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Primary Biliary Cholangitis: Clinical, demographic and immunological characteristics.

Colangite Biliar Primária: Características clínicas, demográficas e imunológicas.

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FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR
PROJETO DE OPÇÃO
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Primary Biliary Cholangitis: Clinical, demographic and immunological characteristics

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PRIMARY BILIARY CHOLANGITIS: CLINICAL, DEMOGRAPHIC AND IMMUNOLOGICAL CHARACTERISTICS

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ABSTRACT

Background and Objective: Primary biliary cholangitis is a rare disease with scarce epidemiological data. The aim of this study was to characterize a cohort of patients in Portugal and to evaluate the response to treatment and development of complications.

Methods: This retrospective observational study included patients with diagnostic criteria of primary biliary cholangitis from a single center. Data on disease presentation, laboratory results, treatment and clinical endpoints were collected and analyzed. Statistical significance was established at $p<0.05$.

Results: Fifty-three patients were included, 89% were women, with mean age of 62 ± 15 years at diagnosis. The majority were asymptomatic (49%), tested positive for AMA (96%), had increased alkaline phosphatase (median= 214 U/L) and were in Ludwig's stage I (42%). Overlap syndrome was diagnosed in seven patients (13%) and nine patients (17%) bared overlap features without assenting biopsy. All patients were treated with ursodeoxycholic acid and 56% achieved biochemical response at one year. Patients with overlap features and higher alkaline phosphatase presented a significantly greater decrease in alkaline phosphatase levels.

Conclusions: The baseline characteristics of this cohort were in agreement with those previously described. Outstandingly, 30% of patients had features of overlap syndrome and presented a steeper reduction in alkaline phosphatase.

Keywords: Primary biliary cholangitis, overlap syndrome, alkaline phosphatase, antimitochondrial antibodies, ursodeoxycholic acid, biochemical response.

INTRODUCTION

Primary biliary cholangitis (PBC), previously called primary biliary cirrhosis, is a rare disease (0.3 to 5.8 per 100,000 inhabitants/year), that predominantly affects women [1]; it is characterized by progressive destruction of small intrahepatic bile ducts with periportal inflammation, fibrosis, and potential cirrhosis [2].

Clinical manifestations related to cholestasis include fatigue and pruritus which can significantly impact the quality of life [3]. Furthermore, chronic cholestasis can lead to osteopenia and osteoporosis, hyperlipidemia and lipossoluble vitamin deficiencies. Although cirrhosis is infrequent, patients are at risk of developing end-stage hepatic disease complications like portal hypertension and hepatocellular carcinoma [2].

As a classic autoimmune disease, progressive T cell predominant lymphocytic cholangitis, and a serologic pattern of reactivity in the form of specific antimitochondrial antibodies (AMA) - densely localized to the apical surface of biliary epithelial cells and associated with apoptosis - are characteristic [4]. Additionally PBC has a strong female predisposition and 53% of the patients have, at least, one concurrent autoimmune disorder [5].

European Association for the Study of the Liver (EASL) defines PBC as the combination of abnormal serum liver tests (elevation of alkaline phosphatase (AP) of liver origin for at least six months) and presence of AMA (≥1:40) and/or AMA type M2 in serum. Liver biopsy is not mandatory for diagnosis, except in the absence of AMA. Moreover, it can be useful in the presence of overlap syndrome and allows assessment of disease stage [6].

Various staging systems have been developed, but Ludwig's is the most widely used: Stage one - portal inflammation, stage two - extension to the periportal areas, stage three - septal fibrosis or inflammatory bridging, and stage four - cirrhosis. [7]

For several years, PBC treatment has been centred in ursodeoxycholic acid (UDCA) and favourable long-term effects are expected in patients with a good biochemical response assessed after one year — serum bilirubin ≤ 1 mg/dL (17 μmol/L), AP ≤ 3x ULN and AST ≤ 2x ULN (*Paris criteria*) or by a decrease of 40% or normalization of

serum AP (*Barcelona criteria*) [6]. However, a significant portion of patients (up to 40%) have suboptimal responses and there is no consensus on how to treat these patients [8].

New therapies are emerging and recently, obeticholic acid, a farnesoid X receptor, showed effective biochemical response on adults with primary biliary cholangitis, and is now a FDA-approved alternative in patients who have an inadequate response to UDCA or who are unable to take UDCA because of side effects [9].

