Ann Ig. 2024 Sep-Oct; 36(5): 614-618. doi: 10.7416/ai.2024.2629

Why are rare diseases underdiagnosed? A clinical management study on detection of primary biliary cholangitis in primary care

Francesco Donato[1], Marie Graciella Pigozzi[1], Giulia Colarieti[1], Marco Festa[1], Erminio Tabaglio[2] for the EPATOMG Working Group*

Keywords: Rare diseases; primary care; chronic cholestasis; liver cirrhosis; alkaline phosphatase
Parole chiave: Malattie rare; assistenza primaria; colestasi cronica; cirrosi epatica; fosfatasi alcalina

Abstract

Background. *There are about 7,000 rare diseases that affect 10% of the world population. Primary biliary cholangitis, an autoimmune chronic liver disease of the interlobular bile ducts, is one of the most common causes of chronic cholestasis. However, it is a rare, often underdiagnosed and undertreated, disease which can lead to cirrhosis and liver failure. We aimed to assess the proportion of undetected primary biliary cholangitis patients in primary care through a clinical management process.*

Methods. *We made two extractions of the clinical data concerning liver diseases, risk factors and laboratory tests from the databases of a sample of general practitioners, with a check and correction of mistakes. The clinical data of the patients without liver disease and major risk factors, and with serum Alkaline Phosphatase above the laboratory reference values, were re-evaluated by each general practitioner with an expert gastroenterologist. The patients with elevated Alkaline Phosphatase values and without evidence of intrahepatic or extrahepatic causes of cholestasis were considered suspected for primary biliary cholangitis and assessed for antimitochondrial antibodies test and specialist' s evaluation, according to present guidelines.*

Results. *A total of 20,480 adults attending 14 general practitioners in the province of Brescia, Northern Italy, were included in the study. Nine patients had a prior primary biliary cholangitis diagnosis, with a prevalence of 43.9/100000. After excluding 2094 (10.2%) patient with liver diseases or other causes of cholestasis, 121 subjects with Alkaline Phosphatase above the reference values were re-evaluated by the general practitioners and gastroenterologist, and 27 patients without symptoms or signs of cholestasis were considered suspected for primary biliary cholangitis: 9 of them were tested for antimitochondrial antibodies, and three new primary biliary cholangitis cases were detected (+33%).*

Discussion and Conclusions. *This study shows that there is a not negligible burden of undetected cases of adult rare diseases that can be diagnosed in primary care, through a disease management procedure, without modifying the routine clinical practice.*

[1] *Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, Unit of Hygiene, Epidemiology, and Public Health, University of Brescia, Italy*
[2] *General Practitioner, ATS Brescia, Italy*
** EPATOMG Working Group: E. Aggogeri, F. Bandera, F. Bettoni, M. Bonavita, F. Donato, A. Festa, R. Fiori, G. Gatta, D. Ghisleri, M. Moretta, A. Olivini, F. Pensieri, M.G. Pigozzi, E.S. Pintossi, F. Plebani, P. Poisa, C. Ricci, G. Rinaldis, H. Skiti, E. Tabaglio, F. Zanotti, S. Zubani*

Annali di Igiene : Medicina Preventiva e di Comunità (Ann Ig)
ISSN 1120-9135 https://www.annali-igiene.it

Introduction

Although the definition of what is a rare disease varies by geographical area and country, in the European Union a disease is considered rare when it affects fewer than 1 in 2,000 people (1). There are about 7,000 rare diseases that affect 10% of the world population (1), and many of them are usually underdiagnosed and undertreated.

Primary biliary cholangitis (PBC) is a chronic inflammatory, autoimmune, cholestatic liver disease that predominantly affects the interlobular bile ducts (2). It is one of the most common causes of chronic cholestasis among old women, with most patients aged 60 -79 years and a female-to-male ratio of 4–6:1 (2). PBC prevalence ranges from 3 to 40 per 100,000 worldwide, and from 12 to 58 per 100,000 in Europe, according to recent meta-analyses (3, 4). An Italian study recently reported a prevalence of 27.9 per 100,000 in the country, through the analysis of a large database of GPs' electronic medical records (5).

Early diagnosis of PBC is fundamental, as treatment with ursodeoxycholic acid, or second line therapy, prevents progression to liver cirrhosis and improves survival (6, 7). The proportion of subjects with early diagnosis of the disease has increased in last decades, probably due to increased routine testing of liver enzymes and awareness of the disease (8).

Current guidelines recommend a two-step approach for PBC diagnosis, consisting of: first, identifying adult asymptomatic subjects with cholestasis lasting 6 months and over by elevated levels of serum Alkaline Phosphatase (ALP) and/or gamma-glutamyltranspeptidase (GGT), and then, after excluding other liver and non-liver causes of ALP and/or GGT increase, determining serum antimitochondrial antibodies (AMA) and/or PBC-specific antinuclear antibodies (ANA) (6, 7). Since ALP can have various sources, also other intrahepatic and extrahepatic causes of ALP elevation must be considered for differential diagnosis (6, 9). However, data regarding guideline adherence in primary care settings and resulting PBC underdiagnosis are lacking.

This study aimed to assess the proportion of subjects with liver enzymes indicative of possible PBC but not investigated for the disease in primary care, leading to underdiagnosis and undertreatment of the disease.

Methods

A few General Practitioners (GPs), an expert gastroenterologist and some University epidemiologists working in the province of Brescia, Italy, set up a Working Group to investigate the prevalence and clinical pattern of PBC in the general population.

Data on history of liver and non-liver chronic diseases, presence of risk factors for liver disease, US examinations and specialists' visits and the latest values of ALP, GGT and AMA, were extracted from the GP's electronic archives. PBC diagnosis was based on the International Classification of Diseases, IX Revision, code 571.6. Only laboratory data and specialists' evaluations performed in the last 5 years were considered. All the data were anonymised at each extraction and a code was randomly assigned to each subject. No change in the GPs' routine clinical activity was done before and after the data extraction and across the clinical management process.

The clinical management process included the following steps:

1. A first data extraction of all GPs' patients aged 18 years and over was made (June 2021). The data were checked, and evident mistakes and missing data were reported to each GP for his/her correction. A second data extraction then was performed.
2. Patients without diagnosis of liver disease and without major risk factors for liver disease (HBV and HCV chronic infections, alcohol abuse, use of drugs, etc.) (6) were considered for subsequent steps.
3. Complete clinical data of the patients with ALP values above the laboratory reference values were evaluated by GPs and the gastroenterologist together.
4. The patients with elevated ALP values and without evidence of intrahepatic or extrahepatic (causes of cholestasis (4) were considered suspected for PBC and recommended for AMA test and specialist' s assessment.
5. Among the AMA positive patients, new PBC cases were diagnosed.

Results

A total of 20,480 adults attending 14 GPs in the province of Brescia, Northern Italy, with a mean age of 52.8 years (SD 19 years), 52.3% women, were included in the study. At the first data extraction, 9 patients with previous PBC diagnosis were identified, with a prevalence of 43.9/100.000 (95% confidence

interval, CIs: 20.1-83.4) (Figure 1). After excluding 2094 (10.2%) patients with liver diseases or with major hepatic risk factors for cholestasis, 121 subjects with ALP values above the reference values were re-evaluated by GPs and the gastroenterologist together. Among them, 94 patients who had hepatic or extrahepatic causes of ALP elevation were excluded from further evaluation, leaving 27 subjects with PBC suspicion. None of them had symptoms or signs of cholestasis. 18 of them were not tested for AMA/ANA due to very old age, presence of other severe diseases or refusal. Ultimately, 9 patients were tested for AMA: 4 were AMA positive and, after specialist's assessment, 3 of them had a definite diagnosis of PBC. One of the newly detected cases had already developed liver cirrhosis.

Overall, 12 patients were diagnosed with PBC after the clinical management procedure, with a mean age of 64 years (SD 13.3 years), 91.7% female. PBC prevalence was 58.6/100,000 (95% CIs: 30.3-102.4). About half of them (4 of 9) had had PBC diagnosis in the past 3 years, 4 (33.3%) had cirrhosis, and 2 (16.7%) PCB-related diseases (autoimmune atrophic gastritis and Crohn's disease).

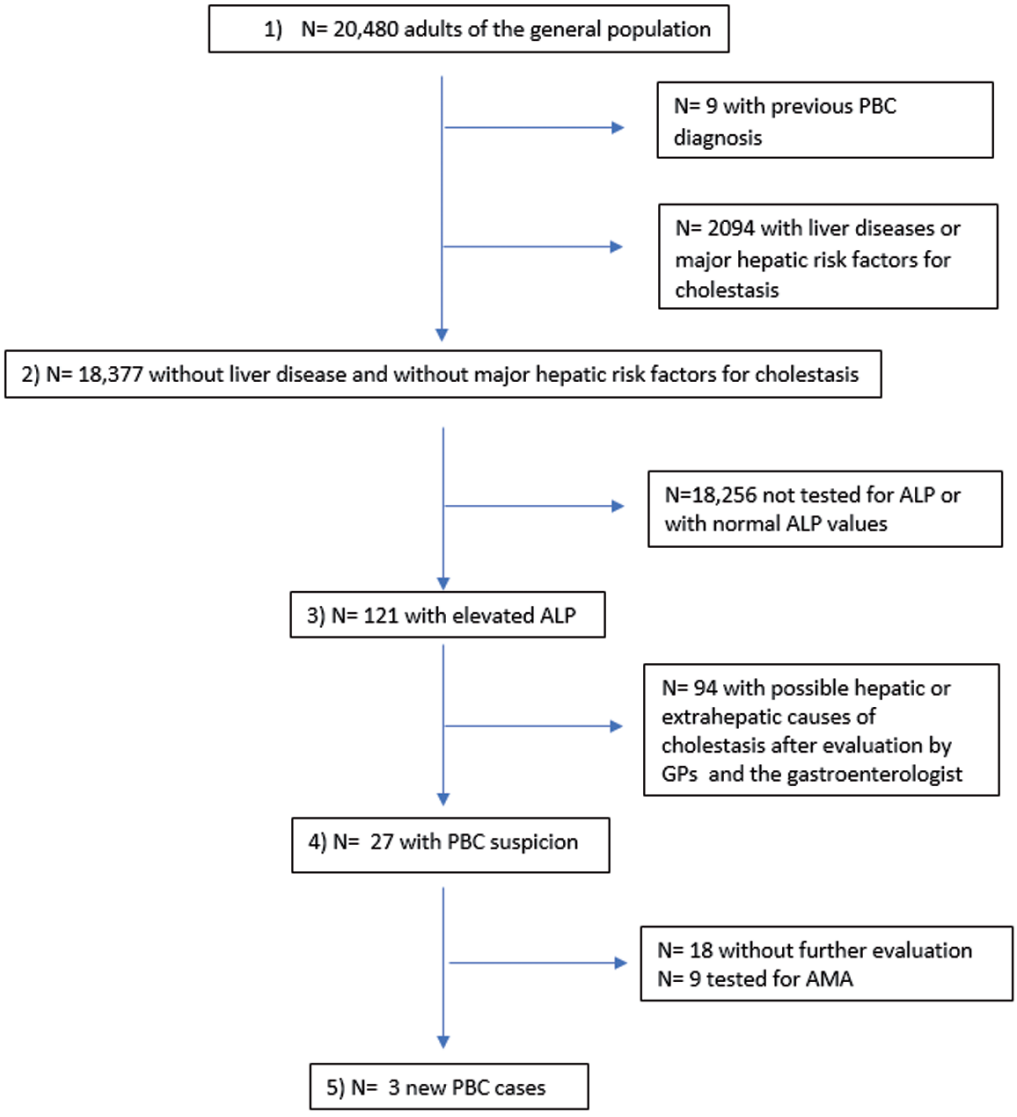

Figure 1 - Flow-chart of the clinical management procedure for detecting General Practitioners' patients with previously undiagnosed primary biliary cholangitis in the adult general population

Discussion

The main finding of this study is the successful implementation of a clinical management procedure in primary care for detection of PBC, a relatively rare and often unrecognized liver disease, following present guidelines (6, 7). The procedure led to the detection of 3 new cases of PBC, with a 33% increase in the disease prevalence. However, other PBC cases probably remained undetected, including: a) subjects with early PBC who did not have an ALP test, or had ALP values within the normality range in past 5 years; b) subjects with ALP elevation but who were not tested for AMA/ANA because they had other possible causes of cholestasis, including hepatic or non-hepatic disease or risk factors for liver disease (6); c) subjects with PBC suspicion but not tested for AMA due to very old age, poor health conditions, or refusal.

The main strength of this study is the use of a population-based database, excluding possible selection bias of case-series. Indeed, demographic data and prevalence of some common diseases such as diabetes, hypertension, cardio-and cerebral-vascular and celiac diseases in the adult population were in line with another GPs' database study on PBC (5) and with Italian national data (10). A second strength of the study is the clinical management process, consisting of a critical assessment of GPs' data, with correction and integration of routinely registered data.

Nonetheless, this study has some limitations. First, the relatively small number of GPs involved in the study, who were volunteers. However, the small number of the participating GPs allowed us to maintain close contacts with each physician through multiple verbal and written communications. Second, only subjects with elevated ALP values in the past 5 years were selected to identify undetected PBC cases. However, the number of subjects with at least one ALP test in the past 5 years varied substantially among the GPs, suggesting differences in GPs' propensity to prescribe the test in clinical practice. Of note, more than half of ALP diagnoses were performed in recent years (2019-2021), probably due to an increase in disease awareness by GPs, in agreement with other studies (3).

Overall, this study on a relatively rare disease shows that underdetection of rare diseases is likely to occur in primary care, mainly due to lack of a comprehensive diagnostic approach, in spite of current guidelines. The recently proposed application of Artificial Intelligence (AI) in healthcare might be helpful to improve the detection of rare diseases and to identify health system barriers causing underdiagnosis in primary care (11).

Conclusions

In conclusion, our study suggests that there is a non negligible proportion of rare diseases in the adult general population, such as PBC, that are underdiagnosed and undertreated in our country, despite the fact that the Italian Health System provides universal, free, primary healthcare and diagnostic approach for most diseases. The underestimation of rare diseases may be even higher in countries lacking a National Health System.

Acknowledgments: The authors thank Dr. Ovidio Brignoli for his thoughtful considerations and support to the study execution.

Abbreviations: ALP, alkaline phosphatase; AMA, antimitochondrial antibody; ANA, antinuclear antibody; GGT, gamma-glutamyl transferase; PBC, primary biliary cholangitis.

Financial support and sponsorship: This is a spontaneous study promoted by the Unit of Hygiene, Epidemiology and Public health, Department of Medical and Surgical Specialities, Radiological Sciences and Public Health, University of Brescia, together with the Gastrointestinal Unit, University of Brescia, and the School for GPs, Brescia area and the Protection Agency (ATS) of Brescia, with the non-conditioning support of Advanz Pharma Specialty Medicine.

Conflicts of interest: There are no conflicts of interest to declare.

Ethics: The project was approved by the Ethical Committee of Spedali Civili of Brescia, Italy (NP 3958) on 14th April 2021.

Riassunto

Perché le malattie rare sono sottodiagnosticate? Uno studio di management clinico sull'individuazione della colangite biliare primitiva in ambito di medicina generale

Introduzione. Ci sono circa 7.000 malattie rare che colpiscono il 10% della popolazione mondiale. La colangite biliare primitiva, un'epatopatia infiammatoria autoimmune dei dotti intraepatici, è una delle cause più comuni di colestasi cronica, che può portare alla cirrosi e all'insufficienza epatica. Tuttavia la colangite biliare primitiva è una malattia rara, e pertanto è spesso sottodiagnosticata e sottotrattata. Lo scopo della ricerca era di stimare la proporzione di casi di colangite biliare primitiva nella popolazione generale non diagnosticati, mediante una procedura di clinical management.

Metodi. Sono state effettuate due estrazioni dei dati relativi a epatopatie, fattori di rischio ed esami di laboratorio presenti nei database di un campione di medici di medicina generale della provincia di Brescia, con controllo e correzione degli errori. I dati clinici dei pazienti senza malattie di fegato o fattori di rischio epatico, e con livelli di fosfatasi alcalina superiori ai valori di riferimento del laboratorio, sono stati rivalutati da ciascun medico di medicina generale

con un esperto gastroenterologo. I soggetti con elevati livelli sierici di fosfatasi alcalina e senza altre cause intraepatiche o extraepatiche di colestasi sono stati considerati sospetti per colangite biliare primitiva e sottoposti a determinazione degli anticorpi anti-mitocondri e ad una valutazione specialistica.

Risultati. Un totale di 20.480 assistiti adulti di 14 medici di medicina generale della provincia di Brescia è stato incluso nello studio. Nove pazienti avevano una diagnosi di colangite biliare primitiva, con una prevalenza di 43.9/100.000. Dopo avere escluso 2.094 (10.2%) pazienti con malattie di fegato o fattori di rischio per colestasi, 121 soggetti con fosfatasi alcalina superiore ai valori di riferimento del laboratorio sono stati rivalutati da ciascun medico di medicina generale e dal gastroenterologo. 27 pazienti senza sintomi o segni di colestasi sono stati presi in considerazione per il sospetto di colangite biliare primitiva: 9 sono stati sottoposti a test per gli anticorpi anti-mitocondri, e tre nuovi casi di colangite biliare primitiva sono stati individuati (+33%).

Discussione e conclusioni. Questo studio mostra che vi è un considerevole numero di casi di malattie rare dell'adulto non individuati, che possono essere riconosciuti in ambito di medicina generale mediante una procedura di management clinico, senza modificare la pratica clinica corrente.

References

1. Haendel M, Vasilevsky N, Unni D, Bologa C, Harris N, Rehm H, et al. How many rare diseases are there? Nat Rev Drug Discov. 2020 Feb;**19**(2):77-78. doi: 10.1038/d41573-019-00180-y.
2. Trivella J, John BV, Levy C. Primary biliary cholangitis: Epidemiology, prognosis, and treatment. Hepatol Commun. 2023 Jun 2;**7**(6):e0179. doi: 10.1097/HC9.0000000000000179.
3. Lv T, Chen S, Li M, Zhang D, Kong Y, Jia J. Regional variation and temporal trend of primary biliary cholangitis epidemiology: A systematic review and meta-analysis. J Gastroenterol Hepatol. 2021 Jun;**36**(6):1423-1434. doi: 10.1111/jgh.15329. Epub 2020 Dec 6.
4. Gazda J, Drazilova S, Janicko M, Jarcuska P. The Epidemiology of Primary Biliary Cholangitis in European Countries: A Systematic Review and Meta-Analysis. Can J Gastroenterol Hepatol. 2021 Jun 19; 2021:9151525. doi: 10.1155/2021/9151525.
5. Marzioni M, Bassanelli C, Ripellino C, Urbinati D, Alvaro D. Epidemiology of primary biliary cholangitis in Italy: Evidence from a real-world database. Dig Liver Dis. 2019 May;**51**(5):724-729. doi: 10.1016/j.dld.2018.11.008. Epub 2018 Nov 17.
6. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017 Jul;**67**(1):145-172. doi: 10.1016/j.jhep.2017.03.022. Epub 2017 Apr 18.
7. Associazione Italiana per lo Studio del Fegato (AISF) e Società Italiana di Medicina Generale (SIMG) Epatopatie autoimmuni e colestatiche. Modello di gestione condivisa tra medici di medicina generale e specialista epatologo. 2018 (Italian Association for the Study of the Liver (AISF) and Italian College of General Practitioners and Primary Care. Autoimmune and colestatic liver diseases. A disease management between the general practitioner and the hepatologist) [In Italian]. Available from: https://www.simg.it/epatopatie-autoimmuni-e-colestatiche-modello-di-gestione-condivisa-tra-medico-di-medicina-generale-e-specialista-epatologo/ [Last accessed: 2024 Mar 6].
8. Murillo Perez CF, Goet JC, Lammers WJ, Gulamhusein A, van Buuren HR, Ponsioen CY, et al; GLOBAL PBC Study Group. Milder disease stage in patients with primary biliary cholangitis over a 44-year period: A changing natural history. Hepatology. 2018 May;**67**(5):1920-1930. doi: 10.1002/hep.29717. Epub 2018 Apr 6.
9. Pollock G, Minuk GY. Diagnostic considerations for cholestatic liver disease. J Gastroenterol Hepatol. 2017 Jul;**32**(7):1303-1309. doi: 10.1111/jgh.13738.
10. Italian National Institute of Health (Istituto Superiore di Sanità, ISS). EpiCentro. Available from: https://www.epicentro.iss.it/en/ [Last accessed: 2024 Mar 6].
11. