

## SHORT REPORT

## Cough responsiveness in neurogenic dysphagia

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**Abstract**

**Objectives**—In neurogenic dysphagia a good cough is important for airway protection. If triggering of cough, or its effectiveness, is impaired this might result in an increased aspiration risk. Capsaicin, an agent which induces cough through sensory nerve stimulation, was used to test cough sensitivity in groups of patients with and without neurogenic dysphagia.

**Methods**—On the basis of swallowing speed (ml/s) in a validated water test 28 alert neurological inpatients (16 women, aged 22–71 years) were classified into 13 with abnormal and 15 with normal swallowing (median swallowing speed 23% and 99%, median volume/swallow 43% and 106% of that predicted for age and sex respectively:  $p < 0.001$ ). Capsaicin nebulised on air in saline was inhaled via a low resistance valve using a mouthpiece and noseclip. Up to seven incremental concentrations of capsaicin ranging from  $0.07$ – $20.0 \times 10^{-4}$  mol/l were each inhaled for up to a minute. A pneumotachograph connected to the expiratory limb gave a paper recording of expiratory air flow. Coughs were recorded as high flow expirations of short duration. Capsaicin concentrations at first cough (threshold) were recorded; concentrations at frequencies of 10 and 20 coughs/minute were interpolated from the dose-reponse curve.

**Results**—Cough threshold tended to be lower in those with abnormal swallowing (non-significant): the (log) concentration of capsaicin producing 10 or 20 coughs/minute also tended to be lower ( $p = 0.12$  and  $0.07$  respectively) in those with abnormal swallowing.

**Conclusion**—Contrary to expectation, these results suggest that cough responsiveness is enhanced in alert patients with neurogenic dysphagia even after allowing for diagnostic category, the possible presence of a bulbar upper motor neuron lesion, or voluntary respiratory capacity. It is concluded that these patients with neurogenic dysphagia do not have a reduced sensitivity of cough triggering.

(J Neurol Neurosurg Psychiatry 1998;64:385–388)

Keywords: neurogenic dysphagia; cough; capsaicin; motor neuron disease; multiple sclerosis

Patients with neurogenic dysphagia have an increased tendency to aspirate. This may be an important cause of the pulmonary complications of neurological disease, and hence morbidity and mortality. One mechanism might be desensitisation of pharyngeal, laryngeal, or tracheal mucosa resulting in failure to clear substances from the upper airway or pharynx and a tendency to silent or clinically overt aspiration. This could either be because the sensory components of the vagus and glossopharyngeal nerves (or their central projections) are involved in the underlying disease process or because of persistent pooling of inadequately cleared pharyngeal contents in the valleculae and pyriform fossae with intermittent trickling into the airway. Instrumentation with nasogastric or tracheal intubation might be further factors in desensitisation. If this hypothesis were true, patients with neurogenic causes of dysphagia might be expected to show evidence of sensory desensitisation before they experience major aspiration events. Capsaicin is an irritant substance which predominantly stimulates C sensory fibre receptors and, when inhaled, leads to reflex coughing. It has been used to study cough in humans and to screen antitussive agents.<sup>1,2</sup> In this pilot study we investigated some neurological patients with and without neurogenic dysphagia to compare their cough sensitivity to capsaicin.

**Methods****PATIENTS**

Twenty eight inpatients on a neurological ward were selected for study. Table 1 shows the diagnoses, sex, age, presence of bulbar or pseudobulbar signs, history of chest infections, and swallowing capacity (see below). To participate patients had to be fully alert, cooperative, to understand the study, to be able to sit up, and to be free of major pulmonary problems at the time of study; none were intubated. All gave their informed consent to the study procedures and the study was approved by the local ethics committee.

