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REDUCED TASTE PERCEPTION IN AL AMYLOIDOSIS. A FREQUENTLY UNNOTICED SENSORY IMPAIRMENT

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ABSTRACT

Background. **Sporadic observations suggest a possible taste impairment in AL amyloidosis, but the frequency and intensity of this sensory anomaly are not known.**

Materials and Methods. **We submitted 21 AL amyloidotic patients, drawn from subjects referred to the Amyloidosis Study Center of the Department of Internal Medicine and Medical Therapy, University of Pavia, to suprathreshold scaling analysis.**

Results. **Taste acuity was reduced in most of them. Every taste showed independent behavior, and 90% of these patients were hypogeusic. True ageusia for one or two tastes was observed in 35% of patients. No patient was aware of reduced taste acuity. Macroglossia did not seem to play a prominent role in dulling tastes.**

Conclusions. **Impairment of taste perception suggests that gustative neuropathy is a frequently unnoticed expression of sensory involvement in AL amyloidosis.**

Key words: AL amyloidosis, taste acuity, gustative neuropathy

It has been observed in various investigations[1-3] that patients suffering from AL amyloidosis present several taste losses. Acuity of one or more fundamental tastes was reduced in most cases, but patients did not spontaneously notice any alterations. Most of the time, taste analysis was accomplished using a *threshold* determination technique, so that patients not recognizing a taste at the maximal solute concentration employed (threshold concentration) were considered *ageusic*.[1]

Threshold concentrations are simply the *base points* of the line relating taste intensity perception to increasing solute concentrations, but the psychophysical function relating solute concentration to intensity perception is not identical in all cases.[4,5] Thus threshold values neither reveal true *ageusia* nor suggest taste abnormalities at suprathreshold concentrations.

In order to obtain more reliable data, suprathreshold examination of taste acuity in patients suffering from AL amyloidosis seemed indicated. Problems related to the evaluation of the absolute intensity of perception have been widely analyzed.[5,6] Most reliable approaches compare abnormal sensory modalities (taste, in our case) to another presumably normal modality reported by the same subject on the same scale. Taste and sound matching, proposed by the *Connecticut Chemosensory Clinical Research Center*,[4] has been largely applied. This technique requires that patients possess perfect hearing, a criterion not frequently met in older patients, Weiffenbach *et al.*[7] matched taste with the extension of a colored table. Different procedures matching taste acuity with color intensity have also been proposed.[8,9] Using one of these last suprathreshold scaling procedures,[9] we studied the psychophysical function connecting solute concentrations to perceived taste intensity in patients suffering from AL amyloidosis. Particular interest was devoted to the quantitative taste behavior of patients found to be *ageusic* with the threshold procedure.

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Materials and Methods

Twenty-one subjects, 12 males and 9 females aged 25-79 years (median 55 years), were enrolled. All patients were affected by histologically verified AL amyloidosis with various organ involvement (heart, liver, kidneys). Three patients (C.R., a 55-year-old woman, G.A.M., a 51-year-old woman and P.C., a 53-year-old man) presented remarkable macroglossia, with documented amyloid deposition in the tongue. No patient showed xerostomia. The solutions used for tasting were indicated by Bartoshuk.[4]

Gustometric assays were compared with values obtained in 20 normal subjects (11 males and 9 females) aged 27-75 years (median 53.5 years). Patients were informed about the purpose of the assay and underwent an accurate oral and dental examination.

A cone section drawn on a sheet and divided into serial layers, each consisting of a color tone whose intensity progressed from the base to the tip (white, rosy-yellow, pink, light red, strong red, purplish), was shown to every patient. It was explained that every color layer corresponded to a range of taste intensity; the feeblest color tonality corresponded to the weakest perception of taste, the highest tonality to the highest perception. Every patient was invited to choose the color layer that best matched his/her perceived intensity of the taste assayed, and to establish whether the sensation experienced was better placed at the bottom or at the top of the layer.

On the back of the sheet, layers were marked with progressive numbers from zero (white basal layer) to 100 (purplish apical layer). Every layer contained 20 numbers (0-20 rosy-yellow, 21-40 pink, and so on).

