INTRODUCTION

The adenocarcinoma of the ampulla of Vater (AAV) presents low prevalence, with annual estimated incidence - in the United States and France - between three to seven cases per million inhabitants(1, 2). It represents 0.5% to 2% of gastrointestinal cancers(3, 4, 5) and is the second most common periampullary malignancy(6). Its occurrence is exponential after the age of 55(7), with peak of mean incidence between the ages of 60 and 70 years(7). Among the periampullary tumors, it has the best prognosis(8, 9).

Jaundice is one of the most common clinical manifestations of AAV (70%-90% of the cases)(8, 9). It is defined by yellowish shades on the skin, sclera and mucous membranes resulting from the deposition of bilirubin in such. It happens when total serum bilirubin values are evidently higher than 3mg/dL(10, 11). Some authors state that the classic clinical depiction of the ampulla of Vater cancer consists of fluctuating jaundice (FJ), Courvoisier’s sign, anemia and weight loss(2, 4, 11, 15). Jaundice, in this case, comes from cholestasis caused by the obstruction of the duodenal papilla neoplasm and its fluctuating pattern is explained by necrosis and tumor desquamation which allows a decrease in biliary stasis and, consequently, a momentary disappearance of the jaundice(2, 4, 11, 15).

However, there is no real definition and differentiation of clinical and laboratory patterns of jaundice fluctuation in AAV in the current medical literature, although some studies describe its physiopathology(10, 13, 16).

Moreover, besides the conceptual difficulty related to the clinical featuring of fluctuating jaundice related to AAV, there are difficulties related to early pre-operative diagnoses in the absence of histological confirmation, besides the possibility of diagnoses mistakes due to benign diseases(11).

The chosen treatment for AAV is the gastroduodenopancreatectomy, or Whipple’s surgery, which must be performed in the earliest stages of the disease in order to promote cure and give better life quality to the patients(6, 17).

The current study aims to assess the actual frequency of fluctuating jaundice as well as to identify the other possible presentation forms of it in AAV.
METHODS

A descriptive, observational and retrospective study performed at the University Hospital Onofre Lopes (HUOL) of the Federal University of Rio Grande do Norte, located in Natal, capital city of Rio Grande do Norte, Brazil.

The sample was selected through the analysis of medical records from patients subjected to pancreatic celiac resections due to AAV, between February 2008 and July 2013, at HUOL.

All patients diagnosed with AAV - confirmed by pathologic examination of the surgical sample - were excluded from the experiment as well as those who presented lack of information and/or underwent invasive procedures before surgery because it could modify the natural history of the disease. Data collection was performed by researchers and gotten straight from the medical charts.

The design of the current study was approved by the Research Ethics Committee of the Norte Rio Grandense League against Cancer, according to decision n. 295676. The menu added the HUOL as an associated Institution according to the ethical principles of Resolution 196/96 of the Brazilian National Health Council. In addition, due to the nature of this study, the Reasearch Ethics Committees from the institutions involved in the project have approved the exemption patients signature in the Free and Clarified Term of Consent.

According to the current study, the concept and different on clinical fluctuating jaundice (CFJ) and laboratory fluctuating jaundice (LFJ) were standardized. CFJ regarded the presence and subsequent disappearing of a yellowish color shade in the skin and in the mucosa as well as the identification of sclerae in the patient. Such symptoms can be perceived by him/her or by the physician during the course of the disease. In case of absence of clear information described in the medical records, we considered CFJ patients as those with total serum bilirubin higher than 3mg/dL as well as those with clinical jaundice. LFJ regarded patients showing variation on the total serum bilirubin throughout the evolution of his/her disease. At least three different dosages of this laboratory test were necessary. The LFJ was subdivided into type A when there was a decrease in the dosage of bilirubin, and the type B, when there was a decrease and a subsequent new increase in bilirubin.

The dosages of total serum bilirubin were performed at the HUOL’s laboratory and it was done by means of the colorimetric method with the Wiener Lab® diagnostic reagent. The method, according to the Wiener Lab protocol, presents amplitude in the coefficient of variation that goes from 1.1% up to 4.7% when values of total serum bilirubin are measured. Therefore, in order to determine whether the fluctuations occurred, i.e., we have calculated a statistically significant variation in patients’ serum bilirubin values, the mean and standard deviation for each one of them and then the variation in the coefficient. Those who obtained variation coefficient up to 4.7% were not included in the diagnosis for fluctuating jaundice, because it was considered as a variation related to the method itself.

RESULTS

The initial sample was collected from 22 patients, most of them male (12 patients) with mean age of 56.2 years. The most prevailing manifestations in patients were: jaundice (100%), weight loss (86.36%), abdominal pain (81.81%), choluria (72.72%), itchy skin (72.72%) and acholic stools (68.18%) (Figure 1).