**TECHNIQUES**

All patients filled in a questionnaire about swallowing, had a clinical examination focusing on bulbar function, and undertook a quantitative test of swallowing.<sup>3</sup> This test has been shown to be reliable and valid and normal values have been obtained in a large sample of carefully screened people without swallowing

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Received 2 June 1997 and in  
revised form 28 August 1997  
Accepted 9 September 1997

Table 1 Diagnoses, sex, age, presence of bulbar or pseudobulbar signs, history of recent chest infection, and swallowing speed in the groups with normal or abnormal swallowing (as defined in text)

Diagnosis of individual cases	Sex	Age (y)	Bulbar signs	Pseudobulbar signs	Chest infection	Swallowing speed (%)
Normal swallowing:						
Hereditary spastic paraplegia plus	F	31	0	0	0	100
Encephalitis	M	52	0	0	0	180
Encephalitis	M	22	0	0	1	56
Multiple sclerosis	M	44	1	0	0	102
Multiple sclerosis	F	34	0	0	0	78
Multiple sclerosis	F	38	0	0	0	76
Multiple sclerosis	F	62	1	0	0	76
Multiple sclerosis	F	38	1	1	0	47
Motor neuron disease	M	55	1	1	0	94
Motor neuron disease	M	48	0	0	0	110
Motor neuron disease	M	66	0	1	1	60
Motor neuron disease	M	45	0	1	0	84
Myasthenia gravis	F	42	1	0	1	58
Myasthenia gravis	M	62	—	—	0	207
Myopathy	F	45	1	0	1	155
Abnormal swallowing:						
Lateral medullary stroke	M	43	1	0	0	2
Parkinsonism	M	49	0	0	0	46
Parkinsonism	M	58	0	0	0	22
Hydrocephalus	F	32	0	1	1	43
Syringomyelia	F	32	1	0	1	36
Encephalitis	F	32	1	0	1	18
Multiple sclerosis	M	40	0	0	0	38
Motor neuron disease	F	59	1	1	1	7
Motor neuron disease	F	55	1	1	0	22
Distal spinal muscular atrophy	F	38	1	0	0	18
Bilateral partial Xth palsy	M	71	1	0	1	2
Oculopharyngeal dystrophy	F	45	1	0	0	15
Mitochondrial disorder	F	42	1	0	0	35

Bulbar signs = the presence (1) or absence (0) of jaw, facial, palatal, pharyngeal, or tongue weakness (or fasciculation) of presumed lower motor neuron or muscular origin or depressed or absent palatal or pharyngeal sensation; pseudobulbar signs = presence (1) or absence (0) of a brisk jaw jerk, facial or jaw weakness or spastic dysarthria of presumed upper motor neuron origin; chest infection = infection either in the past year or during the current acute illness. Swallowing speed is expressed as % predicted (see methods). — Incomplete data at time of testing.

disorders. Briefly, the test consists of drinking a known volume of water, timing from first lip contact to the end of the last swallow, counting the swallows, and observing the patient for coughing during and after the test and voice change after the test. Abnormal swallowing is defined as a swallowing speed (ml/s) or mean volume/swallow (ml) below the 2.5% centile for age and sex, or coughing during the test drink or abnormality of speech after the test drink. In practice those with abnormal qualitative indices always have abnormal quantitative indices. Patients also had measurements of height and weight (for body mass index), forced vital capacity, and maximum inspiratory and expiratory mouth occlusion pressures.

Capsaicin was dissolved in 100% ethyl alcohol to make a stock solution of  $10^{-2}$  M which was freshly diluted for each study using 0.9% saline. The capsaicin solution was nebulised using compressed air and inhaled via a low resistance valve using a well fitting mouthpiece; a nose clip was worn. A 1.0 litre dead space interposed between the nebuliser and mouth piece ensured constant delivery of solution. The expiratory limb of the circuit was connected via a filter to a mesh pneumotachograph giving a hot pen recording (paper speed 1 cm/s) of expiratory airflow. Coughs were seen as high flow expirations of short duration. After a period of acclimatisation to breathing through the circuit and to breathing nebulised saline without capsaicin, up to seven incremental concentrations of capsaicin ( $0.07$ – $20.0 \times 10^{-4}$  mol/l) were each inhaled for up to one minute.<sup>4</sup> Patients were instructed to breathe regularly and to cough if they considered that

they had to. In general the procedure was well tolerated with no significant side effects.

The concentration at which a cough first occurred (cough threshold) was recorded; subsequently the rate of coughing (coughs/min) was recorded at each concentration until the maximum was reached or until the patient wished to discontinue. A dose-response curve was constructed and the concentration of capsaicin at which 10 and 20 coughs/min occurred was determined by linear interpolation. Concentrations were analysed as  $\log_{10}$  functions.

