

ORIGINAL PAPERS

Neurogenic appendicopathy. A report of 8 cases

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ABSTRACT

Introduction: Neurogenic appendicopathy is not a very well-known disease.

Objective: To analyze the experience in the management of neurogenic appendicopathy in a tertiary hospital, assessing its clinical presentation, histological staging, the treatment carried out and its clinical evolution.

Method: The study population included patients with histopathological criteria for neurogenic appendicopathy who did not present with MEN 2B syndrome, neurofibromatosis type I or Cowden syndrome. An analysis was carried out of tissue samples taken from a simple appendectomy after a diagnosis of neurogenic appendicopathy between 2000 and 2013, inclusive. The histopathological criteria were neurogenic hyperplasia with S-100 protein positivity and neuron-specific enolase in the immunohistochemical analysis.

Results: Of the 4,969 samples from the appendectomies analyzed, 0.16% (n = 8) met histopathological criteria of neurogenic appendicopathy. The age at presentation was 27.8 ± 12 years. Four patients were male and four were female. All patients started with abdominal pain in the right iliac fossa (RIF), and were operated on due to a diagnosis of acute appendix, with a simple appendectomy being performed. In four cases, another associated disease accounted for the pain in the RIF. With regard to histopathological type, submucosal neurogenic hyperplasia was present in five patients and fibrous obliteration in three patients. No statistically significant differences were found between the histological types. After surgery, during a mean follow up of 73.2 ± 28 months (15-105), all the patients remained asymptomatic.

Conclusion: Neurogenic appendicopathy is an uncommon entity that can evolve as abdominal pain which is similar to acute appendix. Simple appendectomy is curative.

Key words: Neurogenic appendicopathy. Treatment. Fibrous obliteration. Neurogenic hyperplasia.

INTRODUCTION

Neurogenous hyperplasia of the appendix was first described by Masson in 1928 (1). It involves hyperplasia

of enterochromaffin-like endocrine cells and non myelinated nerve fibers (2). The spectrum of disease for this lesion ranges from intramucosal hyperplasia with intact appendiceal lumen that frequently coexists with nerve growth in submucosal and muscular areas, to transverse obliteration of the appendix formed by variable proportions of fibrous tissue and nerve fibers. The specimens in which fibrous tissue predominate are considered as a final stage of this disease. It is thought that repeated subclinical episodes of minimal inflammation could cause this lesion (3).

Few studies have analyzed this appendicular disease, leading to a lack of understanding about its clinical presentation and the most appropriate treatment (2-6).

The objective of this study was to analyze the experience of managing neurogenic appendicopathy in a tertiary hospital, assessing its clinical presentation, its histological staging, the treatment carried out and its clinical evolution.

MATERIAL AND METHODS

Study population

The study population consisted of patients who met the histopathological criteria of neurogenic appendicopathy.

The microscopic appearance of the lesion consists of a proliferation of fusiform cells organized in short fascicles with lengthened and wavy nuclei in hematoxylin and eosin staining, with S-100 protein and neuron-specific enolase positivity in the immunohistochemical analysis.

Sample selection

An analysis was carried out on the samples taken during the simple appendectomy in a tertiary university hospital between 2000 and 2013, inclusive.

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Inclusion criteria

Patients who fulfilled the following criteria were included:

1. Patients with a histopathological diagnosis of neurogenic appendicopathy in the samples of the simple appendectomy.
2. Complete clinical history and minimum follow-up of one year.
3. Available paraffin slides of the appendices analyzed.

Exclusion criteria

Patients who met the following criteria were excluded:

1. Presenting with MEN 2B syndrome.
2. Presenting with type I neurofibromatosis (Von Recklinghausen's disease).
3. Presenting with Cowden syndrome.

Study methodology

Histopathological reports of surgically resected appendices during simple appendectomies were revised, selecting the cases with an already established histopathological diagnosis of neurogenic hyperplasia, or those in which the presence of the proliferation of nerve cells was described. Afterwards, the paraffin slides were reviewed in order to make a definitive diagnosis and to classify them within three histological types: mucosal hyperplasia, submucosal hyperplasia and fibrous obliteration of the lumen (appendiceal neuroma). Once the histopathological diagnosis had been confirmed, clinical histories were revised to fulfil the data collection protocol.

Variables analyzed

The variables analyzed were taken from the patients' clinical histories and the hospital database. With regard to patients treated in other hospitals, the data were requested from the respective hospitals.

