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INTERRELATIONSHIPS OF THE SYDNEY GRADED VARIABLES: A STUDY OF GASTRIC ENDOSCOPIC BIOPSIES IN EDO-DELTA, NIGERIA.

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ABSTRACT

Introduction: Chronic Gastritis is reported based on semi-quantitative grading of 'the Sydney' morphologic variables. A proportion of patients with chronic Gastritis may progress to atrophic gastritis of varying morphology and grades during their lifetime, with attendant sequelae. A precise prediction of specific pattern of progression and sequelae cannot always be made for a given patient, most likely due to differences in individual and population genetics. More predictable patterns may emerge as subsets of larger populations are studied to detect patterns that may deviate from the expected.

Aim: To evaluate the relationships between the histologic parameters of the Sydney system, in a small Nigerian population.

Materials and Methods: The clinical data and slides processed from paraffin embedded tissue blocks of endoscopic biopsies of 117 patients from the Edo-Delta axis of Nigeria with histologic diagnosis of chronic in the gastritis were studied, statistically analyzed and presented.

Results: There were 117 patients, 60 males and 57 females. Age range:15-86 years; mean age = 48.6 years$\pm$1.56; modal age group, 50-59 years. There is a strong association between the presence of Helicobacter pylori and presence of activity (p value < 0.001) and grade of Helicobacter pylori and grade of activity (p value = 0.029) . Helicobacter pylori presence and atrophy are also related, but the relationship between their grades are not statistically significant (p value = 0.136). Helicobacter pylori presence is not significantly associated with intestinal metaplasia (p value = 0.917); but intestinal metaplasia is strongly related to atrophy (p value < 0.001). Unlike in some studies, we could not establish a statistically significant relationship

between the density of Helicobacter Pylori infection and the grade of mononuclear inflammation (p value = 0.494).

Conclusion: Earlier events in the progression chronic atrophic gastritis are strongly linked to Helicobacter pylori infection. While later events are less strongly linked. The weaker/ non-statistically significant association of Helicobacter pylori with Atrophy and Intestinal Metaplasia suggest that other factors have a role to play in the progression of chronic gastritis to the atrophic /metaplastic

Keywords: Chronic Gastritis, Graded Variables, Helicobacter Pylori, Sydney system.

INTRODUCTION

Gastritis is gastric inflammation associated with mucosal injury. This inflammation is evidenced by an increased infiltrate of lymphocytes, plasma cells, and/or neutrophils in the lamina propria and mucosal epithelium; that may later be accompanied by atrophic and metaplastic changes. The Sydney system of classification of gastritis (1990) and its updated version (1994) classifies gastritis based on topography; morphology and etiology, using semi-quantitative grading of 5 variables. These variables are: chronic inflammation, Helicobacter pylori density, neutrophil infiltration (activity), glandular atrophy and intestinal metaplasia. This system classified gastritis into: acute and chronic gastritis. Acute gastritis may be caused by many factors including various forms of physical and psychological stress, as well as infections and chemicals/toxins.

Based on topography, morphology and etiology, chronic gastritis is further divided into:

- Non-atrophic gastritis, usually due to Helicobacter pylori;
- Atrophic gastritis, which includes :- Autoimmune/diffuse corporal/type A gastritis, as well as the Helicobacter pylori caused Multifocal atrophic/type B and AB
- Special forms of gastritis.

The updated Sydney system morphological variables are semi-quantitatively graded and documenting as, absent (0); mild (1); moderate (2); or marked (3); using the visual analogue scale.

Though there are other histological features of chronic gastritis which are noted but not graded e.g. Surface epithelial damage, erosions and mucus depletion ; Lymphoid follicles; pseudopyloric metaplasia; Foveolar hyperplasia; Pancreatic acinar; Endocrine cell hyperplasia.