Most of the patients have typical features but, not rarely, some present with characteristics of both PBC and autoimmune hepatitis (PBC-AIH overlap syndrome). In these patients, flares of AIH may occur either spontaneously or under UDCA and combination of UDCA and corticosteroids is required in most patients to obtain a complete biochemical response. This syndrome may represent an important unrecognized cause of treatment resistance in PBC patients [10].

Hence, given the heterogeneity of this disease and the lack of demographic studies on the subject, particularly in Portugal, the aim of this study is to characterize a cohort of PBC patients, in order to access demographics, clinical and immunological features, response to treatment and complications of the disease.

METHODS

Participants

The retrospective observational study included patients with diagnostic criteria of PBC and PBC-AIH overlap syndrome, according to *EASL Clinical Pratical Guidelines,* treated and followed at *Hospital São João*. Patients who did not meet these criteria were excluded. Consequently, 53 patients were included in the study.

Data collection

Data was collected, from medical records of patients with diagnosis of PBC from July 2002 and the following variables were evaluated: age at diagnosis, gender and follow-up period; presentation and diagnostic tests. Data on comorbid illnesses, including concurrent autoimmune diseases, and on PBC complications, including development of cirrhosis, ascites, variceal bleeding, hepatic encephalopathy and hepatocellular carcinoma (HCC), were also gathered.

Immunological and histopathological data were also obtained including IgM, IgG, AMA, AMA type M2, anti-nuclear antibody (ANA), anti-smooth muscle antibody (ASMA) titres and liver biopsy. Transient elastography parameters were also collected.

Therapeutic intervention including ursodeoxycholic acid (UDCA), corticosteroid, other immunosuppressive drugs, diuretics and statin was investigated. Liver transplantation was also recorded.

PBC was staged according to *Ludwig's staging system*; *Child-Pugh classification* was used for patients with cirrhosis; and *Barcelona Criteria* were applied to evaluate response to treatment.

Statistical analysis

All data were analyzed by descriptive statistics and Fisher's exact test for categorical variables. Continuous variables were analyzed with independent samples and paired samples T-test, if normal distribution, or Mann-Whitney and Wilcoxon test for non-parametric distribution. Statistical significance was established at $p<0.05$ for all tests. Statistical analysis was performed using SPSS, version 23.

The study protocol was approved by the local Health Ethics Committee.

RESULTS

Patient's baseline characteristics

The study included 53 patients with a mean follow-up period of 7 ± 4 years. As expected, the majority of them were women (89%) with a mean age at diagnosis of 62 years.

A total of 39 patients had clinical reports at diagnosis, of those, the majority were asymptomatic (49%), presenting only with abnormal laboratory findings. Symptomatic patients mainly revealed the typical symptoms of fatigue (26%), pruritus (10%) and jaundice (8%). Abnormal laboratory findings are summarized in *Table 1*. The vast majority of patients were tested positive for AMA (96%) and AMA type M2 (94%) and a significant proportion (45%) were ANA-positive, with predominantly nuclear dot pattern (35%) at indirect immunofluorescence. On the contrary anti-smooth muscle antibodies (ASMA) were rarely tested positive (4%), interestingly, these patients bared characteristics of PBC-AIH overlap syndrome.

Histological samples were obtained by liver biopsy in 75% of the patients, and the bulk of them presented with Ludwig´s stage I at diagnosis (42%).

Nonetheless, demonstrating the deleterious effects that PBC can frequently hold, cirrhosis was found in 22% of the patients at the time of diagnosis.

Additionally, roughly one-third of the patients exhibited a concomitant autoimmune condition and Sjogren's syndrome was the most common comorbid condition documented in the study group.

Finally, PBC-AIH overlap syndrome was diagnosed in seven patients (13%). Conjointly, nine patients (17%) showed, what the authors considered, incomplete criteria for PBC-AIH overlap syndrome. These patients did not present all the required EASL criteria, namely the biopsy specimens did not show moderate to severe interface hepatitis, which would be mandatory for definitive diagnosis. Nevertheless, other features of PBC-AIH were present and these patients underwent corticosteroid and/or immunosuppressive therapy, accordingly with the clinical suspicion.

Follow-up

Treatment

Each of the patients was treated with UDCA for at least one year. Supplementary to this finding, 28% of the patients were further managed with the addition of a corticosteroid (budesonide or prednisolone), an immunosuppressive agent (azathioprine or mycophenolate mofetil) or both.