Regarding patients from the initial sample (22 patients), 15 of them presented pre-operative suspected AAV diagnosis, by means of an endoscopic exams. Out of them, 10 had their diagnosis confirmed by the anatomopathological outcomes from the endoscopic biopsy.

Seven patients did not make the endoscopic exams, however, due to other image complementary exams (CT and magnetic resonance of abdomen; cholangiopancreatography), that have presented strong suspected preoperative diagnosis for papillary tumor or other peri-ampullar cancer.

Two patients had to be excluded from the sampling group because one of them (patient 16) underwent a biliiodigestive bypass and had no record of total serum bilirubin levels before surgery. The other one (patient 18), underwent an endoscopic retrograde cholangiopancreatography with stent placement and had no levels of serum bilirubin before endoscopy. Thus, the study’s final sample consisted of 20 patients. Among them, three were up to 40 years old.

Fluctuating jaundice’s identification and classification process was done by assessing the clinical history and analyzing the identified values of total serum bilirubin (Table 1) (Figure 2). The first measurement of serum bilirubin in the final sample was performed at a median of 19 days (1-173 days) before surgery, meanwhile the last determination occurred at a median of 2 days (1-20 days) before surgical treatment established.

Among the 20 patients sampling group, one of the patients remained anicteric (patient 8). Eleven of them developed progressive jaundice, two developed clinical and laboratory fluctuating jaundice (patients 1 and 10), five developed only laboratory fluctuating jaundice and one showed no significant variation related to total serum bilirubin values (patient 11).
TABLE 1. Values of total serum bilirubin and statistical analysis from the 20 AAV patients in presence of Wiener Lab reagent, from February 2008 up to July 2013

| P  | TB1 | TB2 | TB3 | TB4 | TB5  | MEAN | SD  | CV  |
|----|-----|-----|-----|-----|------|------|-----|-----|
| 1  | 6.3 | 1.8 | --- | --- | ---  | 4.07 | 3.20| 78.80|
| 2  | 28.1| 28.2| 31.0| 21.9| 33.0 | 28.4 | 4.2 | 14.8 |
| 3  | 6.3 | 13.8| --- | --- | ---  | 10.0 | 5.3 | 52.8 |
| 4  | 31.6| 12.5| --- | --- | ---  | 22.0 | 13.5| 61.3 |
| 5  | 14.8| 18.6| --- | --- | ---  | 16.7 | 2.7 | 16.2 |
| 6  | 18.2| 21.1| 24.7| --- | ---  | 21.3 | 3.2 | 15.3 |
| 7  | 18.2| 22.7| 25.4| 24.5| ---  | 22.7 | 3.2 | 14.2 |
| 8  | 0.2 | --- | --- | --- | ---  | ---  | --- | --- |
| 9  | 15.0| 17.4| --- | --- | ---  | 16.2 | 1.7 | 10.5 |
| 10 | 6.5 | 0.8 | 0.5 | 0.4 | 0.3  | 1.7  | 2.6 | 151.6|
| 11 | 15.1| 14.8| 15.0| --- | ---  | 14.9 | 0.1 | 1.0  |
| 12 | 11.3| 6.0 | --- | --- | ---  | 8.6  | 3.7 | 43.3 |
| 13 | 32.5| 27.5| --- | --- | ---  | 30.0 | 3.5 | 11.8 |
| 14 | 11.2| 15.8| --- | --- | ---  | 13.5 | 3.2 | 24.1 |
| 15 | 15.2| 16.0| 20.1| --- | ---  | 17.1 | 2.6 | 15.4 |
| 17 | 13.4| 17.0| --- | --- | ---  | 15.2 | 2.5 | 16.5 |
| 19 | 6.1 | 14.8| 22.2| --- | ---  | 14.3 | 8.0 | 56.1 |
| 20 | 23.4| --- | --- | --- | ---  | ---  | --- | --- |
| 21 | 10.0| 10.4| 11.5| --- | ---  | 10.6 | 0.7 | 7.3  |
| 22 | 15.0| 17.4| 18.7| 19.3| ---  | 17.6 | 1.9 | 10.8 |

P: patient; TB: value of total serum bilirubin; 1: first evaluation of TB; 2: second evaluation of TB; 3: third evaluation of TB; 4: fourth evaluation of TB; 5: fifth evaluation of TB; P: patients; SD: standard deviation; CV: coefficient of variation. Note: Patients 16 and 18 were excluded from the sample (For reasons that read the 4th paragraph of Results).

Among the seven patients with fluctuating jaundice, two were classified as type A, one as type B, and four were not classified due to insufficient levels of total serum bilirubin (less than three dosages).