#### EVALUATION

Patients were divided into those with normal and abnormal swallowing on the basis of the swallowing test. The groups were compared for each of the main factors measured. Numerical data were checked for distribution and comparisons were made using analysis of variance (ANOVA) or non-parametric statistics accordingly using Minitab (Release 8).

#### Results

Twenty eight patients aged 22 to 71 were studied (table 1). Thirteen patients had an abnormal water swallowing test with a mean swallowing speed and average volume/swallow much lower (by definition) than the 15 who performed normally in this test. The two groups were of similar ages, sex distribution, and nutritional status as indicated by body mass index. There was a different distribution of diagnoses (classified into four groups—multiple sclerosis/encephalitis, motor neuron disorders, myopathy and myasthenia, miscellaneous) in the two groups, with the abnormal

Table 2 Demographic details and capsaicin cough indices

Feature	All (n=28, 15 F)	Normal swallow (n=15, 7F)	Abnormal swallow (n=13, 8F)	p Value
Age (mean (SD))	45.7 (12.0)	45.6 (12.3)	45.9 (12.1)	0.96
BMI (mean (SD))	23 (4)	24 (4)	22 (5)	0.21
Swallow speed (% predicted, median (IQR))	52 (22–92)	99 (60–110)	23 (11–37)	<0.001
Volume/swallow (% predicted, median (IQR))	70 (42–105)	106 (72–139)	43 (21–58)	<0.001
Vital capacity (% predicted, median (IQR))	72 (53–91)	68 (63–96)	75 (46–90)	0.63
Max inspiration (mm Hg, median (IQR))	58 (42–72)	67 (47–89)	56 (30–60)	0.045
Max expiration (mm Hg, median (IQR))	78 (39–98)	81 (50–104)	70 (22–87)	0.29
Capsaicin indices (mean (SD))				
Log conc threshold (mean (SD))	-0.296(0.546)	-0.206(0.565)	-0.399(0.526)	0.36
Log conc 10 coughs/min (mean (SD))	0.125(0.457)	0.255(0.418)	-0.026(0.471)	0.12
Log conc 20 coughs/min (mean (SD))	0.409(0.445)	0.550(0.384)	0.245(0.468)	0.07
Log conc slope (mean (SD))	1.041(0.495)	0.994(0.456)	1.095(0.549)	0.61

% predicted is adjusted for age and sex. Units of body mass index are kg/m<sup>2</sup>.

swallowing group having fewer patients with multiple sclerosis and more of the miscellaneous group ( $\chi^2=8.2$ ,  $p<0.05$ ). Forced vital capacity was similar in the two groups but patients with abnormal swallowing had a low maximum inspiratory mouth pressure—a more direct measure of volitional respiratory muscle strength.

In general, those with abnormal swallowing had a tendency to a lower cough threshold, lower concentrations for coughing at 10 and 20 coughs/minute, but the same response slopes. Only the capsaicin concentration causing 20 coughs/min approached significance (table 2). When diagnostic category was included as a covariate in the model, the group difference in concentration at 20 coughs/min was significant ( $p=0.025$ ).

We also reclassified diagnoses into those that, on pathological grounds, might potentially have affected pharyngeal or laryngeal sensory function and those that did not, but this did not seem to determine capsaicin responses. Similarly, on the basis that bulbar upper motor neuron features might result in enhanced sensitivity, diagnoses were reclassified on the presence or absence of these but no association was found. In a univariate analysis we did not find any specific associations between capsaicin responses and patient symptoms or signs.

### Discussion

We have shown that alert patients with defined neurogenic dysphagia, and hence an implicit aspiration risk, have a cough sensitivity similar to or increased compared with patients with normal swallowing. This pilot study, the first of its kind in neurological patients, is subject to several criticisms. No systematic study of capsaicin responses in normal people has been undertaken by us but rather we relied on a patient population for comparison. There was a wide range of cough responsiveness between the patients and a wide variety of diagnoses in each group. A larger more homogeneous population might be needed to show clear differences between groups. Furthermore, it may be useful to relate capsaicin sensitivity specifically to aspiration events or to videofluoroscopic indices such as the presence of vallecula and pyriform fossa pooling. A volitional ability to suppress capsaicin induced cough has been previously shown.<sup>5</sup> Our patients were instructed to cough only if they considered that

they needed to and so varying degrees of voluntary cough suppression may have been present (see below also). Finally, a simplified methodology with single breath challenges<sup>6</sup> in doubling or randomised concentrations would be easier to use in future studies in neurological patients and would reduce possible tachyphylaxis.