The authors analysed the biochemical response to treatment and serum AP exhibited a significant decrease from baseline after one year (median decrease from baseline = 30% (IQR 0 - 45); $p<0.001$) (Table 2). Still, patients without cirrhosis ($p=0.028$), with definite ($p=0.048$) and incomplete ($p=0.024$) PBC-AIH and those positive for ANA ($p=0.001$) featured a more robust decrease in serum AP, when compared to their counterparts (Table 3).

After one year of treatment, out of 41 patients only 32% displayed a *decrease of 40% in serum AP* and, according to the *Barcelona Criteria*, 56% of the patients exhibited a *good biochemical response* to treatment with UDCA. Focusing on the 29 patients with PBC without overlap syndrome, 52% revealed *good biochemical response* to treatment, on the other hand amid the 12 patients with definite and incomplete PBC-AIH overlap syndrome, 67% achieved the endpoint of *good biochemical response*.

Furthermore, significantly more patients with the following characteristics reached the endpoint of *at least 40% decrease in serum AP* when compared to their counterparts: definitive and incomplete PBC-AIH overlap syndrome ($p=0.029$), ANA positive ($p=0.038$), higher baseline serum AP ($p=0.011$) and higher baseline serum AST ($p=0.008$) (Table 4).

Complications

During the follow-up period, 45% of the patients were diagnosed with osteopenic bone disease. Hyperlipidaemia was diagnosed and treated accordingly in 51% of the patients. Interestingly, none of the patients had evidence of cirrhosis development during the follow-up period.

More severe complications were rare, as only two patients had a bleeding event due to oesophageal varices, one developed hepatic encephalopathy associated with ascites and one patient with overlap syndrome presented acute hepatitis with coagulopathy. Two patients required liver transplantation for decompensated cirrhosis. There were no documented cases of hepatobiliary neoplasia.

DISCUSSION

This is the first study on this subject in Portugal and the documented baseline characteristics of the cohort of patients are in agreement with those of other regions, as the majority of them were middle aged women. Female predominance is widely described for PBC, the median ratio of 9-10:1 in case finding studies is among the highest for autoimmune diseases and was also observed in this cohort [11]. Too, the majority were asymptomatic at diagnosis, concordant with the preclinical asymptomatic stages described for PBC that can last for decades [12].

Given the indolent natural history frequently exhibited by PBC patients, the diagnosis relies strongly on incidental findings such as abnormal laboratory tests. Subsequently and as expected, since it is a determinant characteristic, cholestasis indices presented median values above normal (median AP = 214 U/L (IQR 143 - 514)), with lesser increases of enzymes associated with hepatic cytolysis.

In the same way, AMA antibodies play a key role in the diagnosis of these patients, thus the absence of AMA antibodies in patient sera is thought to be associated with underdiagnose, thus reducing incidence and prevalence [11]. The fact that early-phase diagnosis may be built on AMA positivity may also explain geographical variability, according to differences in the access to accurate AMA laboratorial determination. However, this hypothesis should not be a reason to overlook the environmental effects thought to be associated with PBC [13]. This cohort included two AMA-negative patients (4%), parallel to the majority of previous studies. These patients failed to show any significant difference with the far more common AMA-positive group [14, 15]. More recently, the nonexistence of AMA antibodies was associated with worse prognosis, that may be either due to true differences or reflect a delay in case detection [16]. In fact, it may rather be a reflex of technical limitations rather than a true absence. In addition, the mandatory role of biopsy in establishing diagnosis may further contribute for reduced rates of diagnosis and appropriate treatment in these patients, since patients can be unfit for the procedure or the biopsy specimens can be unsatisfactory.

PBC-AIH overlap syndrome was surprisingly common among the cohort, with 30% of the patients baring features consistent with this syndrome. Still, PBC-AIH can be difficult to diagnose, as characteristics form either PBC or AIH may dominate the clinical picture. Besides, the defined criteria for diagnosing PBC-AIH can be difficult to meet, as observed in this cohort by non-satisfactory biopsy despite clinical evidence of the disease. Consequently, the underdiagnose of patients baring this syndrome can lead to inappropriate managing of patients associated with previously observed poorer outcomes [17].