The numerical values corresponding to the zones chosen by the patient were noted.

Suprathreshold analysis of taste acuity aims at grading taste perceptions from normogeusia to complete ageusia. Inadequate evaluation of taste acuity (hypogeusia) was divided into two categories. We defined *complete hypogeusia* as an inadequate evaluation of taste intensity at all solute concentrations, and *partial hypogeusia* as a delayed evaluation of taste acuity perceived correctly only at the strongest solute concentrations.

Results

Some general remarks can be made about the observed data:

a) two patients only evaluated all tastes normally; all others presented complete or incomplete hypogeusia for one or more tastes;

b) among hypogeusic patients, 11 (52.3% of cases) correctly evaluated one or two tastes; 6 (28.5% of cases) correctly evaluated three tastes; 3 (14.2% of cases) were hypogeusic for all tastes;

c) ageusia for one or two tastes was observed in 8 patients (38% of cases).

More detailed analysis of taste acuity shows

Tastes	*Investigated subjects*	*Normogeusia*		*Hypogeusia*					
				Partial		*Complete*		*Ageusia*	
		n°	*%*	*n°*	*%*	*n°*	*%*	*n°*	*%*
Bitter	normal (20)	19	95	–	–	1	5	–	–
	amyloidosis (21)	13	62	–	–	6	28.5	2	9.5
Sweet	normal (20)	20	100	–	–	–	–	–	–
	amyloidosis (21)	10	47.7	–	–	9	42.8	2	9.5
Salt	normal (20)	20	100	–	–	–	–	–	–
	amyloidosis (21)	6	28.5	9	42.9	5	23.8	1	4.7
Sour	normal (20)	14	70	–	–	5	25	1	5
	amyloidosis (21)	3	14.3	6	28.6	6	28.6	6	28.6

Table 1. Taste acuity behavior in a group of AL amyloidosis patients compared with normal subjects.

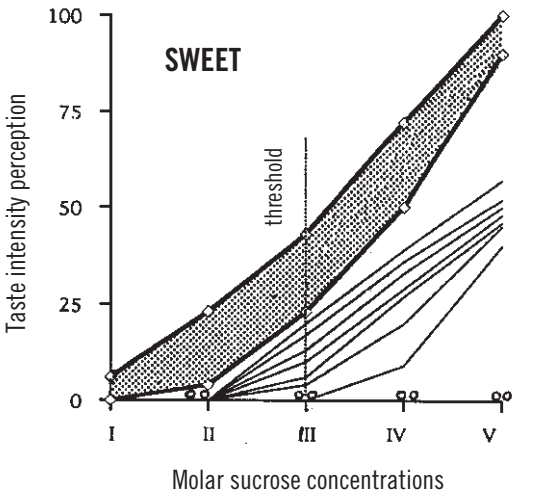

Figure 1. Sweet suprathreshold perception in AL amyloidosis: (°ageusic patients; — hypogeusic patients; shadowed area is normal perception). Hypogeusia is complete in all hypogeusic patients.
On abscissa, molar sucrose concentrations: I: 0.01 M; II: 0.032 M; III: 0.1 M; IV: 0.32 M; V: 1.0 M.

that 4 patients did not recognize sweet and 6 did not recognize salt at 0.10 M sucrose and 0.10 M NaCl, respectively; 6 patients did not recognize bitter at 0.00001 M quinine Cl and 17 did not recognize sour at 0.0032 M citric acid concentration. Since these values correspond to the highest concentrations of threshold procedures,[3] all these patients would have been classified *ageusic* with the threshold approaches. Suprathreshold examination confirmed true ageusia in 8 patients: five were ageusic for one taste only; one patient did not recognize sweet and bitter, another bitter and sour, the third salt and sour. Analytical examination of the perception intensity of every fundamental taste gave the following data (Table 1). No patient recognized *sweet* at the lowest concentration but those identifying it under the threshold concentration showed a normal gustometric perception for all remaining solute concentrations; those who recognized this taste at the threshold demonstrated reduced gustative perception for all successive concentrations (complete hypogeusia). Two patients showed complete ageusia; they reported abnormal sensations ("bitter", "sour", "as an orange fruit") during all the assays for sweet.

