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Ambulatory Detection of Volatile Organic Compounds (VOCs) Associated with Depression

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Abstract

Background: Depression has been associated with dysbiosis and transit disturbances.

Objective: We investigated whether a new ambulatory device (X-PID 8500®) may detect a specific gas associated with depression.

Methods: A retrospective analysis of data collected during routine consultations for Small Intestinal Bowel Overgrowth.

Results: 117 patients were included. 48 patients presented with a peak between 92 and 97 seconds (m-xylene peak). 69 patients did not exhale VOCs detectable within this range. 32 patients had a recent medical history of depression. 22 of them presented with m-xylene peak whereas the 10 remaining patients did not (45.8% *versus* 14.5%; p<0.001). 8 patients presented with ulcerative colitis: 7 of them presented with m-xylene peak (p<0.001). 8 patients have a medical history of severe acne treated with isotretinoin. Only two of them exhaled m-xylene (p<0.001).

Constipation was more frequent in patients with depression (19.4% *versus* 11.8%; p<0.01) and was not associated with m-xylene. Two different mechanisms are possible and are discussed. The probability to find m-xylene peak in a non-depressive patient remains high. However, such a peak may precede a depressive decompensation. Further investigations and follow-up are required to clarify this issue.

Conclusion: X-PID 8500® can detect VOCs associated with a subgroup of depression in clinical ambulatory practice.

Keywords: Breath test; Depression; Chromatography

Introduction

Depression has been associated with numerous gastroenterological pathologies: e.g. constipation [1-3], overweight [4-7], gastroparesis [8-11], Ulcerative Colitis (UC) or Crohn's Disease (CD) [12], Irritable Bowel Syndrome (IBS) [13,14] or periodontitis [15].

Some Volatile Organic Compounds (VOCs) have been associated with central nervous system disturbances in animals [16-18] as well as in human exposed to toxics [19]. These VOCs could be produced by the microbiota [20].

However, to our knowledge, no publication has reported a link between exhaled-VOCs and depression (confirmed by the Hamilton Anxiety Depression Scale) in human. A new ambulatory device, X-PID 8500®; see details in the "Material and Methods" section - may detect 50 ppb of VOCs and can be used in clinical practice since it takes only 2 minutes to get reliable chromatographic curves of exhaled VOCs.

We investigated whether X-PID 8500® may detect a specific gas associated with depression. Herpes viruses were taken into consideration since they are suspected to favour gastroparesis [21-24] or periodontitis [25-30]. Cytomegalovirus has also been implicated in the occurrence of depression [31,32], obesity [33,34], or UC [35].

Material and Methods

This is a descriptive retrospective epidemiological study. Data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth (SIBO), from January 15, 2020 until March 15, 2020. There was no hypothesis testing before data collection, no data collection beyond that which is part of routine clinical practice, no scheduled data analysis before the work has already been done. This retrospective analysis of Case Series cannot therefore be qualified as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research, according to the International Committee of Medical Journal Editors (ICMJE).

Inclusion criteria

Patients consulting for SIBO and who underwent a breath test. Patients should provide with a full medical history, especially

regarding *Herpes simplex*, *Herpes zoster*, periodontitis, constipation, previous treatment of acne with isotretinoin, ulcerative colitis, depression, thyroid pathologies, body weight and height, diabetes mellitus. Diabetes mellitus, when present, should be stabilized. CMV serology and transabdominal plus thyroid ultrasound examinations are routinely performed in patients consulting for SIBO. Patients signed a written consent for the possible retrospective epidemiological use of collected data.

Exclusion criteria

Ongoing tobacco abuse; lack of CMV serology analysis; lack of transabdominal or thyroid ultrasound examination; lack of signed consent for retrospective epidemiological use of data; uncontrolled diabetes mellitus; lack of breath test or recent intake of antibiotic therapy or of essential oils leading to massive destruction of the digestive flora and less than 2 ppm of VOCs at the first measure, after 10 hours of fasting; uncontrolled endocrine disease (including thyroid insufficiency); incomplete data on drug or food complement intake.

