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Olfactory Deficits in Patients Affected by Minimal Hepatic Encephalopathy: A Pilot Study

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Abstract

Minimal hepatic encephalopathy (MHE) is the earliest stage of hepatic encephalopathy and is associated with changes in cognitive functions, in electrophysiological parameters, and in cerebral neurochemical/neurotransmitter homeostasis. MHE can be observed in patients with cirrhosis who have no clinical evidence of hepatic encephalopathy (HE). At present, no data are available on a possible olfactory dysfunction in such a syndrome, although the pathophysiology of HE may alter olfactory functions since some of the neurotransmitters impaired in the syndrome are involved in the transmission of olfactory information. In the present paper, we performed a preliminary study aimed at detecting whether identification and recognition odor memory is altered in patients with MHE. Twelve patients diagnosed as MHE on the basis of their scores at the portosystemic encephalopathy (PSE)-syndrome test battery, and 12 age-matched controls were studied. Consistent with the hypothesis, patients performed significantly worse than controls for both odor identification and recognition tasks. In addition, a significant correlation between the two olfactory tests and the PSE-syndrome test score was found. This pattern supports the notion that olfactory alterations related to cognitive dysfunction in patients with MHE may be linked to the pathophysiology of HE.

Key words: minimal hepatic encephalopathy, odor identification, odor recognition, virus-related cirrhosis

Introduction

It is well established that olfactory system is impaired in several neurological diseases, such as Parkinson's, Alzheimer's, and Korsakoff's (see Gregson *et al.*, 1981; Talamo *et al.*, 1989; Herz and Engen, 1996; Doty, 2001; Zucco *et al.*, 2001), and also in Down syndrome subjects and HIV-infected patients (see Lehrner *et al.*, 1995; Zucco and Savoldelli, 1996; Hornung *et al.*, 1998; Zucco and Ingegneri, 2004). However, only few studies are available on olfactory function in patients affected by various kinds of liver diseases, although it is well known that liver dysfunction might lead to central nervous disorders. The available studies have already investigated the impact of acute (Henkin and Smith, 1971), chronic (Burch *et al.*, 1978; Landis *et al.*, 2004), and end stage liver disease (Bloomfeld *et al.*, 1999). According to these authors, diverse aspects of olfactory function are altered to a variable degree by underlying liver disease. Furthermore, a recent study on chronic liver cirrhosis (Temmel *et al.*, 2005) emphasized the possibility of hepatic encephalopathy (HE) to influence olfactory central tasks. However, no study has so far explicitly focused on olfactory function in relation to HE, even though common pathophysiological mechanisms may suggest the hypothesis that a relationship does exist.

HE may occur in both acute and chronic liver diseases and may range from subtle mental impairment to coma. It is characterized, above all, by an increased concentration of potentially neurotoxic substances (particularly ammonia and manganese) in the brain of the patients (Butterworth, 1996). Such substances exert a deleterious effect on cerebral function, impairing excitatory and inhibitory neurotransmitter systems. Significant alterations were found in monoaminergic and glutamatergic mechanisms in the brain and also in the GABAergic and in the endogenous opioid neurotransmitter systems (Baraldi *et al.*, 1983; Moroni *et al.*, 1983; Baraldi, 1990; Mousseau *et al.*, 1993; Pujol *et al.*, 1993; Behar *et al.*, 1999). In particular, a high level of manganese concentration in the ''globus pallidus'' produces extrapyramidal symptoms in HE patients and the loss of dopamine D2–binding sites, while ammonia causes brain glutamate concentrations increase (Krieger *et al.*, 1995). Glutamate and dopamine are also involved in the transmission of olfactory information: the former is the neurotransmitter of the receptor cells (Trombley and Shepherd, 1993; Berkowicz *et al.*, 1994), while the latter is largely found in the periglomerular cells (Berkowicz and Trombley, 2000; Doty, 2001) although

the olfactory bulb itself contains a remarkable number of neurotransmitters (e.g., inhibitory circuits in the bulb have been found to be mediated by GABA).

