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BACKGROUND: *Acute appendicitis is the most common abdominal emergency. Its etiopathogenesis appears to be multifactorial. Several studies suggested a relationship between the development of acute appendicitis and some environmental factors. Air pollution predisposes some people to develop perforated appendicitis. However, data are relatively scarce and the results still controversial.*
AIM: *Determine the seasonal variation of acute appendicitis and study the association between perforated appendicitis and short-term exposure to climatic factors and to air pollutants.*
METHODS: *A cross-sectional study was conducted including patients hospitalized in the general surgery department of Farhat Hached University Hospital in Sousse for acute appendicitis between January 1st and December 31st, 2014. Climatic conditions were collected from the National Institute of Meteorology. Data on air pollution were given by the National Agency for the Protection of the Environment and obtained by the modeling of the atmospheric pollution. For statistical analysis, we used mean concentrations of each environmental factor corresponding to the day of hospital admission and lagged by the 7 previous days. These factors were compared between the group of patients with perforated appendicitis and patients with nonperforated appendicitis.*
RESULTS: *We collected 246 cases of acute appendicitis. Perforated appendicitis was reported in 15.2% of the cases. The incidence of acute appendicitis was higher during summer. Compared to nonperforated appendicitis, perforated appendicitis was significantly associated with the mean relative humidity of the 5 day lag ($p = 0.046$), rainfall of the 7 day lag ($p = 0.043$), and consultation delay ($p < 10^{-3}$). Furthermore, perforated appendicitis was significantly associated with the daily mean concentration of carbon dioxide ($p = 0.042$), the 2- day lag mean concentration of particulate matter less than 10 µ (PM_{10}) ($p = 0.016$), and the 2-day lag mean concentration of ozone ($p = 0.048$). After multivariate statistical analysis, predictive factors for perforated appendicitis were the consultation delay (OR: 1.621, 95% CI [1.288 - 2.039]; $p<10^{-3}$) and the 2 day lag mean concentration of PM_{10} (OR: 1.066, 95% CI [1.007-1.130]; $p = 0.029$).*
CONCLUSION: *Short-term exposure to particulate matter was associated with perforated appendicitis. Further large-scale studies are needed to support this conclusion.*

KEY WORDS: Air pollution, Appendicitis, perforated appendicitis, Climateparticulate matter

Introduction

Appendicitis is among the most common abdominal conditions requiring admission to emergency surgery departments. Untreated appendicitis may be perforated resulting in high morbidity and mortality rates .[1]
The incidence of acute appendicitis (AA) has been reported to vary substantially by country and geographic region, but the reasons for this variation are unknown [2]. Association with factors like diet and hygienic conditions have been suggested, but are not widely accepted [3]. Difference in the prevalence of appendicitis has been recognized recently by several researchers for environmental factors such as season, humidity, and viruses. [1]

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Indeed, some authors have shown that the occurrence of AA can be influenced by seasonal variations without giving clear explanations [4-7].
On the other side, a previous study suggested that acute appendicitis may be triggered by short-term exposure to air pollution [8]. Such effects might predispose certain individuals to develop appendicitis, or might influence its clinical presentation [9].
As epidemiological data on the relationship between acute appendicitis and environmental factors are relatively few and the issue is still controversial, we conducted this study which compared two groups of patients with perforated and nonperforated appendicitis in a sample of patients admitted to a university hospital of the city. We aimed to find possible associations with season, climatic factors or air pollution.