Depression

The diagnosis of depression was usually already made by the general practitioner of the patient. The depressive mood was confirmed by the Hamilton rating scale for Depression [36,37] according to the French regulatory guidance [38]. The questionnaire was submitted and completed at the time of gas analysis by the X-PID 8500®.

Transabdominal ultrasound examination

Ileal distension was diagnosed as soon as ileal diameter reached 2.2 cm at the ileocoecal junction [39]. Lack of gastro-duodenal voiding was diagnosed when no evacuation of bubbles between the superior mesenteric artery and the aorta was observed after 2 minutes of osteopathic abdominal manoeuvres [40]. Jejunal hypotonia could also be implicated. In that case, the jejunum contains few bubbles and no peristalsis is visualized [39].

Gas measurement

The patient comes after at least 10 hours of fasting. He/she inhales room air and hold his/her breath for 20 seconds. He/she exhales the air in a first neutral plastic bag (1.3 litres) and afterwards he/she exhales at least 100 ml (expected to belong to the expiratory reserve volume) in a second neutral plastic bag (Contralco®, Gignac, France; www.contralco.com). VOCs from the second bag are then immediately measured by the X-PID 8500®, an ambulatory gas chromatograph associated with Photoionization Detection technology [Dräger, Lubeck, Germany; www.draeger.com › Products › Multi-Gas-Detectors].

Isobutylene or methylacetate are detected within 5.6 to 6.4 seconds, isobutyric, butyric and acetic acids between 7.0 and 7.9 seconds, toluene between 39 and 45 seconds, m-xylene or p-xylene between 92 and 97 seconds and o-xylene around 115 seconds.

X-PID 8500® does not detect hydrogen and is therefore not suitable for the detection of SIBO related to sugar-malabsorption. X-PID 8500® was used after breath holding and only after fasting, not after sugar intake.

The air of the first bag is analysed by the Dräger X-am® 8000. We routinely use the Dräger X-am® 8000 [Dräger, Lubeck, Germany; www.draeger.com › Products › Multi-Gas-Detectors] to measure hydrogen before and two hours after the intake of lactulose in order to diagnose SIBO related to sugar-malabsorption. Results will be published separately. This device is also able to measure nitric oxide and hydrogen sulphide.

When SIBO is suspected, VOCs as well as hydrogen, nitric oxide and hydrogen sulphide are measured systematically and concomitantly, with these two methods and devices.

Both devices are easily portable and equipped with powerful pumps. Patients could be placed in separate rooms when necessary. The setup is basic and similar for both devices. It requires only a short tube to connect the bag and the device.

The results are exportable in excel tables.

Statistics

Comparisons of means were performed using independent student's t-test. Comparisons of percentage used two-sample t-tests. Yates correction was used for small samples. The Poisson distribution was used for the analysis of very rare events.

The VOCs peak which has been the most frequently observed in depressive patients was selected to perform the initial statistical analysis according to parameters with an established impact on depressive mood.

Since higher frequency of depression in female is established, a statistical analysis was performed to compare percentages between men and women. Since constipation is an established key factor associated with depression, a statistical analysis was performed to compare patients with and without constipation.

Sensitivity, false positive ratio, negative predictive value, positive predictive value and ROC curve were calculated for the most relevant VOCs peak.

Results

This descriptive retrospective epidemiological analysis included 117 patients. The descriptive demographic data are summarized in table 1. 32 patients (27.4%) had depression. 22 of them presented with a m-xylene peak (68.8%) whereas only 26 non-depressive patients (out of the 85 remaining patients) exhaled detectable m-xylene peak (30.6%; $p<0.001$).

