderson et al., 2001; Slaugenhaupt et al., 2001). The resulting protein deficiency impairs the development of particular sensory (afferent) neurons (Mezey et al., 2003; Close et al., 2006). In addition to relative indifference to pain and insensitivity to temperature (Riley et al., 1949), affected patients are born with signs of cranial nerve dysfunction including afferent baroreflex failure (Norcliffe-Kaufmann et al., 2010), blunted hypoxic ventilatory drive (Filler et al., 1965) and absent corneal reflexes (Mahloudji et al., 1970).

Several lines of evidence suggest abnormalities in the trigeminal nerve (cranial nerve V) and medullary pathways. Post-mortem examinations showed a marked reduction in sensory neuron counts in the trigeminal ganglia (Brown et al., 1964; Aguayo et al., 1971; Pearson et al., 1971; Pearson and Pytel, 1978a; Pearson et al., 1978b) and gross atrophy of the medulla (Brown et al., 1964; Pearson et al., 1971; Pearson and Pytel, 1978a;

* Corresponding author. Address: Dysautonomia Center, 530 First Avenue, Suite 9Q, New York, NY 10016, USA. Tel.: +1 212 263 7225; fax: +1 212 263 7045.
E-mail address: Horacio.Kaufmann@nyumc.org (H. Kaufmann).

http://dx.doi.org/10.1016/j.clinph.2014.06.028
1388-2457/

Pearson et al., 1978c). Patients are born with feeding difficulties, likely due to the inability to coordinate the repetitive sucking and swallowing motor pattern (Geltzer et al., 1964), a primitive mechanism that involves sensory inputs carried by the trigeminal nerve (Barlow, 2009). Poor control of jaw, tongue, cheeks and lip movements persist throughout life, manifesting as chewing difficulties (Mass et al., 1992), dysphagia (Margulies et al., 1968) and dysarthria (Halpern et al., 1967), processes that rely on sensory feedback from trigeminal nerve afferents (Barlow, 2009). Patients appear to have diminished facial sensation and may self-mutilate (Mass and Gadoth, 1994). Patients also develop a peculiar craniofacial appearance with abnormal mandibular growth (Mass, 2012), as seen in other congenital hereditary neuropathies (Varon et al., 2003).

Recent studies from our laboratory support the concept of FD as a disorder of afferent nerve function, with relative sparing of the efferent motor neurons (Norcliffe-Kaufmann et al., 2010; Macefield et al., 2011; Norcliffe-Kaufmann et al., 2012). Surprisingly, brainstem reflexes involving the trigeminal nerves have never been assessed systematically in patients with FD. We expected that patients with FD would have impaired brainstem reflexes, due to either abnormal trigeminal sensory fibers, failure of the interneuronal networks within the brainstem or abnormalities in the efferent motor neurons controlling the craniofacial muscles. Here we used electrophysiological techniques to examine afferent, central and efferent pathways of the trigeminal nerve by evaluating trigeminal-facial and trigeminal-trigeminal brainstem reflexes.

2. Methods

2.1. Participants

From September to November 2012, we studied 28 patients with FD (age 26 ± 12 years; 10 male, 18 female). All had typical clinical histories and confirmation of the gene mutation (Anderson et al., 2001; Slaugenhaupt et al., 2001). Seven patients were taking benzodiazepines (diazepam 4.5 mg/day, clonazepam 1 mg/day, mean dosages). Twenty-five age matched healthy controls were also studied (age 32 ± 17 years; 10 male, 18 female). The procedures were approved by the institutional review board of NYU and informed consent was obtained from all participants.

2.2. Preparation for the study

Subjects were seated in a semi-supine position. Room temperature was maintained constant at 25 °C. All measurements were made using a Nicolet Viking IV EMG machine (VIASYS Healthcare, Madison, Wisconsin). All tests were performed in compliance with standards recommended by the International Federation of Clinical Neurophysiology (Deuschl and Eisen, 1999). Participants were instrumented with Ag/AgCl surface electrodes. The order of the tests was randomized. All responses were measured by the same evaluator that was blinded to whether the tracings were from patients or controls.

3. Electrophysiological recordings and analysis

3.1. Electrical thresholds

The individual thresholds for the detection of electrical stimulation, defined as the minimum intensity the subject could perceive, were determined on the right side only by delivering a series of square pulses of 0.1 ms duration and increasing stimulus intensity in steps of 0.3 mA over the right supraorbital nerve.

3.2. Blink reflex

Participants were instructed to remain immobile and keep their eyes directed towards their knees. Muscular responses were recorded bilaterally with electrodes placed over the orbicularis oculi muscles. The active recording electrode was at the mid-lower lid and the reference electrode was 1 cm lateral to the eye cantus (i.e., 30 mm apart). The ground electrode was placed at the middle of the forehead. The supraorbital nerves on the right and left sides were stimulated percutaneously at the supraorbital foramen using square pulses of 0.2 ms.

For standard recordings, stimulus intensity was set at five to eight times the individual perception threshold (Rossi et al., 1989; Rossi and Vignocchi, 1993; Meincke et al., 1999). To develop the intensity versus response (amplitude and latency) curves, stimuli of increasing intensity (5, 10, 15, 20, 25, 30 and 35 mA) were delivered to the right supraorbital nerve at random intervals between 45 and 60 s. Stimulation was repeated until 3 reproducible recordings were obtained at each level. Only reproducible blink reflex responses were measured and used for analysis. If after 5 stimuli responses were not reproducibly and clearly elicited, stimulation was stopped and responses were designated as absent.

Raw blink reflex responses were superimposed. Onset latencies were identified within the following time windows: R1 (9–24 ms), R2 (27–70 ms), and R3: (70–100 ms) according to published standards (Esteban, 1999; Blumenthal et al., 2005). Computer-generated peak-to-peak amplitude cursors were placed at the highest and lowest points of the superimposed raw responses. To avoid amplitude overestimation, care was taking to exclude peaks exceeding the 95th percentile, as these outlier values were likely artifacts in the measurement of the peak-to-peak amplitude. Manual corrections of automatic cursor positioning were used when necessary. Duration was measured from the onset to the end of the responses. Scale magnification was used to help clearly identify reflex components in the patient recordings.

3.3. Direct stimulation of the facial nerve and EMG of orbicularis oculi muscle

Facial nerve compound muscle action potentials (CMAP) were evaluated on the right side, using direct stimulation of the facial nerve, as previously described (Kimura, 1982). In brief, percutaneous supramaximal electrical stimuli (0.2 ms pulses) were applied to the facial nerve, just anterior to the tragus. Onset latency and peak-to-peak amplitude were measured on the CMAP recorded from the orbicularis oculi muscle. Measurements taken from the mastoid process to the nasion point were used to estimate the length of the facial nerve segments evaluated in both groups. Surface EMG of the right orbicularis oculi muscle was evaluated during light and maximal voluntary contraction.

3.4. Jaw jerk reflex (JJR) and EMG of masseter muscle

EMG responses (bandpass 30 Hz to 3 kHz) were recorded bilaterally with electrodes on the belly of each masseter muscle and reference electrodes at the angle of the mandible. Subjects were instructed to hold their mouths open with the incisor teeth 1 cm apart. An electronic hammer was applied to the chin to trigger the electrophysiological recordings. Two series of four tapping stimuli were applied. Minimal onset latency, maximal peak-to-peak amplitude, and negative-phase duration parameters were evaluated. Surface EMG of the right masseter muscle was evaluated during light and maximal voluntary contraction.