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Ongoing CMV Infection (qPCR+), Nodular Thyroiditis and Periodontitis are Associated with Ileal Distension (Ileal Brake), Cancer and Increased Plasmatic Hyaluronic Acid Levels

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Abstract

Background: Periodontitis (PO) and Nodular Thyroiditis (NT) are associated with CMV infection and metabolic syndrome, and an increased risk of polyps or colorectal cancer.

Objective: We investigated whether oral CMV replication is more frequent in patients with PO+NT and with a medical history of cancer or overweight.

Methods: All data were collected during routine consultations for Small Intestinal Bowel Overgrowth (SIBO).CMV IgG serology, CMV DNA (qPCR) in saliva, plasmatic Hyaluronic Acid (HA) dosage, transabdominal and thyroid ultrasound examinations were routinely performed in SIBO.

Results: 196 patients were included. 70 patients presented with NT, 59 with PO, 32 patients with NT+PO. 26 patients have CMV DNA in their saliva (13.3%). 12 patients had a medical history of cancer.

Patients without NT (116 patients) and without ongoing CMV replication (110) presented with low percentages of cancer, ileal brake or low plasmatic HA levels i.e., 3%, 22% and 43 ± 42 µg/l respectively. Patients (16) with ongoing CMV replication have increased rates of cancer (6%; $p<0.01$) and of ileal brake (50%; $p<0.001$).

Patients without PO and without ongoing CMV replication (119 patients) presented with low percentage of cancer, ileal brake or low plasmatic HA levels: respectively 3%, 19%, 41.5 ± 40 µg/l. Patients (18) with ongoing CMV replication have increased rates of cancer (11%; $p<0.001$) and of ileal brake (39%; $p<0.001$).

Patients (6) with NT+periodontitis and with ongoing CMV infection experienced more frequently cancer (50%) or ileal brake (80%) than those (27) without ongoing CMV infection: respectively 11% ($p<0.001$) and 37% ($p<0.05$). The level of HA was also higher in patients with qPCR+ (98 ± 50 *versus* 56 ± 40; $p<0.05$).

Conclusion: Oral active CMV infection appears to be associated with severe tissue destruction, ileal brake/overweight and medical history of cancer.

Keywords: Nodular Thyroiditis; Periodontitis; CMV; Ileal brake; Hyaluronic acid

Introduction

Periodontitis (PO) concerns more than 10% of the population [1] and is associated with Metabolic Syndrome (MS) [2-5] or cancers of mucosa in contact with the digestive microbiota [6-10].

Chronic mucosal inflammation induced by an oral or a small gut dysbiosis may lead to deleterious interactome [11].

PO has been attributed to specific types of bacteria such as *Fusobacterium nucleatum*, *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannarella forsythia*, *Campylobacter rectus*, *Eubacterium nodatum*, *Peptostreptococcus micros* or *Treponema* species [12,13].

Some cancers have been attributed to *Fusobacterium nucleatum* (which belongs to PO-associated pathogens), especially colonic cancer [14].

The severity of PO is also associated (even attributed by some authors) to the expression of herpes viruses, including cytomegalovirus [15-18]. The association of cytomegalovirus and *Aggregatibacter actinomycetemcomitans* could explain severe progression of PO [19].

Multiple herpesvirus infection is detected in patients with severe chronic PO. Herpes Simplex Virus (HSV)-1 (46.6%) are the most common herpesvirus followed by HSV-2 (34.6%), Epstein-Barr Viruses (EBV) (30.6%), and Cytomegalovirus (CMV) (19.3%) [20]. Cytomegalovirus has also been implicated in the occurrence of central

obesity [21,22], immunosenescence [23,24], gastric cancer [25,26] and early diverticulitis [27,28]. The prevalence of oral cytomegalovirus in gingival crevicular fluid varies according to the severity of the disease and ranges between 12 and 20% [29]. The prevalence of CMV in subgingival plaques reaches 54.5% in patients with chronic PO *versus* 27.5% in healthy patients [30]. The prevalence of thyroid nodules in subjects with colorectal polyps is significantly higher than in healthy controls [31,32].