Helicobacter pylori, which is recognized as a cause of chronic gastritis amongst other factors. Other recognized causes of chronic gastritis include, autoimmunity against gastric parietal cells; other infections; drugs; chemicals and toxins. The association of colonization of the gastric mucosa by Helicobacter pylori with chronic inflammation of the stomach and subsequent development of other gastric lesions was first documented by Robin Warren and Barry Marshal in 1983.[1] Since then evidence has grown to support this and literature is replete with documentation of colonization of the stomach by H. pylori in gastritis, gastric ulcer, gastric mucosal dysplasia, gastric carcinoma and gastric lymphoma. Helicobacter pylori, is the most important aetiologic agent associated with chronic gastritis accounting for 80-90% of cases worldwide[2, 3]. It is also found in 95% of duodenal ulcers and 70-80% of gastric ulcers[4];the lower figure recorded for gastric ulcers being probably a reflection of the frequent finding of atrophic gastritis, and intestinal metaplasia in association with gastric ulcers, considering that areas of atrophy or intestinal metaplasia, are less often, and less densely colonized by H. pylori[5]. Many studies have demonstrated a link between gastric H. pylori infection leading to chronic gastritis and subsequent development of carcinoma, especially in setting of atrophy and intestinal metaplasia. Forty three to eighty three percent of gastric carcinoma biopsies (in different series); and approximately 90% of Mucosa Associated Lymphoid Tissue (MALT) lymphoma biopsies, have been found to be positive for Helicobacter pylori[6].

Chronic inflammation of the gastric mucosa, irrespective of the etiology (usually characterized by mononuclear cell infiltration with or without polymorphs), progressively spreads to involve the whole, or most of the mucosa (usually in the absence of erosions) leading

to injury resulting in atrophy and intestinal metaplasia[7]. These changes have been found to precede, and may progress to, dysplasia with eventual development of carcinoma. Lamina propria and Intraepithelial neutrophil infiltration is a measure of active inflammation on a background of chronic inflammation. Its intensity correlates well with the extent of mucosal damage and often with density of H pylori infection[8,19]. Glandular atrophy is loss of glandular tissue characterized by thinning of the mucosa. Atrophy in the corpus is the absolute or relative reduction in the number of acid secreting glands evidenced by an increased stroma component or a replacement of acid secreting cells by mucus secreting cells (pseudopyloric metaplasia). Minor degrees of atrophy in antrum may be difficult because of the greater amount of connective tissue present. The diagnosis is reinforced by the presence of intestinal metaplasia, although these processes are graded independently. In gastric intestinal metaplasia the surface and foveolar epithelium of the stomach comes to resemble small or large intestinal epithelium, in morphology and histochemistry. Metaplasia almost always reflects some degree of gastric mucosal damage usually chronic gastritis. Studies have documented the association between H pylori infection and increased prevalence of intestinal metaplasia and it has been shown that gastric adenocarcinomas commonly arise in areas affected by intestinal metaplasia[10, 11].

The Sydney system and its Updated version remain relevant today as they were thirty years ago. Sipponnen and Price in their 2010 article, "The Sydney system of Gastritis: 20 years ago"[12] revealed that, the selection of the morphological key variables for the Sydney system were based on relevant papers published in literature some of which were the publications of Schindler in 1947, in which he described a 'superficial gastritis' that may progress to 'atrophic gastritis' with time. Others were reports and studies from Finland and Estonia; as well as the 1972 publication of whitehead Truelove and Gear. These

publications indicated that patients with Chronic gastritis had mononuclear inflammation that results in mucosal injury. This may be associated with polymorphonuclear inflammation (activity), a reflection of the host reaction to Helicobacter pylori infection, particularly cytotoxic strains; which is associated with the risk of progression to atrophy. A proportion of patients with chronic Gastritis may progress to atrophic gastritis of varying morphology and grades during their lifetime; and the complications and diseases associated with chronic gastritis e.g. gastric cancer and duodenal ulcers, are dependent on extent, severity and topography of infection, though a precise prediction of what specific pattern of progression and sequelae that might ensue later, cannot always be made for a given patient. This may not be unrelated to differences in individual and population genetics. The Updated Sydney System was itself an expression of 'disquiet' about the Original Sydney system, but it led to the useful -many will agree- recommendation for additional biopsy from the incisura angularis; and the provision of a visual analogue scale to promote easier and more reproducible of grading of the histologic parameters. In addition,Stolte and Meining, while stating that the Sydney system of comparative grading may permit the identification of high risk phenotypes, opined that 'the Updated Sydney system is not the last word but rather is open to the discovery of new facts' [13].