On these grounds, our study is aimed at exploring the presence of olfactory deficits in patients affected by minimal hepatic encephalopathy (MHE), which represents the earliest stage of HE. MHE refers to some changes in cognitive functions, electrophysiological parameters, cerebral neurochemical/neurotransmitter homeostasis, and cerebral blood flow that can be observed in patients with cirrhosis who have no clinical evidence of HE (Amodio *et al.*, 2004). The absence of clinical evidence of HE is the key to the diagnosis and can only be determined by a detailed assessment of the patients' history and a comprehensive neurological assessment of the cognitive and motor functions. Indeed, the neuropsychological features of MHE point to a disorder of executive functioning, particularly selective attention and psychomotor speed (Ortiz *et al.*, 2005). Furthermore, alterations in electrophysiological variables have been described. For instance, endogenous evoked potentials are, in principle, more likely to reflect the presence of MHE since they are an expression of cognitive phenomena rather than mere stimulus conduction. However, the specificity of the changes observed is unclear at present (Kullman *et al.*, 1995; Montagnese *et al.*, 2004). Therefore, the observation of olfactory deficits in MHE patients could have a clinical value. Since they could be seen as a new pathophysiological criterion needed to discriminate between patients with liver cirrhosis, but without HE, and patients with cirrhosis complicated by HE. Moreover, the olfactory deficits exhibited by MHE patients may contribute to a better understanding of the olfactory processes since the mechanisms involved in the olfactory transmission are substantially affected by the neurochemical alterations observed in the syndrome.

Materials and method

Participants

Two groups of subjects participated in the experiment. The first group included 12 elderly persons (age: $M = 74.2$ year, SD = 5.3) living at home. Subjects were healthy and exhibited no dysfunction in the olfactory system (which had been demonstrated from their past clinical history and their confidential reports). The second group included 12 patients (age: $M = 73.4$ year, SD = 5.6) affected by virus-related cirrhosis with MHE. In addition to a general clinical examination, the patients received nasal endoscopy: no major nasal pathologies were observed. In both groups, the two sexes were represented (first group: five females and seven males; second group: five females and seven males).

The patients were examined at the Internal Medicine Clinic of the University Hospital of Padova, Italy. The diagnosis of cirrhosis was based on case history, clinical examination, biochemical, endoscopic, and ultrasound findings, or on liver biopsy. Diagnostic criteria were: presence of hepatic stigmata on routine clinical examination together with biochemical indexes of decompensated liver disease (low serum albumin, high bilirubin, prolonged prothrombin time, low platelets count), endoscopic or ultrasound signs of portal hypertension, or a history of previous decompensation (ascites, jaundice, bleeding from oesophageal varices). Diagnosis was confirmed by liver biopsy when needed. The severity of liver disease was assessed by the Child–Pugh classification (Child and Turcotte, 1964; Pugh *et al.*, 1973). It takes into account biochemical variables and clinical features (i.e., the amount of albumin and bilirubin, the time of prothrombin, and the presence/absence of ascites and HE). On the basis of their scores (from 5 to 15), patients are assigned to one of three classes of severity (i.e., "A" from 5 to 6; "B" from 7 to 9, and "C" from 10 to 15).

The exclusion criteria were the following:

- Chronic obstructive lung diseases or other severe lung disease with respiratory failure (PaO_2—oxygen arterial partial pressure, <60 mm Hg and/or $PaCO_2$—carbon dioxide arterial partial pressure, >50 mm Hg); renal insufficiency (creatinine plasma level >200 μmol/l); coronary heart disease or heart failure of any origin (New York Heart Association class >1); previous neurological focal episodes or other neurological illness; bouts of overt HE in the month preceding the study; bleeding or infections in the 15 days preceding the evaluation; history of psychiatric diseases; and history of consumption of psychotropic drugs or alcohol abuse.
- Temporary or permanent affections to the olfactory system (e.g., influenza, nasal trauma, allergic rhinitis, polyps, sinusitis, and head injury).

Demographic, biochemical, clinical, and cognitive data of MHE patients are given in Table 1.