Methods

A cross-sectional study was performed in the General Surgical Department of Farhat Hached University Hospital of Sousse and included all patients hospitalized for acute appendicitis from January 1st to December 31st 2014.
Sousse is a city located in the Center of Tunisia. It belongs to the lower semi-arid bioclimatic stage and has a 4 - season climate. Temperatures are generally fairly mild: 11.2 °C for the month of January (the coldest month) and 26.3 °C for the month of August (the hottest month). The monthly thermal amplitudes are generally less than 10 °C.
Medical data were collected from the physical examinations and medical files. The diagnosis was based on clinical and paraclinical data, per-operative findings and the results of pathological examination.
For each patient, climatic and air pollution data corresponding to the day of hospitalization were collected. The two groups of perforated and nonperforated acute appendicitis were compared.
Air pollution data were obtained through air pollution modeling, which is a numerical tool used to describe the causal relationship between emissions, meteorology, atmospheric concentrations, deposition, and other factors. Air pollution measurements give quantitative information about ambient concentrations (hourly concentrations) and deposition, at specific locations and times. We used the data from the modeling platform of the National Agency for Protection of the Environment (ANPE). This platform was validated and calibrated for two years. The measured air pollutants were carbon dioxide (CO_2), ozone (O_3), sulfur dioxide (SO_2), oxides of nitrogen (NO_X), carbon monoxide (CO) and particulate matter (PM) less than 10 m in diameter (PM_{10}) and less than 2.5 m ($PM_{2.5}$).
We used Microsoft Excel to calculate the mean concentrations of each pollutant on the day of hospital admission and lagged by 1,2,3… and 7 days (from 1-d to 7-d) before hospital admission.
The weather parameters were collected from the National Institute of Meteorology (www.meteo.tn). The different climatic measures required for our study were taken from the monitoring station located in the city center. They were temperature (°C), relative humidity (%), atmospheric pressure (hectopascal), rainfall, force and direction of wind. We also used the average of each parameter on the day of hospital admission and lagged by 1,2,3,4,5,6 and 7 days (from 1-d to 7-d) before.
Data analysis was performed using SPSS for Windows, version 20.0. The differences between perforated and nonperforated appendicitis groups in terms of pollutants concentrations and weather parameters were analyzed using Student's « t »test. Chi-square test was used for the comparison of nominal data. A p value less than 0.05 was considered statistically significant. Logistic regression was used to estimate the risk of perforated appendicitis adjusted for daily average temperature and relative humidity.

Results

During the study period, we collected 246 cases of acute appendicitis. Perforated appendicitis was present in 37 cases (15.2% of the patients). The mean age of the patients was 27 ± 15.8 years with a peak incidence of appendicitis observed in patients aged 10-19 years (31.7% of the patients). Sex ratio was 1.23 (136 men and 110 women).The mean duration from the onset of symptoms until admission to hospital for all patients was 1.9 ± 1.3 days. Almost half of the patients (48.5%) consulted in less than 24 hours.
The mean age was 29.6 years in the group of perforated appendicitis versus 26.6 years in the nonperforated appendicitis group, with no statistically significant difference (p = 0.283). Male predominance was noted in both groups (59.5% versus 54.9%) with no statistically

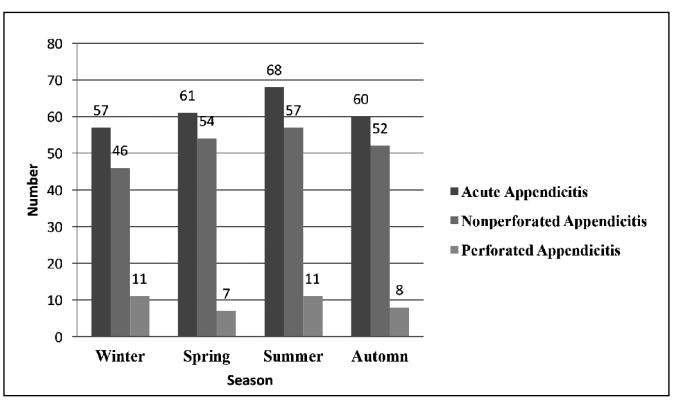

Fig. 1: Distribution of acute appendicitis, perforated and nonperforated appendicitis by season.

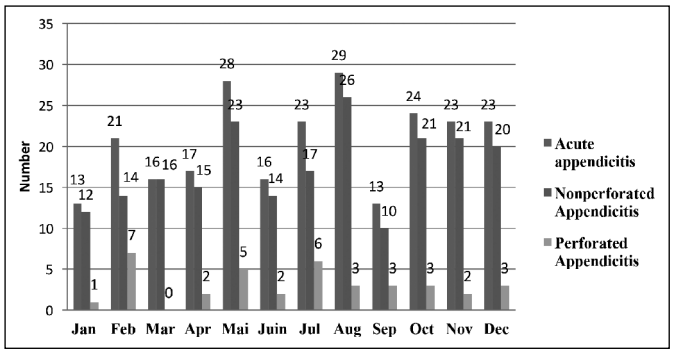

Fig. 2: Distribution of acute appendicitis, perforated and nonperforated appendicitis by month.

significant difference (p = 0.579). The interval between the onset of symptoms and admission was significantly increased in the perforated appendicitis group (2.9 days versus 1.7 days, p $<10^{-3}$).