The conjugated bilirubin variation pattern was similar to that of total bilirubin for the 20 patients from the final sampling (Table 2) (Figure 3).

TABLE 2. Values of conjugated serum bilirubin from the 20 AAV patients in presence of Wiener Lab reagent, from February 2008 up to July 2013

| Patients | CB1 | CB2 | CB3 | CB4 | CB5 |
|----------|-----|-----|-----|-----|-----|
| 1        | 4.5 | 1.1 | --- | --- | --- |
| 2        | 17.8| 17.2| 19.2| 13.3| 19.4|
| 3        | 4.2 | 12.4| --- | --- | --- |
| 4        | 18.6| 7.7 | --- | --- | --- |
| 5        | 7.1 | 9.2 | --- | --- | --- |
| 6        | 12.1| 13.8| 16.1| --- | --- |
| 7        | 9.8 | --- | 18.2| 17.3| --- |
| 8        | 0.1 | --- | --- | --- | --- |
| 9        | 11.4| 13.6| --- | --- | --- |
| 10       | 4.9 | 0.3 | 0.4 | 0.2 | 0.1 |
| 11       | 9.2 | 9.9 | 8.5 | --- | --- |
| 12       | 7.9 | 4.2 | --- | --- | --- |
| 13       | 14.5| 11.7| --- | --- | --- |
| 14       | 7.7 | 10.1| --- | --- | --- |
| 15       | 11.4| 12.3| 16.6| --- | --- |
| 17       | 7.5 | 9.0 | --- | --- | --- |
| 19       | 4.0 | 12.0| 13.3| --- | --- |
| 20       | 15.9| --- | --- | --- | --- |
| 21       | 8.0 | 8.4 | 9.7 | --- | --- |
| 22       | 10.0| 11.3| 10.5| 11.4| --- |

CB: value of conjugated bilirubin; 1: first evaluation of CB; 2: second evaluation of CB; 3: third evaluation of CB; 4: fourth evaluation of CB; 5: fifth evaluation of CB. Note: Patients 16 and 18 were excluded from the sample (For reasons that read the 4th paragraph of Results).
Within the initial sample with 22 patients, the most frequent identified symptoms were jaundice, abdominal pain, weight loss, just as presented by other studies\(^6, 7, 14, 17, 19\).

It should be noticed that, to date, the standardization of the jaundice fluctuation in AAV had neither been discussed by other studies, nor a classification on the depictions of clinical and laboratory jaundice had been suggested, as reported in the current study\(^1-4, 8-13, 15, 16, 18\).

Although some authors disclose that fluctuating jaundice is a classic clinical manifestation during the natural history of AAV\(^7, 11, 15, 20\), this sign - if we consider the semantic essence of jaundice in its clinical depiction - , was found in two patients from the sample.

Jaundice non-fluctuation, i.e., the presence of persistent and progressive jaundice was the prevalent depiction in AAV. It was observed in 11 patients. Such fact reinforces the probable exception character of the fluctuating jaundice occurrence demonstrated in our study, in its laboratory presentation form, in seven cases and, more rarely, in its clinical form (two cases).

Finally, this low fluctuating jaundice frequency can also be found in other studies. It happened in two cases within a sample of 35 patients (Hayes et al.)\(^10\); in two cases within a sample of 37 patients (Moody et al.)\(^13\); and in four cases within a sample of 15 patients (Ponka et al.)\(^16\). Furthermore, it is important to emphasize that only one patient in this series of cases, throughout the natural evolution of his/her illness, never presented jaundice signs, i.e., he/she remained anicteric.

In conclusion, despite the small sampling group presented in the aforementioned series of cases, lack of clinical and laboratory information in medical charts, through a little more than five years - due to the low incidence of AAV - , it can be suggested that fluctuating jaundice, based on concepts standardization proposal, presents itself as low frequency situation during AAV’s natural history. Clinical fluctuating jaundice is really an exception condition. Thus, as an indirect consequence, there is the need for conducting studies with a larger sample, possibly multicenter studies - due rarity of the disease - in order to really promote the final definition for fluctuating jaundice in AAV.

**Authors’ contributions**

Alves JR mentored medical students in the literature review and data collection, and he was the final reviewer of the article writing, and responsible for the translation into English, as well as for the text formatting and for the process of submitting the article. Amico EC performed most of the surgeries on patients and contributed to the revision of the article writing. Sousa DLB performed the statistical analysis and contributed to the final revision. Oliveira PVV and Maranhão IGO conducted a literature review and participated in the writing of the manuscript. All authors read and approved the final version of the article.
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Received 6/9/2014
Accepted 3/11/2014