A statistical analysis was therefore performed according to the m-xylene peak. All parameters with an established impact on depressive mood were taken into consideration. See table 2 for statistically significant parameters and results. Other parameters not presented in table 2 were not statistically significant regarding the difference between the two groups: altered gastric voiding (70.8% *versus* 58.0%), jejunal hypotonia (36.2% *versus* 21.7%), constipation (12.8% *versus* 14.5%), periodontitis (50.0% *versus* 53.6%), overweight (39.6% *versus* 49.3%), adenocarcinoma (10.6% *versus* 13.0%) or nodular thyroiditis (19.1% *versus* 26.1%). Since higher frequency of

Table 1: Descriptive demographic data of the 117 included patients, according to the m-xylene peak.

	Patients with m-xylene peak (48 patients)	Patients without m-xylene peak (69 patients)
Males (39 patients)	14	25
Females (78 patients)	34	44
Age	47.6 ± 18.9	49.7 ± 19.4
Body weight	63.3 ± 17.1	64.1 ± 16.3
Height	167.9 ± 9.5	164.0 ± 17.3
Body Mass Index	22.2 ± 4.8	25.3 ± 17.8

Table 2: Comparison of statistically significant parameters between patients with or without m-xylene peak.

	Patients with m-xylene peak (48 patients)	Patients without m-xylene peak (69 patients)	P values
Depression	22 (45.8%)	10 (14.5%)	<0.001
Ulcerative colitis	7 (14.6%)	1 (1.4%)	<0.001
Isotretinoin use	2 (4.2%)	6 (8.7%)	<0.001
IgG CMV+	2 (4.2%)	9 (13%)	<0.001
Crohn's disease	0	4	<0.001
Exhaled VOCs between 39 and 45 seconds	29 (60.4%)	29 (42.0%)	<0.05
Herpetic flares	16 (33.3%)	34 (49.3%)	<0.05

The percentages are equal to the number of cases per cell divided by the number of cases with m-xylene peak or without m-xylene peak.

Table 3: Comparison of key parameters between male and female.

	Male (39 cases)	Female (78 cases)	P values
Constipation	1 (2.6%)	15 (19.2%)	<0.001
Adenocarcinoma	2 (5.1%)	12 (15.4%)	<0.001
Depression	7 (17.9%)	25 (32.1%)	<0.01
Overweight	17 (43.6%)	20 (25.6%)	<0.01
Isotretinoin	4 (10.3%)	5 (6.4%)	<0.01
Ulcerative colitis	2 (5%)	6 (8%)	<0.05
Age (years of age ± SD)	45 ± 19	51 ± 19	>0.05
m-xylene peak	16 (41.0%)	31 (39.7%)	>0.05
Herpetic flares	16 (41.0%)	35 (44.9%)	>0.05
IgG CMV+	3 (8%)	8 (10.3%)	>0.05
Crohn's disease	1 (2.6 %)	3 (4%)	>0.05

The percentages are equal to the number of cases per cell divided by the number of males or females.

depression in female is established, a statistical analysis was performed to compare percentages between men and women (see table 3).

Since constipation is an established key factor associated with depression, a statistical analysis was performed to compare patients with and without constipation (see table 4). This analysis confirms that constipation and depression are statistically linked ($p<0.01$). The m-xylene peak does not characterize the group with constipation.

A higher percentage of adenocarcinoma in female should be emphasized (15.4% *versus* 5.1%; $p<0.001$). In addition, all reports of adenocarcinoma concerns patients without constipation (0% *versus* 13.8%; $p<0.001$). Although not statistically significant, the difference of age between male and female (45 ± 19 *versus* 51 ± 19) may explain the difference of percentages of cancer between these two populations, especially when earlier age of occurrence of cancer in female is taken into account (1 in 50 for men of less than 50 years of age *versus* 1 in 21 for women from 50 to 59 years of age [41]).

The sensitivity of m-xylene peak regarding depression is equal to 80% and the false positive rate is equal to 27% (the specificity is therefore equal to 73%). The negative predictive value of the m-xylene peak is equal to 86.4% and the positive predictive value is equal to 81.3%.