The following variables were analyzed:

1. Histopathological variables of neurogenic appendicopathy:
 - a) Mucosal neurogenous hyperplasia: the proliferation of nerve cells only occurs within the mucosa.
 - b) Submucosal neurogenous hyperplasia: the proliferation of nerve cells occurs in the area of the submucosa and even at the muscular layer.
 - c) Fibrous obliteration with neural transformation of the appendiceal lumen (appendiceal neuron): the appendiceal lumen is totally obliterated by variable quantities of fibrous tissue and nerve fibers.
2. Frequency divided by the total number of appendectomies performed.
3. Sociopersonal: age and sex.
4. Clinical:
 - a) Personal antecedents.
 - b) Clinical characteristics.
 - c) Temperature (°C). Febrile was defined as a temperature between ≥ 37.5 °C and < 38 °C and a fever as a temperature ≥ 38 °C.

- d) Analytical data: leucocytes and % neutrophils. Leucocytosis is defined as the number of leucocytes in blood $> 11,000$.
- e) Abdominal ultrasound data.
5. Surgical:
 - a) Type of surgical intervention.
 - b) Surgical approach.
 - c) Intraoperative findings.
 - d) Surgical time.
 - e) Postsurgical complications.
 - f) Pathological anatomy.
6. Follow up: percentage remission of clinical symptoms.

Statistical analysis

Statistical analysis was carried out using SPSS 21.0 software (IBM Software Group, Attention: Licensing, 233 S. Wacker Dr., Chicago, IL 60606, USA). For categorical variables, the data have been expressed using frequencies. For the comparison of groups with qualitative variables an analysis of contingency tables was carried out using Pearson's Chi-squared test, using Fisher's exact test where appropriate. The quantitative variables have been expressed as means \pm standard deviation. Normal distribution of the variables has been checked by the Saphiro-Wilk test. For the comparison of quantitative variables among the groups studied when these followed a normal distribution, the two means were compared using the Student's t-test for the independent variables, and when the variables did not follow a normal distribution, a nonparametric test was used, Mann-Whitney's U-test. A value of $p < 0.05$ was considered to be statistically significant.

RESULTS

Frequency

Of the 4,969 appendices analyzed, eight patients met the selection criteria, with neurogenic appendicopathy occurring in 0.16% of all the simple appendectomies.

Form of presentation

Mean age of presentation was 27.8 ± 12 years (7-43), with four male patients. With regard to clinical symptoms, all the patients ($n = 8$) initially experienced abdominal pain in the RIF with signs of peritoneal irritation in this area. Seven patients had a fever, with a mean temperature of 36.9 ± 0.7 °C (36.2-38.5). The mean number of hours with pain was 36 ± 48 hours (12-144). In the blood test, the mean leucocyte value was $10,896.5 \pm 4,347.1$ (5,980-17,900) and the mean percentage of neutrophils was $73.3 \pm 13.1\%$ (49.1-90.1). Two patients had leucocytosis (cases 4 and 8) due to pelvic inflammatory disease and acute appendicitis respectively. An abdominal ultrasound was carried out in five patients, the findings being compatible with acute appendicitis in four cases and the cecal appendix was not seen in the other case (Table I).

Table I. Description of the neurogenic appendicopathy series of this study

Case	Age	Sex	Pain (hours)	Temp (°C)	Leucocytes (% neutrophils)	Abdominal ultrasound	Intraoperative pathological findings	Pathological anatomy		
								Histopathological type	Length and diameter (cm)	
1	34	Male	24	36.3	10,439 (73.6%)	Not carried out	No findings	Fibrous obliteration	6	0.6
2	43	Female	12	36.2	5,980 (49.1%)	Compatible with AA	Broken ovarian follicle	Submucosal hyperplasia	7	0.5
3	18	Female	12	36.9	8,300 (70.7%)	Not carried out	Ileitis	Submucosal hyperplasia	6.5	0.6
4	42	Female	144	37.1	17,900 (81.0%)	Not carried out	EIP	Submucosal hyperplasia	6	0.6
5	29	Female	12	36.5	6,990 (61.1%)	Compatible with AA	No findings	Submucosal hyperplasia	5.5	0.5
6	25	Male	24	36.9	9,140 (77.6%)	Compatible with AA	No findings	Fibrous obliteration	8	0.5
7	25	Male	24	38.5	11,780 (83.5%)	Appendix not seen	No findings	Fibrous obliteration	4	0.5
8	7	Male	12	36.8	16,640 (90.1%)	Compatible with AA	Acute appendicitis	Submucosal hyperplasia	6.5	0.5

PID: Pelvic inflammatory disease; AA: Acute appendix; Temp: Temperature.