In preliminary studies, we reported that severe PO is associated with an increased level of Low Molecular Weight-Hyaluronic Acid (LMW-HA), and with an increased risk of adenocarcinoma [33-35] or of thyroiditis [36].

LMW-HA is known to increase endothelial permeability, to stimulate receptors of cancer stem cells and to favour cancer cells metastasis [37-40].

We investigated whether oral replication of CMV is associated with a medical history of cancer, overweight, thyroid nodules, and an increased plasmatic level of LMW-HA.

Material and Methods

All data were collected during the normal course of routine gastroenterological consultations for Small Intestinal Bowel Overgrowth, from April 16, 2018 until April 15, 2019. 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 qualify as "research" and does not requires approval from ethics boards designed to protect humans involved in clinical research.

Inclusion criteria

Patients consulting for SIBO. Patients should provide with a full medical history, especially regarding PO, thyroid pathologies, body weight and height, diabetes mellitus. Diabetes mellitus, when present, should be stabilized. CMV IgG serology, CMV DNA (qPCR) in saliva and plasmatic Hyaluronic Acid (HA) dosage are routinely performed in patients consulting for SIBO. All patients coming for SIBO underwent a breath test, a transabdominal ultrasound and a thyroid ultrasound (also routinely performed in SIBO).

Patients signed a written consent for the epidemiological use of collected data; as all other patients consulting in the gastroenterological clinic.

Exclusion criteria

Ongoing tobacco abuse; lack of CMV DNA analysis; lack of by breath test or transabdominal ultrasound; lack of signed consent for epidemiological use of data; uncontrolled diabetes mellitus.

DNA viral or bacterial analysis

CMV DNA was detected by qPCR (Amplix® from Alldiag®; reagents: Bioneer®) in oral swabs. Samples were collected at -18°C and all analysed the same day in a centralized lab.

Ultrasound

Ileal brake was diagnosed as soon as ileal diameter reached 2.2 cm at the ileo-coecal junction [41]. Nodular thyroiditis was diagnosed as soon as nodules above 3 mm were measured.

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.

Results

This descriptive research study included 196 patients.70 patients presented with nodular thyroiditis, 59 with PO, 32 patients with NT associated with PO. 26 patients have CMV DNA in their saliva (13.3%). 12 patients had a medical history of cancer. The descriptive demographic data according to NT and PO status is summarized in table 1.

The mean body weight of patients with an ileal brake was higher than those without an ileal brake (80.3 kg ± 19.3 *versus* 62.6 kg ± 14.2; $p<0.001$) although their height was similar (167 cm ± 22 *versus* 167 cm ± 13).

Patients without NT and without ongoing CMV infection presented with low percentage of cancer or of ileal brake i.e., 3% and 22% respectively. Patients with ongoing CMV replication have increased rates of cancer (6%; $p<0.01$) and of ileal brake (50%; $p<0.001$) (Table 2).

Patients without PO and without ongoing CMV infection presented with low percentage of cancer or of ileal brake i.e., 3% and 19% respectively. Patients with ongoing CMV replication have increased rates of cancer (11%; $p<0.001$) and of ileal brake (39%; $p<0.001$) (Table 2).

Patients with NT+PO have higher percentage of cancer (19%) or ileal brake (50%) and higher level of HA (69 ± 42) than those with NT only or PO only ($p<0.001$ in all instances) (Table 3).

Patients with NT+PO and with ongoing CMV infection experienced more frequently cancer (50%) or ileal brake (80%) than those without ongoing CMV infection: respectively 11% ($p<0.001$) and 37% ($p<0.05$). The level of LMW-HA was also higher in patients with qPCR+ (98 ± 50 *versus* 56 ± 40; $p<0.05$) (Table 4).