While the incidence of acute appendicitis was higher during summer, the highest incidence of perforated appendicitis was observed equally in winter and summer (Fig. 1) without significant association (p=0,655). The months of August and May were marked by the highest incidence of AA reported in 11.8% and 11.4% respectively. The highest incidence of perforated appendicitis was observed during the month of February (18.9%) (Fig. 2) with no statistically significant difference (p = 0.259).

Compared to nonperforated appendicitis, perforated appendicitis was significantly associated with the average relative humidity of the 5- day lag (p = 0.046) (Table I) and rainfall of the 7-day lag (p = 0.043) (Table II). No significant association was found between perforated appendicitis and temperature, atmospheric pressure, wind direction and speed.

Furthermore, univariate analysis showed that perforated appendicitis was significantly associated with the daily mean concentration of carbon dioxide (p = 0.042) (Table III), the 2- day lag mean concentration of ozone (p = 0.048)(Table IV) and the 2- day lag mean concentration of particulate matter less than 10 µ (PM_{10}) (p = 0.016)(Table V).

TABLE I - *Association between perforated, nonperforated appendicitis and relative humidity*

	Nonperforated Appendicitis	Perforated Appendicitis	p
Mean relative humidity (%)	65,8	68,1	0,290
Mean relative humidity 1-day lag (%)	67,3	68,5	0,479
Mean relative humidity 3-day lag (%)	67,5	64,3	0,068
Mean relative humidity 5-day lag (%)	**66,6**	**62,8**	**0,046**
Mean relative humidity 7-day lag (%)	73,7	69,1	0,685

TABLE II - *Association between perforated, nonperforated appendicitis and rainfall*

	Nonperforated Appendicitis	Perforated Appendicitis	p
$Rainfalld_0$ (days)	31	2	0,194
Rainfall1-day lag (days)	38	7	0,925
Rainfall3-day lag (days)	37	6	0,817
Rainfall5-day lag (days)	39	3	0,114
Rainfall7-day lag (days)	**33**	**11**	**0,043**

TABLE III - *Association between perforated, nonperforated appendicitis and mean concentration of carbon dioxide(CO_2)*

	Nonperforated Appendicitis	Perforated Appendicitis	p
CO_2mean concentration d_0 (µg/m³)	**169880,57**	**302209,85**	**0,042**
CO_2mean concentrationof 1-day lag (µg/m³)	163336,04	221630,49	0,429
CO_2mean concentrationof 2-day lag (µg/m³)	159911,91	262112,01	0,080
CO_2mean concentrationof 3-day lag (µg/m³)	194341,81	150748,65	0,492
CO_2mean concentrationof 4-day lag (µg/m³)	248115,54	228759,55	0,828
CO_2mean concentrationof 5-day lag(µg/m³)	182668,75	188157,71	0,931
CO_2mean concentrationof 6-day lag (µg/m³)	201526,54	95246,88	0,104
CO_2mean concentrationof 7-day lag (µg/m³)	170477,74	151985,99	0,789

TABLE IV - *Association between perforated, nonperforated appendicitis and mean concentration of mean concentration of ozone (O_3)*

	Nonperforated Appendicitis	Perforated Appendicitis	P
O_3 mean concentration d_0 (µg/m³)	0,036255	0,034486	0,270
O_3mean concentration of 1-day lag (µg/m³)	0,036507	0,035085	0,367
O_3 mean concentration of 2-day lag (µg/m³)	**0,036075**	**0,032791**	**0,048**
O_3mean concentration of 3-day lag (µg/m³)	0,035820	0,034565	0,470
O_3mean concentration of 4-day lag (µg/m³)	0,036575	0,034708	0,301
O_3mean concentration of 5-day lag(µg/m³)	0,036478	0,034858	0,378
O_3mean concentration of 6-day lag (µg/m³)	0,036366	0,035202	0,537
O_3mean concentrationof 7-day lag (µg/m³)	0,036456	0,034847	0,374