Given the broad range of possibilities in the progression and outcome of chronic gastritis; and the interplay of host genetics and disease etiology; clearer patterns may yet emerge when large populations are studied as subsets. There is a need for continued evaluation of subsets of large populations to detect patterns that may deviate from the expected. It is imperative, if there is to be a firm basis for the adoption of recommended diagnostic, prognostic and therapeutic (international/global) guidelines, or the management of H. pylori associated lesions and gastric diseases in general. This study focuses on evaluating the significance and the relationships between the histologic parameters of the

Sydney system, in a small Nigerian population.

MATERIALS AND METHODS

A study of gastric endoscopic biopsies from 117 patients with chronic gastritis was done. Relevant demographic and clinical information was extracted from recordsat the University of Benin Teaching Hospital; and the Biogenics Laboratory Benin. These centers serve Edo-delta region of the country. Original slides were retrieved for review. Formalin fixed and paraffin embedded tissue blocks were sectioned at 2-3μm and stained with Haematoxylin and Eosin. Modified giemsa stain, and Alcian blue/ PAS stain were used for verification of Helicobacter pylori and demonstration of intestinal metaplasia respectively.

All biopsies were evaluated and graded based on the Sydney parameters. Data was analyzed, and tested to for relationships between parameters. Statistical significance was set at p-value less than 0.05 (<0.05).

RESULTS

Age and sex distribution

In this study of endoscopic biopsies of 117 patients with chronic gastritis, ages ranged between 15 and 86 years, with a mean age of 48.6 years$\pm$1.56 SD and a modal age group of 50-59 years accounting for 27.4% of cases (Table I).There were 60 males and 57 females. There was a slight predominance of male patients giving a Male-female ratio of 1.05:1.

Relationships between Graded variables.

All patients in this study (100%) had mononuclear inflammation; 64.9% had neutrophilic inflammation; 59% were Helicobacter Pylori positive; 53% had atrophy and 16.2% had intestinal Metaplasia.

There was a strong relationship between H. pylori density, and the grade of Inflammatory Activity (p-value = 0.029); and an even stronger relationship between the presence of Helicobacter pylori infection and the presence of inflammatory activity (p-value <0.001) (Table II). Though Helicobacter pylori is an established cause of Chronic gastritis, Helicobacter pylori was present in 59% of cases, there was no statistically significant relationship between

the density of H. pylori colonization and the grade of mononuclear inflammation. (p-value = 0.494) (Table III).

The presence of atrophy was strongly related to the Helicobacter pylori positivity,(p-value =0.001) (Table IV), but the strength of association between the grade of atrophy and the density of colonization and was not statistically significant (p-value =0.136).
The presence of Helicobacter pylori was not significantly associated with Intestinal Metaplasia, (p-value =0.917). However there was a strong association between the presence of Atrophy and that of Intestinal Metaplasia. (p-value <0.001)(Table V).

DISCUSSION

In this study of 117 patients with chronic gastritis. The ages of the 117 patients ranged between 15 and 86 years. The mean age was 48.6 years and the modal age group was 50-59 years. Chronic Inflammation was first noticed in the 2nd decade peaking in the 6th decade and tailing off in the 8th decade, this pattern is the same observed in other Nigerian studies[14, 15]. Studies from Europe and Japan showed that chronic gastritis is uncommon in children and young adults, suggesting a later age at acquisition of infection, but a higher percentage (approx. 90%) of persons, 60 years and above have some form of gastritis[16].

All patients in this study (100%) had mononuclear inflammation; 64.9% had neutrophilic inflammation; 59% were Helicobacter Pylori positive; 53% had atrophy and 16.2% had intestinal Metaplasia. We observed no statistically significant relationship between the degree of mononuclear inflammation and the density of H. pylori infection. This has been our experience[17]but different from findings in other studies[14, 15]. This does not rule out an existence of a relationship between the mere presence of mononuclear inflammation and the existence of H. pylori infection. That there is an association between Helicobacter pylori infection and the presence of mononuclear inflammation in the mucosa is reflected in the age distribution of patients with chronic gastritis and that of the Helicobacter pylori infected population which is similar, though the peak age is a decade earlier(Figure 1). A

general population based study, rather than a study based on dyspeptic/ symptomatic patients may better demonstrate statistically the significance/ strength of association between Helicobacter pylori infection and the mere presence of mononuclear inflammation in the mucosa (irrespective of the grade/density of inflammation or infection).