Neuropsychological assessment

The diagnosis of MHE was done on the basis of the patients' performances on some neuropsychological tests (the PSE-syndrome test battery) which set out to assess memory, attention, motor speed and accuracy, visual perception, and other psychological functions, precociously altered in such disease (see Van der Rijt, 1984; Schomerus and Hamster, 1998; Weissenborn, 1998, 2002; Amodio *et al.*, 1999, 2001; Weissenborn *et al.*, 2001).

The PSE-syndrome test battery consists of the following five subtests: 1) the trail making test-A, 2) the trail making test-B, 3) the digit symbol test, 4) the serial dotting test, and 5) the line tracing test (LTT). The result for each subtest is the time needed to perform the task. The LTT reveals two results (i.e., time to perform the task and error score); therefore the subjects achieve on the whole six subtest results and

Table 1 Demographic, biochemical, clinical, and cognitive data of MHE patients with virus-related cirrhosis

Indexes	Patients											
	1	2	3	4	5	6	7	8	9	10	11	12
Age	74	77	69	74	74	82	78	72	72	68	77	60
Sex	f.	f.	m.	f.	m.	f.	m.	m.	f.	m.	m.	m.
C.P. class	C	C	A	A	A	B	A	B	A	A	B	B
Al. g/l	24.11	25.88	36.3	29.31	27.16	36	50.8	34.6	31.2	43.69	32.6	28.8
Pt. %	50	57	69	99	97	69	81	58	67	91	65	76
Bil. μmol/l	34.7	52.4	11.8	16.2	19.6	44.2	40	50.2	23.5	20.7	25.7	18.3
Na mmol/l	141	141	141	136	140	140	139	136	135	139	136	70
K mmol/l	5	4.3	3.9	5	3.6	4.3	4.2	4.8	4.2	3.9	3.8	4.4
Ast. U/l	65	45	102	92	109	109	54	44	130	40	36	94
Alt. U/l	26	31	68	11	17	12	77	36	68	32	23	61
Creat. mmol/l	70	80	79	89	62	70	110	100	93	72	70	115
Ur. mmol/l	13.4	6.2	6.3	5.4	3.2	3.4	5.5	6.10	5.3	5.1	9.1	9.8
Ascites	mod.	mod.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	abs.	mod.	mod.
Hb. g/l	89	146	96	136	156	120	131	103	135	141	121	141
Oe. Var.	abs.	pres.	abs.	abs.	abs.	abs.	abs.	pres.	abs.	abs.	pres.	pres.
Shunt p.s.	pres.	pres.	abs.	abs.	abs.	abs.	pres.	abs.	pres.	abs.	abs.	abs.
H. Nod.	pres.	pres.	abs.	pres.	pres.	pres.	pres.	abs.	pres.	pres.	pres.	pres.
PHES	−12	−7	−7	−7	−7	−5	−5	−8	−12	−15	−13	−7

C.P. class = Child–Pugh class; Al. = albumin; Pt. = phtrombin activity; Bil. = bilirubin; Ast and Alt = aspartate transaminase and alanine transaminase; Creat. = creatinine; Ur. = urea; Hb. = hemoglobin; Oe. Var. = oesophageal varices; Shunt p.s. = shunt portal systemic; H. Nod. = hepatic nodules; f. = female; m. = male; pres. = present; abs. = absent; mod. = moderate.

thus can score between +6 and −18 (since the highest score for each subtest is 1 and the lowest score is −3). The final total score is the "psychometric hepatic encephalopathy score" (or PHES). MHE results range from −5 to −18. The PHES of the patients in the day of the study ranged from −5 to −15 (M = −8.7; SD = −3.4), therefore confirming the condition of MHE in all of them.