TABLE V - *Association between perforated, nonperforated appendicitis and mean concentration of particulate matter less than 10 µm in diameter (PM_{10})*

	Nonperforated Appendicitis	Perforated Appendicitis	P
PM_{10} mean concentration d_0 (µg/m³)	5,87	7,57	0,149
PM_{10} mean concentration of 1-day lag (µg/m³)	5,61	6,91	0,290
PM_{10} mean concentration of 2-day lag (µg/m³)	**5,52**	**7,80**	**0,016**
PM_{10} mean concentration of 3-day lag (µg/m³)	6,05	6,01	0,971
PM_{10} mean concentration of 4-day lag (µg/m³)	7,179	6,91	0,858
PM_{10} mean concentration of 5-day lag(µg/m³)	5,84	6,11	0,806
PM_{10} mean concentration of 6-day lag (µg/m³)	6,39	5,07	0,222
PM_{10} mean concentration of 7-day lag (µg/m³)	5,55	4,47	0,339

After adjusting for daily average temperature and relative humidity, the predictive factors for perforated appendicitis were the consultation delay (OR: 1.621, 95% CI [1.288-2.039], p $<10^{-3}$) and the 2- day lag mean concentration ofPM_{10} (OR: 1.066, 95% CI [1.007-1.130], p = 0.029).

Discussion

Acute appendicitis (AA) is the most common abdominal emergency. However, its pathogenesis is unclear.
The medical practice shows that perforated appendicitis is not always explained by a longer duration of symptoms. Peritonitis can occur rapidly after the onset of symptomatology. Moreover, the consultation delay is not always correlated to a perforated appendicitis.
The spatio-temporal distribution of reported cases of appendicitis suggests that environmental exposures may contribute to its pathogenesis. The variation in the incidence of appendicitis between different countries [10-12], with a marked decrease in developed countries over the last few decades matching with the enactment of legislation that led to reductions in the concentrations of several outdoor air [9] support this theory.
In this context, this study was carried out with the aim to determine the seasonal variation of acute appendicitis and study the association between perforated appendicitis and short-term exposure to climatic factors and to air pollutants.
Our study has some limitations that should be considered. Actually, the size of the population was reduced probably because of the duration of the study and its monocentric character. In addition, the study was limited to one city while variations in environmental conditions in various cities of the country are well known.
However, it remains the first study conducted in a developing country to investigate the effect of short-term exposure of air pollutants on the occurrence of perforated appendicitis. The collection of air pollution data has been based on the modeling of the dispersion of pollutants in the atmosphere. We used data from the modeling platform of the National Agency for Protection of the Environment, which has been validated and calibrated for two years. This method has the advantage of taking into account location-specific geographical features such as population density or proximity to roads to describe small-scale spatial variations in air pollutant levels and thus not restrict its results to areas near the measurement stations. Besides, we used the 1-day, 2-day… and the 7-day lags before hospital admission to account for delays in the onset of appendicitis and presentation to hospital [8].
In our study, the highest incidence of AA was observed in summer, while the lowest was observed in winter. Our results are consistent with studies in South Korea [12,] The

United States [13], and India [14] showing a peak during the summer season and a lowest incidence during the winter season.

The reasons for increased incidence of AA during the warm period are not clear, although various speculations have been proposed such as the effect of dehydration, lower bowel movements or the effects of diet [15].

Another study reported that during summer, individuals are most likely to be outside and are served mainly high-carbohydrate and low-fiber diets in fast food restaurants. The authors assume that such a dietary regimen can lead to constipation and increase exposure to infectious agents, which can lead to acute appendicitis [16].

This increase may also reflect an infectious etiology [13], [16,17]. Such hypothesis was supported by the presence of concomitant peaks for other enteric infections [17].

In contrast, according to Sulu B et al. [1], in their study conducted in Kars, a city located in the eastern most part of Turkey, the frequency of appendicitis was the highest during winter. These findings were also noted in Kirman [18], a region with an altitude similar to that of Kars. The authors suggested a role of altitude in the seasonal variation of AA rate [1].Thus, for low altitude regions such as our city, Ontario [4], Jersey City [5], Ferrara [19] and Shahr-e-Rey [20], an increase in appendectomy rates was observed during summer.