UDCA is the only therapy broadly recommended for PBC, consequently every included patient have been treated accordingly and none exhibited major adverse effects causing interruption of the treatment. Interestingly, none of the patients developed cirrhosis during the follow-up period. Although this could be related to the sample size, it may translate the beneficial effect of UDCA therapy in hindering PBC clinical course, nonetheless previous studies documented some degree of progression to cirrhosis [18-20]. However, in the authors centre, serial paired biopsies are not routine and chronic liver disease assessment after diagnosis is made through ultrasound and elastography. Besides, the limiting size of the cohort may explain this finding.

Despite being the only specific therapy, UCDA is far from being flawless and the authors observed, in concert with previous studies [21], an incomplete biochemical response in 44% of the patients.

Baseline characteristics have been associated with different degrees of response to UDCA, namely pre-treatment cirrhosis [22]. Accordingly, in this cohort, patients with cirrhosis at diagnosis exhibited significant less robust decreases in AP ($p=0.028$). Both higher AP baseline values and PBC-AIH overlap syndrome have been associated with incomplete responses to UCDA [17, 21, 23]. Remarkably, in this cohort significantly more patients with higher levels of AP exhibited a decrease of 40% or more in serum AP when compared to patients with less prominent values ($p=0.011$). Then as well, patients with PBC-AIH overlap exhibited steeper decreases in serum AP ($p=0.048$) and reached the endpoint of 40% decrease in serum AP more frequently than their counterparts ($p=0.029$).

Inappropriate biochemical response is rather relevant because it is associated with development of liver-dependent symptoms and poorer outcomes [24-26] and double dosage is not associated with better responses [27]. So, the need for new therapies is evident. Obeticholic acid is the first FDA-approved alternative for the treatment of incomplete responders to UDCA [9]. Other therapeutic approaches are being investigated and better understanding of etiopathogenesis can further contribute to an improved management of PBC patients in the future [28].

As a retrospective observational study, some limitations have to be considered. In fact, the data was limited to that already recorded, so complete data was not available for all the patients. Besides, being a single-centre study of a rare disease, the number of patients was also limited, so prevalence and incidence analyses could not be made based on this data. Additionally, due to the lack of adverse events in our cohort, survival analyses were unfeasible.

Although it is rare, PBC can compromise serious adverse outcomes and therapy is not always effective in achieving good responses, subsequently, PBC should not be overlooked, and further studies are needed to better characterize this disease. Specifically regarding better understanding of the complex clinical phenotype and the development of new possibilities for the management of a significant proportion of incomplete responders.

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Tables

Table 1. Patient's baseline characteristics.

Variable	Value
Age at diagnosis (years), mean ± SD	62.0 ± 14.8
Gender, n (%)	
Male	6 (11)
Female	47 (89)
Presentation, n (%)	
Asymptomatic	19 (49)
Fatigue	10 (26)
Pruritus	4 (10)
Jaundice	3 (7)
Other	3 (7)
Liver biopsy, n (%)	
Yes	39 (75)
No	13 (25)
Histological Stage, n (%)	
I	16 (42)
II	5 (13)
III	8 (21)
IV	7 (18)
Normal histology	1 (3)
Insufficient sample	1 (3)
Cirrhosis, n (%)	
Present	11 (22)
Absent	40 (78)
Associated AI Disorders – n (%)	
Present	17 (32)
Absent	36 (68)
AP (U/L)	**N=43**
Median (IQR)	214 (143; 514)
GGT (U/L)	**N=43**
Median (IQR)	300 (149; 477)

AST (U/L)	**N=43**
Median (IQR)	49 (36; 88)
ALT (U/L)	**N=42**
Median (IQR)	60 (31; 122)
Bilirubin (mg/dL)	**N=43**
Median (IQR)	0.9 (0.6; 1.3)
Albumin (mg/dL)	**N=42**
Mean ± SD	42.0 ± 3.1
Platelets (x10^3/μL)	**N=41**
Mean ± SD	215 ± 69
IgM (mg/dL)	**N=28**
Mean ± SD	433 ± 208
IgG (mg/dL)	**N=30**
Mean ± SD	1618 ± 442
AMA, n (%)	
Positive	50 (96)
Negative	2 (4)
AMA type M2, n (%)	
Positive	43 (94)
Negative	3 (6)
ANA, n (%)	
Positive	23 (45)
Negative	28 (55)
ASMA, n (%)	
Positive	2 (4)
Negative	44 (96)

Abbreviations: AI, autoimmune; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; ALT, alanine aminotransferase; AP, alkaline phosphatase; ASMA, anti-smooth-muscle antibodies; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; Ig, Immunoglobulin.

