Sneeze-related area in the medulla: localization of the human sneezing centre?

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Sneezing is a rarely referred symptom in neurological practice. In the cat, a sneeze-evoking centre is located in the medulla. The existence of a sneezing centre is not confirmed in humans. We present a case with abnormal sneezing secondary to a strategic infarct in the right latero-medullary region. A 66 year-old male suddenly presented paroxysmal sneezing followed by ataxia, right sided-motor and sensory symptoms and hoarseness. The application of stimuli to the right nasal fossa did not evoke sneezing nor the wish to sneeze. The same stimuli to the contralateral nasal fossa evoked normal sneezing. The preservation of the superficial sensitivity of the nasal fossa indicates that the lesion was localized in the hypothetical human sneezing centre, very close to the spinal trigeminal tract and nucleus. This centre appears to be bilateral and functionally independent on both sides.
INTRODUCTION

Sneezing, in contrast to other protective reflexes such as vomiting, is not a frequently manifested symptom in neurological practice. In most cases, patients complain of hyperactivity of the reflex, usually due to nasal irritation, prompting an evaluation by otorhino-laryngology or allergy physicians. Some cases of abnormal sneezing may be of psychogenic origin especially in young adolescent girls.\(^1\)\(^2\) However, hypoactivity of the sneezing reflex, or difficulty in provoking sneezing or the urge to sneeze, is an infrequent neurological symptom.

Sneezing abnormalities are usually due to irritation of the trigeminal nerve terminals in the nasal mucosa. In the last few years, some clinical reports of sneezing abnormalities secondary to neurological diseases have been published and reviewed.\(^1\)\(^2\)\(^6\) Although there is information from animal studies, the neurology of the sneeze reflex in humans, which basically has two phases, an initial spasmodic inspiratory phase followed by a nasal and oral expiratory phase, is still poorly understood. Patient-description may provide valuable data concerning the pathophysiology and central pathways involved with this symptom.
CASE REPORT

The patient is a 66 year-old male diabetic fisherman. He reported mild non-treated hypertension and stopped smoking 10 years before.

Previously well, on a fishing trip, he suddenly presented intense, violent and repetitive sneezing. After approximately 20 sneezes in an interval of 3-4 minutes, he presented ataxia with a right steering gait, clumsiness in the right limbs, right facial drooping, dysphonia and right facial paresthesias.

He was admitted to the hospital. Blood pressure was 160/90 mm Hg. Cardiac and carotid auscultations were normal. The neurological examination showed a normal mental state, dysphonia, right partial Horner with miosis, slight right facial palsy, right limb ataxia and slight superficial hypoesthesia in the right malar area. The corneal reflex and sensitivity was normal. Gait was abnormal with steering to the right. The rest of the examination was normal.

The electrocardiogram showed a sinus rhythm at 80 per second. The magnetic resonance imaging (MRI) of the brain is shown in figure 1. An angiogram of the brain and cervical blood vessels was normal.

The facial sensory symptoms disappeared after a few days and permission was obtained from the patient to perform stimulation tests. These were performed one week after the stroke with fine cotton tips and capsaicin diluted to 25 µg/ml.

Stimulation of the right nasal fossa with a cotton tip did not provoke the sneeze reflex or the urge to sneeze. However, he conserved touch sensibility and felt the cotton stimuli in this area. Careful application of topical capsaicin diluted to 25 µg/ml to the right anterior nasal fossa provoked an uncomfortable burning-like sensation and local rhinorrhea; however, sneezing was not precipitated.

Stimulation of the left nasal fossa with careful repetitive cotton tip touches provoked both the urge to sneeze and some normal sneezes. Stimulation of the same area after
application of one drop of topical capsaicin diluted to 25 µg/ml provoked local intense pain, nasal secretion and repetitive sneezing; the pain subsided after topical application of lidocaine.

Approximately 4 months after the stroke, he was totally asymptomatic and was able to sneeze normally.
DISCUSSION

The rare presentation of paroxysmal and violent sneezing as the initial symptom of an acute lateral medullary infarct in this patient permitted us to perform a pathophysiological study of this symptom.

Once the neurological deficits were manifest, the patient presented an inability to sneeze both spontaneously and after stimulation of the distal right nasal fossa by mechanical stimuli (cotton tip). Chemical stimuli (capsaicin) applied to the ipsilateral anterior nasal fossa did not evoke sneezing nor the urge to sneeze. However, capsaicin provoked rhinorrea and a burning sensation. Applying the same stimuli to the contralateral distal nasal mucosa, the patient presented normal sneezing.