Otherwise, in northern Saudi Arabia, incidence of acute appendicitis increased in the spring months coinciding with the onset of the sandstorm season [21]. This increase has been explained by the intense challenge to the mucosa associated lymphoid tissue from allergens, bacteria and viruses present in the dust.

According to Oguntola AS.et al [22], incidence of AA was higher during the rainy season (April to September) in Nigeria. Higher prevalence of humidity, infections and pollen allergens during this period could contribute to a higher incidence of appendicitis.

Other authors also postulated that seasonal variation in exposure to allergens and viral and bacterial infections, as well as changes in humidity, would explain the seasonal variation in AA [3,23,24].

In our study, the highest incidence of perforated appendicitis was noted in winter and summer with a non-statistically significant difference (p = 0.655). Thus, it does not appear to be influenced by seasonal variations. Our results agree with those found by Al-Omran Mand al [4] who described that the influence of seasonal variations is less evident in the case of perforated appendicitis.

For Sulu B et al [1], perforated appendicitis was seen in summer and autumn (for both, 27.6%; p<0.05). Similarly, Nabipour F [18] reported higher frequencies of perforated appendicitis at the same period (p=0.031). The author also reported a relation between seasonal incidence and type of histopathology; the incidence of AA was higher in winter (35.2%), suppurative appendicitis was higher in spring (27.5% of cases) and gangrenous appendicitis was higher in summer (27.1% of cases).

In an American study that included children under the age of 18, the authors concluded that the incidence of perforated appendicitis was the highest in autumn (25.8%). Patients were more likely to have perforated appendicitis in autumn (OR: 1.12, 95% CI: 1.04-1.21) and winter (OR: 1.11, 95% CI: 1.03- 1.20) than spring or summer [25]. In an Italian study, cases of AA with peritonitis were more frequent in summer (p = 0.002) [19]. Nevertheless, the physiologic cause for seasonal variation in perforated appendicitis rates is unknown [25].

In the present study, perforated appendicitis was associated with the average relative humidity of the 5-day lag compared to nonperforated appendicitis (p = 0.046). It has been reported that relative humidity could influence the incidence of AA [4,12,19,26]. Studies have focused on both humidity increases [24,27] and decreases [28]. Brumer M et al [28] found a significant negative correlation between humidity and AA. The loss of body water caused by the decrease in humidity may result in fecal stasis, dehydration and inflammation, thereby increasing the risk of plugging in the appendix lumen [1]. In contrast, other authors did not find an association between humidity and the occurrence of AA [1,15,29].

In our study, perforated appendicitis was also associated significantly with the rainfall of the 7-day lag (p = 0.043). Several studies have found an increase in AA during the rainy season [22,23], but the authors did not explain this association by the effect of rain in itself but rather by the humidity it induces. Others aimed to study the effect of rainfall on the incidence of AA but no correlation has been found [29].

On the other hand, a significant association was found, in our study, between 2- day lag mean concentration of PM_{10} and perforated appendicitis (OR: 1.066, 95% CI [1.007-1.130]; p = 0.029). We suggest that short-term exposure to particulate matter is a predictive factor in the occurrence of perforated appendicitis.

Our results are in line with a recent Canadian study which found that the incidence of appendicitis was significantly associated with short-term exposure to air pollution[8]. However, those investigators found that an increase in the interquartile range of the 5-day average of ozone was associated with appendicitis (OR:1.14, 95% CI [1.03–1.25]); in summer (July–August), the effects were most pronounced for ozone (OR: 1.32, 95% CI [1.10–1.57]), sulfurdioxide (OR: 1.30, 95% CI [1.03–1.63]), nitrogen dioxide (OR:1.76, 95% CI [1.20–2.58]), carbon monoxide (OR: 1.35, 95%CI [1.01–1.80]) and PM_{10} (OR: 1.20, 95% CI [1.05–1.38]).

According to Kaplan GG et al 9, higher levels of ambient ozone exposure may increase the risk of perforated appendicitis.

However, other studies have found no relation between hospital admission for acute appendicitis and air pollution [30,31].