Thus, suprathreshold examination showed that 9.5% of our patients were ageusic for sweet, 42.8% were completely hypogeusic and 47.7% were normal (Figure 1).

Bitter was correctly evaluated by 13 out of 21 patients; six showed reduced gustometric perception for all solute concentrations and two were completly ageusic. Macroglossia was observed in two hypogeusic patients and in one (P.C., 53-year-old) with normal taste perception for bitter. Ageusic patients did not show macroscopic lingual alterations. After tasting the most concentrated solutions, they observed: *It is very unpleasant, but I don't know*. On the whole, the perception intensity of bitter was not adequate in nearly 38% of amyloidosis patients, and hypogeusia for bitter was constantly complete.

Six out of 21 subjects recognized *salt* under the threshold concentration, 9 identified it at the threshold and one showed complete ageusia.

All patients who recognized this taste below the threshold concentration revealed normal taste intensity further on; among patients identifying salt at the threshold, six demonstrated satisfactory quantitative taste perception at higher concentrations and three showed persistent hypogeusia.

Five patients recognized salt at suprathreshold concentrations; two of these showed complete hypogeusia.

So, the quantitative perception of salt was normal in 28.5% of our cases, showed delayed adequacy (partial hypogeusia) in 42.5% and was constantly inadequate (complete hypogeusia) in 23.8%. Complete ageusia was observed in only one patient (Figure 2).

Just one patient recognized *sour* under the threshold concentration and two recognized it at the threshold; all three of these subjects showed normal quantitative taste perception for the remaining solutions. Twelve patients recognized this taste at suprathreshold concentrations: six showed partial and six complete hypogeusia. Six patients were also completely ageusic. Ageusic patients did not perceive any taste until the highest concentrations were tested, and only at the IVth or Vth concentration level did some of them affirm: *It is very bad; it seems to be lemon, but I don't know*. Thus, quantitative analysis of the perception of sour revealed that partial hypogeusia, complete hypogeusia and

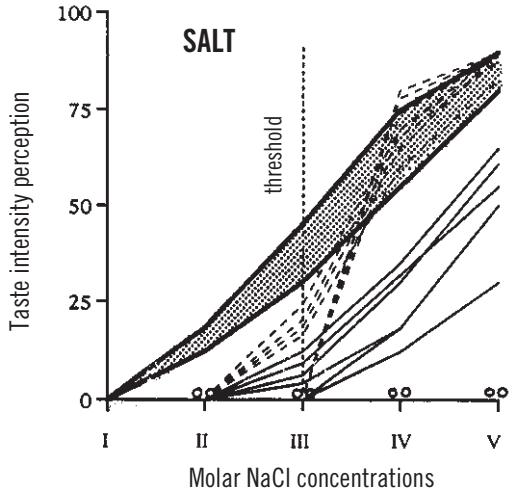

Figure 2. Salt suprathershold perception in AL amyloidosis: hypogeusia is complete (—) in five patients only; most hypogeusic patients recover normal taste perception at suprathreshold NaCl concentration (- - - partial hypogeusia).
On abscissa, molar NaCl concentrations: I: 0.01 M; II: 0.032 M; III: 0.1 M; IV: 0.32 M; V: 1.0 M.

ageusia were equally distributed in 85.71% of patients.

A comparison between reduction in taste acuity and amyloid organ involvement did not offer conclusive correlations; the most severe hypogeusias were observed in patients with renal insufficiency or with extensive organ infiltrations. Surprisingly, hypogeusia was less severe in patients with sensitive neuropathies. In our opinion, these observations emphasize the fortuity of neurologic involvement in AL amyloidosis patients. Deterioration of taste perception does not seem to be significantly influenced by the age or sex of the patients. Whether taste acuity worsens with disease progression also remains an unanswered question. Our data (three cases submitted to suprathreshold taste examination after a six-month interval) seem to support this possibility, but they are too few to permit any valid conclusions.