We measured swallowing ability quantitatively using a water test and defined neurogenic dysphagia using normative data from a large population, carefully screened to avoid conditions known to be associated with dysphagia. This operational definition of abnormal swallowing was preferred to using the patients' complaint of abnormal swallowing, because it has previously been found that some patients, notably those with multiple sclerosis,<sup>7</sup> have clear abnormalities of swallowing yet do not complain of it.

Cough has both reflex and behavioural components which contribute to its activation. An effectively triggered cough is an important factor in airway protection in patients who have neurogenic dysphagia. Capsaicin thresholds and concentrations causing 10–20 coughs/minute were lower in patients with abnormal swallowing than in those with normal swallowing. In this study no patient had loss of pharyngeal sensation (tested clinically in a standardised manner) but significantly more than normal did have loss of either the palatal or pharyngeal motor response to stimulation. However, comparison of the capsaicin responses of these subgroups showed no differences. We were not able to test either the force or the effectiveness of coughing in this study: the effectiveness is likely to depend on inspiratory and expiratory muscle strength as well as on laryngeal and vocal cord function. A small previous study<sup>8</sup> showed reduced cough responsiveness to citric acid in patients with aspiration pneumonia compared with patients with stroke or dementia although the level of consciousness of patients in this study was not stated. One patient with myotonic dystrophy in type II respiratory failure was found to have an abnormally high capsaicin threshold.<sup>9</sup> In our alert patients with neurogenic dysphagia but no aspiration pneumonia cough responsiveness was not reduced. Thus our data do not support a progressive desensitisation resulting from repeated airway penetration or aspiration as a cause of increased aspiration risk.

In principle, it might be anticipated that patients with corticobulbar pyramidal tract lesions have hyperexcitable cough reflexes by analogy with a brisk jaw jerk and brisk tendon reflexes. Indeed it has been previously shown, using semiquantitative clinical testing of bulbar reflexes, that patients with motor neuron disease do have brisker palatal and pharyngeal reflexes than normal subjects.<sup>10</sup> As noted above, there is clearly a considerable capacity to suppress the cough response to capsaicin<sup>9</sup>; if such voluntary suppression were a function mediated by fast motor pathways such as the pyramidal tracts a lesion of these pathways might result in an impaired ability to prevent cough so that, as a group, such patients would seem to have lower capsaicin indices. We cannot say for certain whether such a factor might have been important in our subjects. On the instructions they were given (see methods) some tendency to try and suppress cough may have been unavoidable. Ten patients would not have been expected to have corticobulbar pyramidal features on pathological grounds. Comparison of this group with the other 18 patients did not show any evidence to confirm the view that lower capsaicin indices might be associated with an upper motor neuron lesion. However, this aspect would certainly bear more formal study.

Capsaicin inhalation is a potent trigger for coughing and there may be sex differences in sensitivity.<sup>11</sup> The trigger is suppressed by intravenous morphine,<sup>12</sup> inhaled lignocaine,<sup>13</sup> and the GABA agonist baclofen<sup>14</sup> but not codeine, a recognised antitussive agent.<sup>15</sup> Increased sensitivity to capsaicin is found in chronic cough of any cause and improves with treatment<sup>16</sup>; we do not know whether patients with abnormal swallowing cough more than those with normal swallowing but a non-specific increased sensitivity secondary to chronic cough itself or to low grade upper airway inflammation secondary to minor aspiration remains a possibility.

We conclude that this technique offers a novel way of probing the functional effectiveness of coughing in neurogenic dysphagia; cough triggering seems, if anything, more effective in dysphagic patients but further assessment of patients known to aspirate or to have videofluoroscopic predictors of aspiration may be of value.

We are grateful to Professor R Eccles, the Common Cold and Nasal Research Centre, University of Wales, Cardiff, for his helpful advice.

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