Treatment

Diagnosis was acute appendicitis in all the patients (n = 8), which is why surgery was performed in all cases. Regarding the surgical approach used, seven patients were operated on by a laparoscopic approach and one by a McBurney incision. In terms of intraoperative findings, in four patients there were pathological findings: a broken ovarian follicle with a minimal quantity of intra-abdominal blood flow (case 2), ileitis (case 3), pelvic inflammatory disease (case 4) and acute appendicitis (case 8). The cecal appendix was macroscopically normal in seven patients, being pathological in the case associated with acute appendix (case 8).

In all the patients simple appendectomy was performed, except in case 2, in which the blood content was aspirated from the bottom of the Douglas pouch and the RIF of the broken ovarian follicle. Mean surgical time was 45.6 ± 18.2 minutes (20-75). One patient had complications, in this case bleeding from the left inferior epigastric artery due to an iatrogenic lesion when one of the trocars was introduced.

Histology

In the histopathological analysis, the mean length of the cecal appendix was 6.1 ± 1.1 cm (4-8) and the mean diameter was 0.5 ± 0.05 cm (0.5-0.6). Regarding the type of histopathology, five patients had submucosal neurogenic hyperplasia and three had a fibrous obliteration of the lumen of the appendix (Fig. 1). In case number 8 acute, purulent appendicitis was found together with neuronal hyperplasia phenomena.

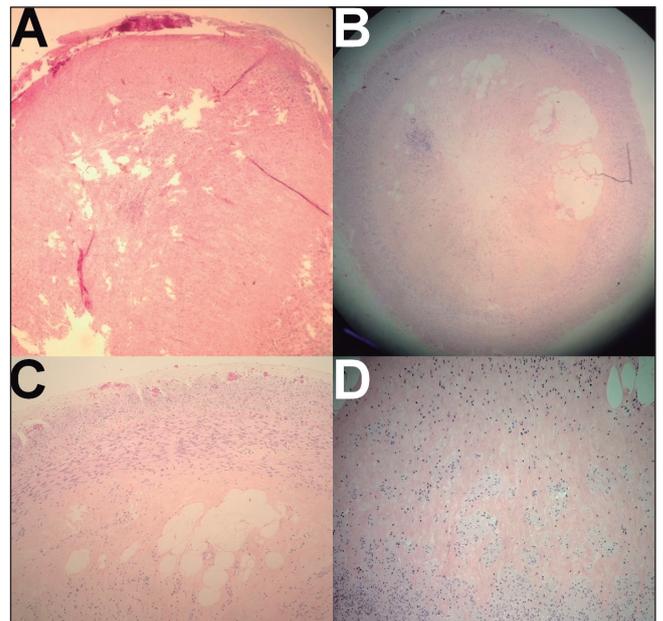


Fig. 1. Histopathology. A. 20x magnification of a longitudinal cross section of the apical region of the appendix, in which its lymphoid tissue is not identified, this being replaced by the proliferation of fusiform cells of neural morphology (hematoxylin and eosin staining). B. 10x magnification of the cross section of the appendix with no evidence of its lymphoid tissue, with replacement by tissue with a neural appearance and adipose tissue (hematoxylin and eosin staining). C. 20x magnification of the wall of the appendix with the presence of ovoid-fusiform cells with a neural appearance (hematoxylin and eosin staining). D. 40x magnification of the wall of the appendix in which we can observe fibrous tracts and proliferation of medium-sized cells which are fusiform-ovoid and stroma of a neural morphology (hematoxylin and eosin staining).

Follow-up

After appendectomy, with a mean follow up of 73.2 ± 28 months (15-105), all the patients were asymptomatic, and no longer had abdominal pain similar to what had been described previously.

A comparison between different groups of neurogenic appendicopathy

Assessment according to histological type

Statistically significant differences were not found between the patients with submucosal neurogenic appendicopathy and the patients with fibrous obliteration of the appendicular lumen in terms of age (27.8 ± 15.5 vs 28 ± 5.1 years; $p = 0.881$), sex (male:female ratio) (1:4 vs 3:0; $p = 0.143$), temperature (36.7 ± 0.3 vs 37.2 ± 1.1 °C; $p = 0.505$), leucocytes ($11,162 \pm 5,653.7$ vs $10,453 \pm 1,320$; $p = 0.800$), neutrophils (70.4 ± 16.1 vs $78.2 \pm 4.9\%$; $p = 0.457$), length of the cecal appendix (6.3 ± 0.5 vs 6 ± 2 cm; $p = 0.753$), and diameter of the cecal appendix (0.54 ± 0.05 vs 0.53 ± 0.05 cm; $p = 0.860$).