Discussion

Oral active CMV infection can be detected by qPCR. The prevalence of oral cytomegalovirus in gingival crevicular fluid varies according to the severity of the disease and ranges between 12 to 20% [29]. In this work we found CMV-DNA in 13.6% of patients with PO. This figure is much lower than the prevalence mentioned in studies focussed on subgingival plaques. In this latter instance the expected percentage would be close to 27.5% in healthy patients and 54.5% of patients with PO [30]. Saliva or gingival crevicular fluid appears therefore less contaminated than subgingival plaques.

Table 1: Descriptive demographic data according to PO and NT status.

	Gender	Age	Body weight (kg)	Height (cm)
NT without PO (38 patients)	Male: 29% Female: 71%	49 ± 14	69.0 ± 21.4	168.2 ± 8.0
PO without NT (27 patients)	Male: 45% Female: 55%	48 ± 15	67.9 ± 14.1	169.6 ± 13.4
NT and PO (32 patients)	Male: 38% Female: 62%	56 ± 12	68.0 ± 19.6	169.8 ± 8.7
Neither NT nor PO (99 patients)	Male: 41% Female: 59%	46 ± 12	64.8 ± 16.4	169.4 ± 8.8
Total (196 patients)	Male: 39% Female: 61%	49 ± 13	68.5 ± 18.1	169.3 ± 9.6

Table 2: Percentages of patients with cancer, ileal brake and plasmatic HA concentrations according to NT, PO and/or CMV status.

	NT (70 patients)	No NT (126 patients)	PO (59 patients)	No PO (137 patients)
qPCR CMV + CMV IgG +	6 patients 2 cancers (33%)* 4 ileal brakes (67%) Plasmatic HA: 51 ± 22 µg/l	16 patients 1 cancer (6%)* 8 ileal brake (50%) Plasmatic HA: 52 ± 41 µg/l	8 patients 2 cancers (25%)** 5 ileal brakes (62.5%)! Plasmatic HA: 56 ± 42 µg/l	18 patients 2 cancers (11%)** 7 ileal brakes (39%)! Plasmatic HA: 49 ± 31 µg/l
qPCR CMV + CMV IgG -	4 patients (all with lymphopenia and hypogammaglobulinemia) 1 cancer (25%) No ileal brake (0%) Plasmatic HA: 8.5 ± 2.1	None	None	None
qPCR CMV - CMV IgG +	36 patients 3 cancers (8%) 10 ileal brakes (27%) Plasmatic HA: 53 ± 50 µg/l	40 patients 2 cancers (5%) 10 ileal brakes (25%) Plasmatic HA: 43 ± 40 µg/l	36 patients 3 cancers (8%) 13 ileal brakes (36%) Plasmatic HA: 55 ± 56 µg/l	45 patients Two cancers (4%) 11 ileal brakes (24%) Plasmatic HA: 44 ± 40 µg/l
qPCR CMV - CMV IgG -	24 patients 2 cancers (8%) 6 ileal brake (25%) Plasmatic HA: 49 ± 47 µg/l	70 patients One cancer (2%) 14 ileal brakes (20%) Plasmatic HA: 43 ± 42 µg/l	15 patients One cancer (7%) 4 ileal brakes (27%) Plasmatic HA: 50 ± 46 µg/l	74 patients Two cancers (3%) 12 ileal brakes (16%) Plasmatic HA: 40 ± 38 µg/l

*p<0.01
**p<0.001
!p<0.001

Table 3: Percentages of patients with cancer, ileal brake and plasmatic HA concentrations according to NT and/or PO status.

	NT (70 patients)	No NT (126 patients)
PO	32 patients 6 cancers (19%)* 16 ileal brakes (50%)! Plasmatic HA: 69 ± 42 µg/l §	27 patients 2 cancers (7%)* 6 ileal brakes (22%)! Plasmatic HA: 42 ± 23 µg/l §
No PO	38 patients 2 cancers (5%) 13 ileal brakes (34%) Plasmatic HA: 43 ± 23	99 patients 2 cancers (2%) 17 ileal brakes (17%) Plasmatic HA: 45 ± 25

*p<0.001
!p<0.001
§p<0.001

Table 4: Percentages of patients with cancer, ileal brake and plasmatic HA concentrations according to NT+PO and/or CMV status (results from patients with NT only or with PO only (68 patients) are not included).