The presence of Helicobacter pylori shows a strong association with the presence of Inflammatory activity (p- value <0.001). This is the trend in many studies[2, 14, 15, 18].The density of Helicobacter pylori infection generally did not correlate well with the severity of the graded variables except Activity (p-value =0.029).The natural history of chronic gastritis is that a percentage of patients progress to Chronic Atrophic Gastritis, which is characterized by atrophy and intestinal metaplasia. This is the basis of the sub-classification of Chronic Gastritis into the Non-atrophic and Atrophic forms by the Updated Sydney Classification System (Appendix I). In this study, 62 patients (53%) had Chronic Atrophic Gastritis, 55 patients (47%) had Non-atrophic Chronic Gastritis; with both groups having helicobacter pylori positive and negative cases. It is believed that majority of the non-helicobacter pylori positive biopsies are Helicobacter pylori associated lesions, this is suggested by seroprevalence studies[19]. The use of medication cannot be ruled out in the Helicobacter pylori Negative groups. It has been said that the progression of Chronic Gastritis to the atrophic form can occur, independent of the Helicobacter pylori organism even if it is the initiating factor. According to Kuipers and Meijer,

> "Helicobacter pylori gastritis progresses to gland loss and intestinal metaplasia in a considerable proportion of colonized subjects. The progression to atrophic gastritis is a slow process, occurring with an incidence of 1-2% per year. The progression of chronic H. pylori gastritis is the same in Africa as in Europe and South America...."[20]

This would suggest that, marked differences in rates of atrophy

between regions are, not expected. Moreover with an incidence rate of 1-2% per year, 30-60% of patients with chronic gastritis will have varying degrees of atrophy by 50years of age. The rates of atrophy and intestinal metaplasia recorded in this study are 53% and 16.2% respectively. Although, the rate of intestinal metaplasia is as commonly observed, the percentage of patients with atrophy is intermediate between that documented in multicenter large population studies in Japan, with atrophy rates as high as 82.9%; and the rates commonly reported in this country and some others (range: 11.6%-29.8%) [21, 14, 15, 22].

There is a strong association between H. pylori infection and atrophy, p-value =0.004. The density of H pylori infection, however, does not correlate well with the degree of atrophy (p-value =0.136). The association between Helicobacter pylori and intestinal metaplasia is not statistically significant. However, intestinal metaplasia is very strongly associated with atrophy – p-value <0.001. The strong association between intestinal metaplasia and atrophy however supports the fact that the metaplastic changes occur in the setting of atrophy. Sushan et al, in Nepal documented similar trends of association between the grade of Helicobacter pylori and chronic inflammation as well as activity; but no statistically significant association with grades of atrophy and grades of intestinal metaplasia. [23]Jayanthi et al, in India however recorded a statistically significant association between Helicobacter pylori positivity and all other graded variables, different from our observation.[24]

Our findings suggest that earlier events in the pathophysiology of chronic atrophic gastritis i.e. chronic inflammation; activity are strongly linked to Helicobacter pylori infection while the weaker/ non-statistically significant association with Atrophy and Intestinal Metaplasia suggest that other factors have a role to play in the progression of chronic gastritis to the atrophic /metaplastic phenotypes. Other factors that have been proposed include genetic, macro- and micro- environmental factors[19].

CONCLUSION

Chronic Gastritis has a broad histopathological and

topographical spectrum and leads to patterns of disease that have been well recognized and characterized. There is a strong association between the presence of Helicobacter pylori and activity; and to lesser extent atrophy. The association between H. pylori infection and intestinal metaplasia is not statistically significant but the presence of intestinal metaplasia, strongly correlates with that of atrophy.In contrast to other studies our study does not show a statistically significant relationship between the density of Helicobacter Pylori infection and the grade of mononuclear inflammation.

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TABLES

TABLE I. Age distribution of patients.

Age group	Frequency	Percentage
0-9	0	
10-19	1	0.9%
20-29	8	6.8%
30-39	12	10.3%
40-49	25	21.4%
50-59	32	27.4%
60-69	22	18.8%
70-79	12	10.3%
80-89	5	4.3%
Total	**117**	**100%**

TABLE II. H. pylori density and grade of Activity.