Assessment according to the presence of intra-abdominal pathology associated with neurogenic appendicopathy

As described in the section on treatment, four patients presented with associated intra-abdominal pathology. No significant differences were found between the patients who had intra-abdominal disease associated with neurogenic appendicopathy and those who did not in terms of age (27.5 ± 17.8 vs 28.2 ± 4.2 years; $p = 0.940$), sex (male:female ratio) (1:3 vs 3:1; $p = 0.486$), temperature (36.7 ± 0.3 vs 37 ± 0.9 °C; $p = 0.596$), leucocytes ($12,205 \pm 5,947$ vs $9,587 \pm 2,039.5$; $p = 0.455$), neutrophils (72.7 ± 17.6 vs $73.9 \pm 9.4\%$; $p = 0.907$), length of the cecal appendix (6.5 ± 0.4 vs 5.8 ± 1.6 cm; $p = 0.490$), diameter of the cecal appendix (0.55 ± 0.05 vs 0.52 ± 0.05 cm; $p = 0.495$), and histopathological type (submucosal hyperplasia: fibrous obliteration) (4:0 vs 1:3; $p = 0.143$).

DISCUSSION

Neurogenous hyperplasia of the appendix is a neural hyperplasia at the vermiform appendix, it is not familial, and should not be confused with other intestinal nerve lesions such as the mucosal neuromas of MEN 2B syndrome, ganglioneuromatosis and neurofibromas of type I neurofibromatosis (Von Recklinghausen's disease), and schwannomas, perineuriomas and ganglioneuromatosis of Cowden syndrome (7,8). Therefore, this is not a tumor lesion but rather a hyperplasia.

There are three microscopic histological patterns of neurogenous hyperplasia of the appendix: lumen obliteration (appendiceal neuroma), mucosal hyperplasia and submucosal hyperplasia. Appendiceal neuromas consist of a proliferation of fusiform cells in a myxoid background that contains fatty tissue, connective tissue and eosinophil infiltration. The fusiform cells are S-100 protein and neuron-specific enolase positive (4-6).

Neurogenic appendicopathy is an uncommon pathology that is not well-known, and it is difficult to establish its frequency, with inconsistent data provided by the literature (6,10-14) (Table II). It has been reported more often in males (6) than in females (9,10) depending on the series, and in adolescents and adults (10,11). In our series it accounts for 0.16% of all the samples of simple appendectomy, with no preference for either of the sexes. It is notable that submucosal neurogenous hyperplasia is more frequent in females while fibrous obliteration of the appendiceal lumen is more common in males, in addition to the absence of a histological pattern of mucosal neurogenous hyperplasia that is reported in the literature.

Neurogenic appendicopathy is an incidental finding in some cases (15) and clinically it can simulate the symptoms of acute appendicitis (4,14), sometimes being the cause of chronic and recurrent pain in the right iliac fossa (16,17). Clinical history, a physical examination, and complementary examinations are not able to preoperatively differentiate neurogenic appendicopathy (10,11). Some authors state that it should be suspected in patients with recurrent pain in the RIF (14), although this situation has not occurred in our series.

This diagnostic difficulty means that it is impossible to know the real incidence of this disease, given that only the cases that have required surgery and those in which the histopathological diagnosis is obtained afterwards are known. Thus, in our series, diagnosis is obtained in patients that have been operated on for abdominal pain in

Table II. Frequency of neurogenous hyperplasia of the appendix in the most important series in the scientific literature

Study	Frequency of neurogenic appendicopathy (%)
Olsen BS et al. (1987) (3)	82.3
Güller U et al. (2001) (6)	17.1
Franke C et al. (2002) (10)	18.4
Franke C et al. (2002)(11) (children)	< 14 years: 4.8 > 14 years: 24.2
Akbulut S et al. (2011)(12)	Series: 0.019 Revision: 0.002
Yilmaz M et al. (2013)(13)	3.8
Sesia SB et al. (2013)(14) (children)	7.5

the RIF and who have had a simple appendectomy. It is notable that in half of the cases intraoperative pathological findings were found that could account for that pain, with neurogenic appendicopathy being an incidental finding. In this regard, only in the four remaining cases, in which there were no pathological intraoperative findings, could the pain in the RIF be attributed to neurogenic hyperplasia of the appendix, a group in which the most common histopathological type was fibrous obliteration. Consequently, fibrous obliteration with neural transformation could be the histopathological type most frequently involved in the RIF pain of patients without intraoperative pathological findings.

Given everything thus far, once a patient with abdominal pain has been operated on, appendectomy should be performed even if there are no pathological findings (6,18). As a general rule, it has been seen that patients improve clinically after appendectomy.

To conclude, we could say that neurogenic appendicopathy is an uncommon entity that can first appear in young people with pain in the right iliac fossa, simulating acute appendicitis. Its diagnosis is incidental, based on the histological analysis of the cecal appendix after appendectomy.

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