The mechanisms by which air pollution may increase the risk of appendicitis are unknown. Exposure to air

pollutants, either through inhalation or ingestion, may induce inflammatory responses that are also evident in appendicitis [8].
Most inhaled particles deposited in the nasopharyngeal compartment and airways are removed through mucociliary clearance and swallowed within a day and thus, gastrointestinal effects may be due to direct effects of particles [32].
A literature review presented a number of plausible mechanisms by which air pollution exposure might impact the intestine; many of them are extrapolated from research in lungs and other organs. Air pollutants are potentially directly cytotoxic to intestinal epithelial cells, cell permeabilization, and activation of signaling pathways leading to innate inflammation. Immune cells are directly activated by pollutants. Commensal gut microbiota could also be affected by pollution [33].
Although perforated appendicitis may result from a delay in diagnosing appendicitis, emerging evidence suggests that perforated appendicitis also may represent a distinct disease phenotype. For example, perforated appendicitis may have a divergent immunological pathogenesis (T helper 17 predominant) as compared with non perforated appendicitis [9]. Potential effects of air pollution on pro inflammatory immune responses, and on the host microbiome could contribute to the development of perforated appendicitis [9].

Conclusion

Our findings suggest that the risk of developing perforated appendicitis may be increased by short term exposure to PM_{10}. The mechanisms of this phenomenon are still unclear although some hypotheses have been suggested. Further prospective studies are needed to support this conclusion.

Riassunto

L'appendicite acuta è il più comune tipo di emergenza addominale. La sua patogenesi appare multifattoriale, e molti studi suggeriscono una relazione tra la sua insorgenza ed alcuni fattori ambientali. L'inquinamento atmosferico predispone alcuni individui allo sviluppo dell'appendicite perforata, ma i dati sono relativamente scarsi e i risultati ancora controversi.
Questo studio si è proposto di determinare la variazione stagionale dell'appendicite acuta e l'associazione della perforazione appendicolare con l'esposizione di breve durata ai fattori climatici e all'inquinamento atmosferico. Lo studio trasversale è stato fatto includendo pazienti ricoverati nel dipartimento di chirurgia generale dell'Ospedale Universitario Farhat Hached di Sousse per appendicite acuta tra il 1° gennaio ed il 31 dicembre 2014.
Le condizioni climatiche di questo periodo sono state quelle raccolte dall'Istituto Nazionale di Meteorologia, i dati sull'inquinamento atmosferico dall'Agenzia Nazionale per la protezione dell'ambiente ottenuti dal modello di polluzione armosferica. Per l'analisi statistica è stata utilizzata la concentrazione media di ciascun fattore ambientale corrispondente al giorno del ricovero ospedaliero esteso ai 7 giorni precedenti.
Questi fattori sono stati confrontati tra il gruppo di pazienti con appendicite perforata e quello delle appendiciti senza perforazione.
Dei 246 casi di appendicite acuta raccolti, i casi di appendicite perforate riguardava il 15,2% del totale. L'incidenza della appendicite acuta è risultata più elevata durante l'estate.
Al confronto con l'appendicite senza perforazione, la perforazione appendicolare è risultata significativamente associata con l'umidità media relativa del 5 giorni precedenti il ricovero ($p=0.046$), con la pioggia dei 7 giorni precedenti ($p = 0.043$), e con il ritardo di ricorso al medico ($p <10^{-3}$). Inoltre l'appendicite perforata è risultata significativamente associate con la concentrazione media giornaliera dell'anidride carbonica ($p = 0.042$), la concentrazione media nei due giorni precedenti il ricovero del microparticolato inferiore ai 10 µ (PM_{10}) ($p = 0.016$), e la concentrazione di ozono dei due giorni precedenti ($p = 0.048$).
Dopo analisi statistica multivariate I fattori predittivi dell'appendicite perforate sono risultati il ritardo di consultazione del medico, (OR: 1.621, 95% CI [1.288 - 2.039]; $p<10^{-3}$) e la concentrazione nei due giorni precedenti il ricovero del PM_{10} (OR: 1.066, 95% CI [1.007-1.130]; $p = 0.029$).
In conclusione l'esposizione per breve tempo al microparticolato è risultato associato con l'appendicite perforata. Ulteriori studi a larga scala sono necessari per confermare questo risultato.

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