Capsaicin, the active ingredient obtained from hot chili peppers, stimulates the nasal small unmyelinated C-fiber afferent nerves to release various tachykinins. These nerves, with their somata in the trigeminal ganglion, transmit the information to the central nervous systems through the trigeminal dorsal horn in the medulla and lead to sneezing and a sense of pain. Although various peptides and tachynins may be involved, it appears that the capsaicin-induced release of substance P is the most potent trigger of the sneezing response. Capsaicin also precipitates sneezing via a local axon reflex.

The sneezing reflex may be divided in two phases:

1. Nasal or sensitive phase: stimulation of the nasal mucosa by chemical or physical irritants. The afferent pathways are through the olfactory and ethmoidal nerves, which converge in the putative “sneezing centre” in the medulla. From this point, preganglionic fibers emit impulses by through of the superficial petrosal and sphenopalatine ganglion stimulating the blood vessels and glands, giving rise to nasal secretion and edema.

   This gives rise to a rise of the trigeminal stimulation with summation of the input to the sneezing centre, where integration occurs; upon reaching a threshold, the next
2. Efferent or respiratory phase: starts once a critical number of inspiratory and expiratory neurons are recruited.

It consists in eye closing, deep inspiration, and then a forced expiration with initial closing of the glottis, and increasing intrapulmonary pressure.

The sudden dilatation of the glottis gives rise to an explosive exit of air through the mouth and nose, washing mucosal debris and irritants.

The sneezing reflex may be modulated by cortical and voluntary mechanisms. The nasal phase could be precipitated various mechanisms including the stimulation of trigeminal fibers of the of the ophthalmic division, exposition to bright or blue light and male orgasm.

Analogous reflexes to sneezing such as coughing, as well as respiration, are probably mediated by the same inspiratory and expiratory neurons but are activated by different nuclei in the brainstem. These neurons project to diverse brainstem nuclei though the vagus, phrenic and intercostals nerves. Both coughing and sneezing can be suppressed by spinal section.

In the cat, the stimulation of a strategic continuous strip located in the ventromedial part of the spinal trigeminal nucleus in close proximity to the bilateral pontino-medular lateral reticular formation, precipitates sneezing. This area is hypothesized as being the sneeze centre in this animal model. Support for the existence and location of the “sneezing centre” also comes from the presence of c-fos-like reactivity in specific areas in the cat brainstem when the nasal mucosa is stimulated by air puff. In the human, neither the existence nor location of a sneezing centre has been heretofore confirmed, although in the last few years, various reports suggest that medullary-located structures participate in the human sneeze reflex.

Touch sensitive pathways from the face and nasal fossa are transmitted via large
diameter myelinated fibers to the principal trigeminal sensory nucleus in the brainstem. Free nerve endings, the nociceptor sense organs, when activated result in the excitation of small-diameter unmyelinated C afferent nerve fibers and provide nociceptive information to the trigeminal spinal tract nucleus. This nucleus, long sausage-like structure stretching from midpons to the C2-3 segment, comprises three subnuclei: oralis, interpolaris, and caudalis. Subnucleus caudalis seems to be the principal brainstem relay site of V nociceptive information.

In the patient presented herein, the preservation of touch and pain sensitivity from both sides of the face and nasal mucosa indicates the integrity of the trigeminal afferent sensitive pathways and suggests that the lesion causing the sneezing abnormality is located in, or in close proximity to, the hypothetical sneezing area or centre. The neuroimaging results indicate that this area is located proximal to the interpolaris-caudalis area of the trigeminal spinal tract and nucleus (figure 1). The radiological lesion is ipsilateral to the clinical deficit, and it is probable that a similar structure may exist in the contralateral medulla. Since local nasal disease was excluded, the inability to provoke sneezing stimulating the right nasal fossa, but not the left nasal fossa, supports the hypothesis that both these sneezing areas in the medulla are functionally independent, in contrast to recently published studies. Asymmetry from the central pathways involved in sneezing has also been inferred from animal studies. These have shown that the mechanical stimulation of either nostril activate nasal muscles asymmetrically, with the response being greater in the contralateral than in the ipsilateral side, diverting expired air through the ipsilateral side and thus removing the irritant substances from the nose. This asymmetrical response of the nasal muscles is reflexively mediated through trigeminal afferents.

The repetitive sneezes heralding the stroke were probably related to ischemic irritation of the sneeze reflex-related structures in the medulla and arterial wall abnormalities were
excluded.

To conclude, this case presentation provides evidence for the existence of a human sneeze area or centre located in the rostral medulla.
REFERENCES


FIGEND to FIGURE 1

MRI. T2 weighted images. Sagittal (A), coronal (C), and axial (B and D) sections showing a hyperintense signal proximal to the interpolaris-caudalis area of the trigeminal spinal tract and nucleus (arrows).