	NT+PO (33 patients)	Neither NT nor PO (95 patients)
qPCR CMV + CMV IgG +	6 patients 3 cancers (50%)* 5 ileal brakes (80%)! Plasmatic HA: 98 ± 50µg/l §	11 patients One cancer (9%)* 4 ileal brakes (36%) Plasmatic HA: 48 ± 38µg/l §
qPCR CMV + CMV IgG -	None	None
qPCR CMV - CMV IgG +	23 patients=19 3 cancers (13%) 9 ileal brakes (39%) Plasmatic HA: 57 ± 34	34 patients 2 cancers (6%) 8 ileal brakes (24%) Plasmatic HA: 47 ± 45
qPCR CMV - CMV IgG -	4 patients No cancer One ileal brake (25%) Plasmatic HA: 52 ± 41	50 patients 1 cancer (2%) 6 ileal brakes (12%) Plasmatic HA: 42 ± 35

*p<0.001
!p<0.05
§p<0.05

The overall seroprevalence of CMV in the adult population in Europe can be estimated to be approximately 57% [42], which is close to our findings (50%).

Cytomegalovirus and periodontal bacteria could interact and favour severe PO [19]. Replication of viruses could be required for tissue damages.

In this descriptive research study, IgG seroprevalence without CMV replication is not associated with tissue inflammation or tissue destruction. However, active CMV replication is more frequent in patients with PO+NT. In this instance, high plasmatic LMW-HA levels, ileal break/overweight and a medical history of cancer (respectively $p<0.001$, $p<0.05$ and $p<0.001$) confirm global inflammation and tissue destruction.

Periodontal-concomitant local dysbiosis, which includes EBV, *Helicobacter pylori* or *Porphyromonas gingivalis*, may trigger inflammation and induce immunosuppression [43-45]. Consequently, oral CMV replication may be explained by immunosuppression caused by oral agents. However, CMV itself is an established cause of immunosenescence and premature global aging, in particular through accelerated methylation [46-47]. Obesity is also considered as a factor of premature aging due to dysmethylation [48].

Since the detection of DNA methylation signatures of thyroid nodules is considered to be a reliable method to differentiate malignant and benign thyroid lesions [49-53], methylation can explain a synergic detrimental effect of obesity and CMV replication on the thyroid.

Metabolic, endocrine or cytokine secretions may also be involved in the inflammatory process. Ileal brake is a physiological reflex implicated in satiety [54-56]. Ileal inflation induces GLP-1 synthesis which blocks gastroduodenal voiding. A diameter of the ileocecal junction higher than 2.2 cm after 10 hours fasting (measured with a transabdominal ultrasound examination) highly suggests chronic ileal distension associated with an altered GLP-1 synthesis and a metabolic syndrome [41].

Altered GLP-1 synthesis may explain the association between PO and cardio-metabolic risk increase [57,58]. It also 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 [59,60].

NT is related to metabolic syndrome and metabolic disturbances [61-65]. However, this descriptive research study does not confirm NT or PO alone as risk factors of ileal brake, cancer or tissues destruction.

In addition, although early CMV infection may increase the risk of obesity and metabolic trait [66-68], previous CMV infection (CMV positive serology) without detectable oral CMV replication was not associated in this study with severe diseases in adults older than 50 years of age. To our knowledge, not previous study investigated the link between CMV oral active replication and obesity.

Conclusion

Oral active CMV replication appears to be associated with severe tissue destruction, ileal brake/overweight and a medical history of cancer. Clinician should check for NT and PO in their patients, especially when overweight is present. Ileal brake is an interesting parameter, easy and inexpensive to detect with transabdominal ultrasound examination. Plasmatic LMW-HA levels and qPCR for detection of CMV-DNA in saliva could be of interest in patients with PO+NT in order to screen those with an increased risk of severe tissue destruction.

Acknowledgment(s) and Conflicts of Interest

No conflict of interest to disclose.

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