Density of h. Pylori .	No activity	Mild activity	Moderate activity	Marked activity	Total
Mild	3	6	9	3	21
Moderate	3	13	5	9	30
Marked	0	2	11	5	18
Total	6	21	25	17	69

X^2=14.086 df=6 p-value=0.029.

TABLE III. Density of H. pylori colonization and grade of Mononuclear inflammation.

DENSITY OF H. PYLORI	MILD GASTRITIS	MODERATE GASTRITIS	MARKED GASTRITIS	TOTAL
MILD	1	11	9	21
MODERATE	4	13	13	30
MARKED	0	9	9	18
TOTAL	5	33	31	69

X^2=3.393 df=6 p-value=0.494

TABLE V. Association between Helicobacter pylori Infection and Atrophy.

Helicobacter pylori infection	Atrophic	Non-atrophic	Total
Present	45	24	69
Absent	17	31	48
Total	62	55	117

X^2=10.092 df=1 p-value=0.001.

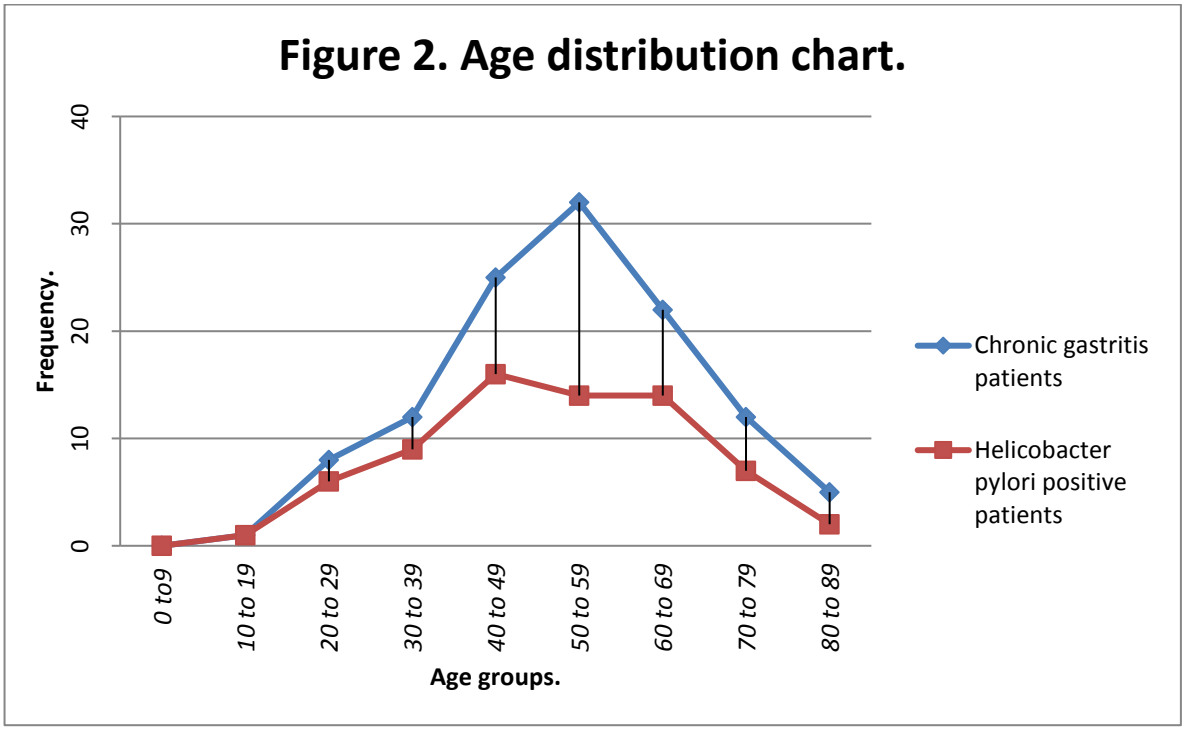
TABLE VI. Association between Atrophy and Intestinal metaplasia.

Atrophy	Intestinal metaplasia Present	Intestinal metaplasia Absent	Total
Present	18	44	62
Absent	1	54	55
Total	19	98	117

X^2=15.87 df=1 p-value is <0.001.

FIGURES

FIGURE I.



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