Table 2. Decrease (%) from baseline biochemical characteristics (alkaline phosphatase, aspartate aminotransferase and total bilirubin) after one year of treatment.

Decrease from baseline	N	(%), Median (IQR)	*p*
AP	41	30 (0; 45)	<0.001*#
AST	40	20 (0; 47)	0.161*
Bilirubin	39	4 (-8; 22)	0.075#

*Paired samples Test #Related-Samples Wilcoxon Signed Rank Test
Abbreviations: AP, alkaline phosphatase; AST, aspartate aminotransferase.

Table 3. AP decrease (%) from baseline assessed after one year of treatment based on patient's baseline characteristics.

AP decrease from baseline	**N**	**(%), Median (IQR)**	***p***
Cirrhosis			
Present	10	3 (-22; 38)	0.028*
Absent	31	32 (1; 48)	
PBC-AIH			
Present	5	35 (29; 76)	0.048*
Incomplete	7	48 (40; 64)	0.024*
Absent	29	5 (-5; 37)	
ANA			
Positive	19	40 (29; 64)	0.001*
Negative	21	2 (-10; 33)	

*Independent-samples T-test

Abbreviations: ANA, antinuclear antibodies; PBC-AIH, Primary Biliary Cirrhosis-Autoimmune Hepatitis overlap syndrome.

Table 4. Evaluation of the endpoint of biochemical response to treatment – decrease of at least 40% in serum AP - based on patient's baseline characteristics.

Decrease in serum AP	**≥ 40%**	**<40%**	*p*
PBC-AIH			
Present/incomplete, n (%)	7 (58)	5 (42)	0.029*
Absent, n (%)	6 (21)	23 (79)	
ANA			
Positive, n (%)	9 (47)	10 (53)	0.038*
Negative, n (%)	3 (14)	18 (86)	
Baseline AP (U/L), median (IQR)	420 (197; 613)	171 (100; 343)	0.011*
Baseline AST (U/L), median (IQR)	85 (57; 149)	40 (33; 74)	0.008*
Baseline Bilirubin (mg/dL), median (IQR)	1.1 (0.7; 1.7)	0.9 (0.6; 1.1)	0.159*

*Independent-samples T-test

Abbreviations: ANA, antinuclear antibodies; AP, alkaline phosphatase; AST, aspartate aminotransferase; PBC-AIH, Primary Biliary Cirrhosis-Autoimmune Hepatitis overlap syndrome.

ANEXO 1

Normas da Revista

GUIDE FOR AUTHORS

INTRODUCTION

Clinics and Research in Hepatology and Gastroenterology publishes high quality papers in the field of hepatology and gastroenterology in English language. The editors put the accent on rapid communication of new research and clinical developments and so called "hot topic" issues. Following a clear Editorial line, besides original articles and case reports, each issue features editorials, commentaries, a seminar, mini-reviews, pictorial reviews and several keynotes. The journal encourages research and discussion between all those involved in the specialty on an international level. Articles in press are online and indexed in the international databases (Current Contents, Pubmed, Scopus, Science Direct).

Types of article

EDITORIALS are invited comments on topically issues in liver diseases or major articles published in the journal or elsewhere. The length of an editorial should not exceed 1,500 words excluding references. Please limit reference count to a maximum of 20 references. A table and a figure can be included. Please provide a title page.
COMMENTARIES are brief comments not exceeding 1,200 words that could be accompanied by one figure aimed to discuss recent published clinical or basic papers. Commentaries must be accompanied by a title page and a very brief summary. Commentaries are reviewed by the Editors before a final decision for publication is made. Revisions may be required.
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RESEARCH LETTERS present concise and important new information on study results. No abstract and no paragraph headings: 1750 words, maximum 15 references and 1 table or 1 figure
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IMAGE OF THE MONTH is a striking clinical image that is meant to challenge and inform readers.
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All authors should have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

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ANEXO 2

Aprovação da Comissão de Ética para a Saúde

DIRECÇÃO CLÍNICA 22-17
9/3/2017

AUTORIZADO

CONSELHO DE ADMINISTRAÇÃO REUNIÃO DE 16 MAR 2017
Presidente do Conselho de Administração
(Dr. António Oliveira e Silva)
Diretor Clínico (Prof. Dr. José Artur Paiva) | Enfermeira Diretora (Enf.ª Filomena Cardoso) | Vogal Executivo (Dr. Luís Porto Gomes) | Vogal Executivo (Dr. Renato G. Matos)

• Centro Hospitalar São João •
Ao CA
com parecer

Unidade de Investigação

Tomei conhecimento. Nada a opor.