Odorants

Forty olfactory stimuli contained in small test tubes and fitted with rubber plugs were used. The stoppers were connected to a cotton swab wrapped around the end of a stick. Substances were almost all natural and pleasant. Some of them were commonly found in the home (e.g., garlic, shoe polish, and household cleaning products), while others were essences and essential oils from Italian factories. They were replaced every 48 h, so that their concentration was kept under control. Odorants were of medium and comparable intensities. Ten stimuli were used as targets and 30 as distractors. The target stimuli were: camphor, cinnamon, garlic, ink, lavender, lemon, oregano, shoe polish cream, soya, and tar. A list of the 30 distractors used is shown in Table 2.

Procedure

Firstly, participants were individually administered the neuropsychological examination. Then, some questions were given to them to examine the olfactory efficiency. These questions were extracted from a questionnaire devised by the first author for which a standardization is still underway. The olfactory test consisted of two tasks (see Zucco, 2003; Zucco and Ingegneri, 2004). On the recognition task, each trial comprised the presentation of a target odorant and a recognition set of four odorants. Each participant smelled the target for about 4 s randomly chosen from the set of 10. A few seconds after that, the participant was presented four test tubes one at a time, one of which contained the previously sniffed odorant, and he/she was required to recognize the target. Six-second interstimulus intervals between odor presentations were used to avoid carryover adaptation effects; between trials 20–25 s rest was provided. All the glasses containing the odorants (both targets and distractors) were

Table 2 The 30 odorants used as distractors

Anchovy paste	Honey	Rose
Banana	Jasmine	Rum
Boot grease	Juniper	Sulfur
Chocolate	Lavender	Strawberry
Clove	Licorice	Tobacco
Coffee	Mustard	Tomato
Denatured alcohol	Onion	Turpentine
Dish-washing liquid	Oregano	Vanilla
Fennel	Paint	Vinegar
Gasoline	Pine	Violet

associated to a number, and the selection was made by a sequence of computer generated random numbers. For each target three distractors were selected. All the targets and distractors were used.

On the identification task, the subject had to sniff for about 4 s an odorant randomly selected from the set of 10, while the experimenter read aloud four alternative verbal labels. Each participant had to identify the correct label for the odorant. During both tasks, subjects were required to close their eyes. The distance between the stimulus and the subject's nose was always kept under control (i.e., the odorants were kept approximately 2 cm in front of both nostrils). The experiment took place in well-ventilated rooms. The order of tasks were counterbalanced among subjects. Responses were scored for accuracy.

Results

Figure 1 shows the mean number of correct responses and the standard deviations for the two groups. Correct responses were analyzed by a two-way mixed-design analysis of variance, with groups (elderly vs. MHE patients) and tasks (identification vs. recognition) as factors.

The factor ''groups'' reached a statistically significant level: $F(1, 22) = 56.29$, $P < 0.0001$.

Six partial correlation analyses were then carried out to compare the scores of the recognition and identification tasks with the PHESs. The analyses were partialized for the biochemical variables accounting for the severity of liver disease (i.e, the amount of albumin and bilirubin and the time of prothrombin). All the analyses reached significance.

Recognition scores versus PHESs: $r = 0.58$, $P < 0.05$ (albumin); $r = 0.56$, $P < 0.05$ (prothrombin); $r = 0.56$, $P < 0.05$ (bilirubin).

Identification scores versus PHESs: $r = 0.50$, $P < 0.05$ (albumin); $r = 0.52$, $P < 0.05$ (prothrombin); $r = 0.53$, $P < 0.05$ (bilirubin).

These results suggest that the lesser the neuropsychological scores, the worse the performance on the olfactory tests.

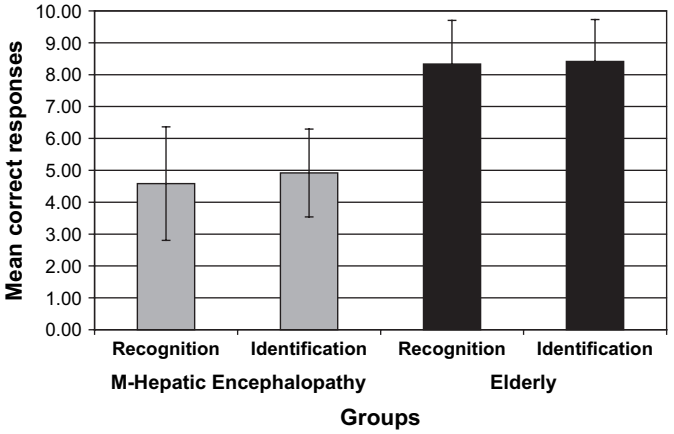

Figure 1 Odor recognition and identification scores (mean ± SD) for MHE patients and controls.