Discussion

Many sensory neuropathies are observed in AL amyloidosis and the clinical picture of the disease is frequently marked by their symptoms.[10-14]

Peripheral sensory and motor paralysis, hoarseness or change of voice, lightheadedness, orthostatic hypotension, impotence, sphincteral alterations, carpal tunnel syndrome are the most common manifestations. Clinical features are similar to those observed in neuropathies associated with monoclonal gammopathies.[14] Since the cranial nerves are generally unaltered in these cases, this feature is considered a significant symptomatic difference between AL amyloidosis and familial amyloidotic polyneuropathy (familial amyloidosis).[15,16]

Cranial nerve integrity in AL amyloidosis is not, however, absolute. Adie's syndrome is sporadically observed and several taste losses have been documented.[1-3,12]

In preliminary research Marinone *et al.*[1] emphasized a significant reduction in the activity of several fundamental tastes in nearly 60% of AL amyloidosis patients. Taste losses appeared precociously and persisted throughout the entire disease evolution; their severity was not related to the severity or the duration of the illness. Most patients did not notice hypo- or ageusia on their own.

Threshold determination of taste acuity, as it has been employed in many studies, is not a good clinical indicator of variations in taste; consequently nobody at present knows the quantitative extent of taste losses in AL amyloidosis patients. Suprathreshold scaling of solute concentrations reveals that hypogeusia, to varying degrees and for various tastes, is the most frequent sensory anomaly in AL amyloidosis. In our series, all patients but two were affected, and all four tastes were independently involved. True ageusia was less frequent. We observed eight ageusic patients out of 21 cases. Three presented ageusia for two tastes: sweet and bitter in the first, salt and sour in the second, bitter and sour in the third case. Five patients were ageusic only for sour.

As far as hypogeusic patients are concerned, it is noteworthy that those who did not recognize sweet or bitter at the threshold concentration never recovered normal quantitative perception with more concentrated solutions; their hypogeusia was complete. On the contrary, patients who did not recognize salt or sour at the thresh-

old concentration frequently recovered normal taste acuity at higher concentrations; they presented a partial hypogeusia.

The mechanisms of sensory transduction seem to be simpler for salt and sour than for sweet and bitter.[17] Clinically, the varying degree to which AL amyloidosis patients recover recognition intensity for electrolytes (H^+ in citric acid; Na^+ in sodium chloride) as compared to organic compounds (glucose and quinine) confirms the different and independent modalities of taste perception for these heterogeneous chemical categories.

Among patients with documented amyloid deposition in the tongue (three cases), only one showed normal quantitative perception for bitter. Two presented partial hypogeusia for bitter and sweet, while salt and sour perception was highly deficient in all three (two patients were ageusic for sour).

These observations further confirm the functional independence of different tastes, even in severe and diffuse anatomical lesions of the tongue.

In conclusion:

1) taste losses represent a very frequent sensory alteration in patients suffering from AL amyloidosis. Every taste demonstrates independent behavior;

2) true ageusia is not frequent; it never involved all tastes in any of our patients. Complete hypogeusia prevails for sweet and bitter. Partial hypogeusia is frequent for salt and sour;

3) AL amyloidosis patients are unaware of their reduced taste acuity. None of the 40 subjects studied by us with different approaches spontaneously noticed any taste alterations. A patient observed by Ujike *et al.*[2] presented xerostomia and complained of hypogeusia, and De Moor *et al.*[3] observed a patient who complained of macroglossia, dysphagia and cacogeusia.

The role of saliva in taste perception is well known[18,19] and xerostomia has a strikingly deleterious effect on taste appreciation. It should also be noted that taste perception derives from an interaction of multiple cranial nerves. Limited damage to this physiological network can be without consequence on the general perception of taste; some fibers from cranial nerve VII, for instance, inhibit the function of cranial nerve IX fibers. Their lesion enhances taste appreciation in some lingual regions.[20] Dysgeusia with perioral sensory loss is frequently observed in patients suffering from familial amyloid polyneuropathy. This characteristic represents an interesting differential symptom between AL and familial amyloidosis. In our opinion, it would be interesting to analyze and compare taste loss modalities in both pathological conditions.