15 de Fevereiro de 2017

A Coordenadora da Unidade de Investigação

(Prof.ª Doutora Ana Azevedo)

Aprovado. Ao CA.

(Prof.ª Doutora Ana Azevedo)

Exmo. Senhor

Presidente da Comissão de Ética para a Saúde do

Centro Hospitalar de S. João – EPE

Assunto: Pedido de apreciação e parecer para estudo/projecto de investigação

Nome do Investigador Principal:

Fernando Guilherme Ribeiro Maré

Título do projecto de investigação:

Primary Biliary Cholangitis: Clinical, demographic and immunological characteristics

Pretendendo realizar no(s) Serviço(s) de Gastrenterologia do Centro Hospitalar de S. João – EPE o estudo/projecto de investigação em epígrafe, solicito a V. Exa., na qualidade de Investigador/Promotor, a sua apreciação e a elaboração do respectivo parecer.

Para o efeito, anexo toda a documentação referida no dossier dessa Comissão respeitante a estudos/projectos de investigação.

Com os melhores cumprimentos.

Porto, 02 / Dezembro / 2016

O INVESTIGADOR/PROMOTOR

Fernando Maré

7. SEGURO

a. *Este estudo/projecto de investigação prevê intervenção clínica que implique a existência de um seguro para os participantes?*

SIM ☐ (Se sim, junte, por favor, cópia da Apólice de Seguro respectiva)
NÃO ☐
NÃO APLICÁVEL ☑

8. TERMO DE RESPONSABILIDADE

Eu, Fernando Guilherme Ribeiro Mané,
abaixo-assinado, na qualidade de Investigador Principal, declaro por minha honra que as informações prestadas neste questionário são verdadeiras. Mais declaro que, durante o estudo, serão respeitadas as recomendações constantes da Declaração de Helsínquia (com as emendas de Tóquio 1975, Veneza 1983, Hong-Kong 1989, Somerset West 1996 e Edimburgo 2000) e da Organização Mundial da Saúde, no que se refere à experimentação que envolve seres humanos. Aceito, também, a recomendação da CES de que o recrutamento para este estudo se fará junto de doentes que não tenham participado em outro estudo no decurso do actual internamento ou da mesma consulta.

Porto, 03 / Janeiro / 20 16

Fernando Guilherme Ribeiro Mané

O Investigador Principal

PARECER DA COMISSÃO DE ÉTICA PARA A SAÚDE DO CENTRO HOSPITALAR DE S. JOÃO

emitido na reunião plenária da CES de 13 / Janeiro / 2016

A Comissão de Ética para a Saúde APROVA por unanimidade o parecer do Relator, pelo que nada tem a opor à realização deste projecto de investigação.

Parecer da Comissão de Ética para a Saúde do
Centro Hospitalar de São João / Faculdade de Medicina da Universidade do Porto

Título do Projecto: Primary Biliary Cholangitis: clinical, demographic and immunological characteristics.

Nome da Investigadora Principal: Fernando Guilherme Ribeiro Mané

Onde decorre o Estudo: Serviço de Gastroenterologia do Centro Hospitalar de São João. Tem autorização do Diretor de Serviço. Apresenta Declaração de Elo de Ligação.

Objectivos do Estudo:
Estratificação dos doentes com Colangite Biliar Primária seguidos no Serviço de Gastroenterologia do Hospital São João em termos de apresentação clínica, distribuição demográfica e características imunológicas que se sabe estarem associadas a esta patologia.

Benefício/risco: N/A

Confidencialidade dos dados:
Toda a informação é confidencial e será utilizada apenas para fins de investigação. A informação que permite a identificação do participante (nome, contactos) será arquivada separadamente da restante informação e apenas será acessível aos responsáveis pela investigação.

Respeito pela liberdade e autonomia do sujeito de ensaio: N/A

***Curriculum* da investigadora**: Adequado à investigação.

Data previsível da conclusão do estudo: 2017

Conclusão: Proponho um parecer favorável à realização deste projecto de investigação.

Porto, 30 de Janeiro de 2017

O Relator, John Preto