Discussion

Our study clearly shows that MHE is associated with a decrease in olfactory ability since the group of MHE patients exhibited worse performance on both recognition and identification olfactory tasks compared to an age-matched control group. In addition, the finding of a significant correlation between neuropsychological scores and olfactory performance support the hypothesis that odor recognition and identification tasks may represent useful clinical examinations to detect the patients affected by MHE. Also, as the partial correlation analyses have shown, the olfactory deficits observed in MHE patients do not seem to be dependent on the severity of liver disease.

With respect to the mechanisms at the basis of the olfactory deficits observed in MHE patients, these might implicate alterations in dopaminergic and glutamatergic neurotransmissions since both pathways are involved in the transmission of olfactory information (Trombley and Shepherd, 1993; Doty, 2001; Zucco *et al.*, 2001) and are altered in HE (Butterworth, 1996, 1997, 2002).

Indeed, the accumulation of manganese in basal ganglia in cirrhotic patients causes downregulation of D2 dopamine receptors and extrapyramidal symptoms (Baraldi *et al.*, 1983; Mousseau *et al.*, 1993; Pujol *et al.*, 1993). In addition, high cerebral ammonia levels increase glutamate synthesis and liberation (Moroni *et al.*, 1983). The excess of ammonia is removed by synthesizing glutamine from alpha-ketoglutarate and glutamate by means of the enzymes glutamate synthetase and glutamine synthetase in astrocytes. The excess of glutamine is then liberated in the extracellular space and retransformed into glutamate in the neurons by means of the enzyme glutamine deaminase. The glutamine, therefore, may be considered to be the final product of the brain depuration from toxic substances. It is important to stress that even an excess of glutamate in extracellular space is toxic for neurons (neuron excitotoxicity).

Furthermore, ammonia alters the inhibitory GABAergic neurotransmission with a reduction of glutamate decarboxylase—the enzyme synthesizing GABA (Baraldi, 1990; Behar *et al.*, 1999). As a consequence, an upregulation of GABA receptors ensue (Baraldi and Zeneroli, 1982) which, in turn, increases GABAergic tone leading to neuronal inhibition. The role of ammonia on GABAergic neurotransmission may contribute toward a greater understanding of the relationship between biochemical alterations implicated in HE and olfactory functions since it is known that GABA exerts its inhibitory action in the olfactory bulb (e.g., granule cells are GABAergic inhibitory interneurones).

Therefore, it is plausible to think that the worse performance exhibited by cirrhotic patients with MHE on both recognition and identification olfactory tasks compared to age-matched healthy controls might be due to a dysfunction in some neurotransmitters which, in turn, are involved in the pathophysiology of MHE.

In conclusion, final evidence of the relationship between biochemical changes in MHE syndrome and olfactory deficits requires further experimental steps, namely:

- an analysis of the relationship between the neurotoxins implicated in the pathophysiology of HE and the olfactory performances. (We hypothesize that the greater the amount of the first the worse the performance. If this will be definitively demonstrated, then the olfactory tasks could actually represent a new pathophysiological criterion in the evaluation of HE, perhaps independent from the results of the neuropsychological tests.);
- histological analyses of some olfactory structures (e.g., the bulbs) in patients who died from HE (or during MHE), in order to detect the presence (if any) of alterations;
- an evaluation of the parallel changes in olfactory performance and in MHE indexes (cognitive and electrophysiological) at the patients' follow up; and
- an examination of olfactory ability of patients affected by a different degree of cirrhosis (both virus related and alcohol related) to exclude the possibility that olfactory deficits observed in HE are due to some other unknown mechanisms altering olfactory system in cirrhosis.

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