The pathogenesis of taste losses in AL amyloidosis has not been investigated yet. Since amyloid deposition has been observed in the peripheral nerves of AL amyloidosis patients with peripheral sensory-motor deficiencies,[13] it would be reasonable to suppose that taste anomalies follow sensory nerve lesions induced by amyloid deposition. Monoclonal immunoglobulins have recently been identified in the serum of most AL amyloidosis patients,[21] and nerve fibers can be heavily compromized by monoclonal antibodies.[22] So the physiopathology of taste anomalies in AL amyloidosis is still open to study. From a clinical point of view, however, it seems important to underline that taste anomalies are a frequently underestimated expression of sensory neuropathies in AL amyloidosis.

References

1. Marinone MG, Marinone G, Quaglini S, Merlini GP, Cattaneo V. Le alterazioni gustative dei pazienti affetti da amiloidosi AL. Ricerche preliminari. Minerva Stomatologica 1994; 43:473-7.
2. Ujike H, Yamamoto M, Hara J. Taste loss as an initial symptom of primary amyloidosis. J Neurol Neurosurg Psychiatry 1987; 50:111-2.
3. De Moor S, Van Mark E, Peetermans J. Cacogeusia in amyloidosis associated with plasma-cell dyscrasia. Eur J Cancer 1994; 30:362-4.
4. Bartoshuk LM. Clinical evaluation of the sense of taste. Ear Nose Throat J 1989; 68:331-8.
5. Bartoshuk LM, Gent J, Catalanotto FA, Goodspeed RB. Clinical evaluation of taste. Am J Otolaryngol 1983; 4:257-60.
6. Linden RWA. Taste. Br Dent J 1993; 175:243-53.
7. Weiffenbach JM, Cowart BJ, Baum BJ. Taste intensity perception in aging. J Gerontol 1986; 41:460-8.
8. Marks LE, Borg G, Westerhund J. Differences in taste perception assessed by magnitude matching and by category-ratio scaling. Chem Senses 1992; 17:507-18.
9. Marinone MG, Marinone G, Nai C. L'analisi gustometrica nella pratica clinica. Proposta di un test di immediato impiego. Boll Soc Med Chir Cremona 1994; 1:67-71.
10. Kelly JJ jr, Kyle RA, O'Brien PC, Dyck PJ. The natural history

of peripheral neuropathy in primary systemic amyloidosis. Ann Neurol 1979; 6:1-7.
11. Penner Y, Youinou P, Lavel G, Le Goff P, Balouet G, Le Menn G. Waldenstrom's macroglobulinemia and peripheral amyloid neuropathy. Ann Med Intern 1981; 132:257-60.
12. Kyle RA, Greipp PR. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc 1983; 58:665-83.
13. Kyle RA. Primary systemic amyloidosis (AL) in 1990. Amyloid and amyloidosis. Dordrecht:Kluwer, 1990.
14. Marinone G, Quaglini S, Bellotti V, et al. AL amyloidosis: clinical and therapeutic aspects of an Italian study protocol. Amyloid and Amyloidosis 1994; 2:206-8.
15. Hölmgren G. Diagnosis of familiar amyloidosis. Clin Genet 1988; 33:176-80.
16. Yamamura Y, Kito S, Harada T, et al. Sporadic late onset case of familial amyloid polyneuropathy, type 1. A clinical study. Amyloid and Amyloidosis. Dordrecht:Kluwer, 1990.
17. Shepherd Gordon M. Sensory transduction. Entering the mainstream of membrane signaling. Cell 1991; 67:845-51.
18. Getchell TV, Doty RL, Bartoshuk LM, Snow JB, eds. Smell and taste in health and disease. New York:Raven Press, 1991.
19. Spielman AI. Interaction of saliva and taste. J Dent Res 1990; 69:838-43.
20. Kveton JF, Bartoshuk LM. The effect of unilateral chorda tympani damage on taste. Laryngoscope 1994; 104:25-9.
21. Perfetti V, Garini P, Colli-Vignarelli M, Marinone MG, Zorzoli I, Merlini GP. Diagnostic approach to and follow-up of difficult cases of AL amyloidosis. Haematologica 1995; 80: 409-15.
22. Nemni R, Gerosa E, Piccolo G, Merlini GP. Neuropathies associated with monoclonal gammopathies. Haematologica 1994; 79:557-66.