Table 4: Comparison of key parameters between patients with or without constipation.

	Constipation (16 cases)	No constipation (101 cases)	P values
Adenocarcinoma	0 (0%)	14 (13.8%)	<0.001
Ulcerative colitis	0 (0%)	8 (8.0%)	<0.001
Crohn's disease	0 (0%)	4 (4%)	<0.001
Depression	5 (43.8%)	25 (24.8%)	<0.01
Isotretinoin	2 (12.5%)	7 (6.9%)	<0.01
Age (years of age)	50 ± 17	55 ± 17	>0.05
Overweight	8 (50.0%)	45 (44.6%)	>0.05
m-xylene peak	6 (37.5%)	41 (40.6%)	>0.05
Herpetic flares	8 (50.0%)	43 (42.6%)	>0.05
IgG CMV+	2 (12.5%)	9 (9%)	>0.05

The percentages are equal to the number of cases per cell divided by the number of cases with constipation or without constipation.

Discussion

The m-xylene peak may help to identify a new subgroup of patients at risk of depression, different from the one with constipation. This peak is independent of gender, of constipation of gastroparesis/herpetic infections. Therefore, a new mechanism leading to depressive mood and associated to m-xylene peak is possible.

We stated that the m-xylene peak could include the gas m-xylene which is known to induce central nervous system toxicity in human workers, especially in case of concomitant ethanol ingestion [19]. In animals, the m-xylene-induced central nervous system toxicity, especially when associated with toluene (peak between 39- and 45 seconds) is established [17-19]. UC is associated with high levels of exhaled VOCs [42-45] including pentanes and hexanes [46].

Isotretinoin has been reported to favour malabsorption, probably due to mTor inhibition and decrease in small-gut-epithelial stem cell population. Consequently, microbiota is altered, leading to modifications of exhaled VOCs such as increased methylacetate levels [47]. Isotretinoin could therefore skew the distribution of exhaled VOCs towards methylacetate (extracted within less than 8 seconds), decreasing the m-xylene peak.

Exhaled VOCs strongly correlate with alterations of the gut microbiome in CD [48] which is characterized by a low diversity of microbiome [49] and low level of VOCs [50-53].

In CD, depression is mainly associated with flares [12]. It is noteworthy to specify that SIBO may spuriously mimic CD flares [54]. In such instances, depression may not be related to CD-related gas but to SIBO-related ones. It is then not surprising that ambulatory patients with stabilized CD did not exhale the m-xylene peak.

IgG CMV+ has been associated with depression [31,32]. In this descriptive study, IgG CMV+ was inversely associated with the m-xylene peak ($p<0.001$). Although CMV infection is frequently reported in UC [36], its prevalence remains low (6/1000 patients) and cannot skew our results. Herpetic flares were not associated with the m-xylene peak. We can therefore hypothesize that the m-xylene peak cannot be attributed to herpes-induced gut dysmotility.

The sensitivity of the m-xylene peak regarding the diagnosis of depression is equal to 80% and specificity 73%. The negative predictive value of the m-xylene peak is equal to 86.4% and the positive predictive value is equal to 81.3%. Although the probability to find the m-xylene peak in a non-depressive patient remains high, these figures suggest the use of this ambulatory, harmless and inexpensive method in usual clinical practice, especially in patients without constipation. In addition, the m-xylene peak may precede a depressive decompensation or may be a scar of previous depressive episode(s). Further investigations and follow-up are required to clarify this issue.

In order to oversimplify the physician's diagnostic (and perhaps etiopathogenic) tree we suggest classifying depression into two categories: category 1 with the m-xylene peak, no constipation and a high risk of UC and category 2 with constipation, no m-xylene peak and low risk of UC.

Constipation, methane production and secondary bile acids (hindgut involvement)

Constipation is associated with methanogenesis and depression [1-3,55-57]. Fecal analysis in depressive patients display altered microbiota [58,59]. Studies in mice confirmed that faecal transplantation may induce depression in healthy animals [60]. Then one group of depression appears clearly associated with colonic dysbiosis.

Methanogenesis is not associated with overweight [61] and decreases the synthesis of long chain fatty acid like ceramides [62]. Methanogenesis is blocked by secondary bile acids which are deconjugated by altered small gut bacteria and therefore SIBO [63]. Constipation associated with methanogenesis is due to isolated cecal or colonic dysbiosis which does not deconjugate bile acids since bile acids are reabsorbed in the ileum and therefore do not reach the caecum. In constipated patients producing methane, breath test with lactulose fails to detect hydrogen [64]. Transabdominal ultrasound examination detects ceco-ileal reflux with the ileum inflated by gas, as well as decreased gastroduodenal voiding without jejunal movements and without jejunal inflammation [39]. Depression is associated with Irritable Bowel Syndrome (IBS) [65,66].

IBS subjects with methane on lactulose breath test have lower postprandial serotonin levels than subjects with hydrogen [64]. In IBS patients, constipation is correlated with a decreased density of endocrine cells secreting serotonin [65-67]. Antibiofilm agents may activate colonic serotonin receptors [68]. This latter point may explain the link between constipation, dysbiosis and depression.

Colorectal immunity and constipation are linked. CD3+ and CD4+ cell counts in rectal and terminal ileal are lower in patients with IBS, especially in those with constipation [69]. Compared to male IBS-patients, female IBS-patients had greater numbers of mast cells and lower numbers of CD3+ and CD8+ T cells in the colo-rectal mucosa [70].

Altered gastroduodenal voiding (foregut involvement): A link with herpetic infections?

Gastroparesis is associated with depression and decreased quality of life [8-11]. Gastroparesis is associated with obesity [71]. Gastroparesis may be a physiologic consequence of ileal distension [72] which induces GLP-1 synthesis which is implicated in satiety and blocks gastroduodenal voiding [73-76]. A diameter of the ileocecal junction higher than 2.2 cm after 10 hours fasting highly suggests chronic ileal distension associated with an altered GLP-1 synthesis and a metabolic syndrome [39].

Altered GLP-1 synthesis triggers CMV-induced inflammation of adipocytes with chronic low-grade inflammation due to an increased production of IL-6 leading to osteopenia, cardiovascular diseases and type 2 Diabetes mellitus [76,77]. This latter point may explain why IgG CMV+ is inversely associated with the m-xylene peak.

Diabetes mellitus, herpetic infections, neurodegenerative diseases and some medications (such as anticholinergic agents) may induce gastroparesis [21]. *Herpes simplex* type 1 infects myenteric neurons [22], activates macrophages which produce reactive oxygen and peroxide-nitrogen species. These oxidative agents directly harm enteric neurons resulting in gastrointestinal dysmotility [23,24]. Our descriptive study did not find any convincing association between on one hand depression and on the other hand herpes infections, gastroparesis or overweight.

All collected information suggests that depressive patients could be classified within two groups: one with m-xylene peak (not influenced by gender, constipation, gastroparesis/overweight or herpetic flares) and one with constipation (influenced by gender; however not influenced by gastroparesis/overweight or herpetic flare). The latter group could be associated with altered colonic secretion of serotonin.

Conclusion

The breath test performed by X-PID 8500® was able to detect a peak associated with depression. It appears to mainly concern a sub-group of patients without constipation.

Although the positive predictive value of the m-xylene peak regarding depression is only equal to 81.3%, this peak is reliable enough to plea for the use of this ambulatory new device in medical gastroenterology devoted to microbiota analysis, especially because it may also precede a depressive decompensation and may therefore alert for increased surveillance. Further investigation and follow-up of non-depressive patients with the m-xylene peak is ongoing.

Conflicts of Interest

No conflict of interest to disclose.

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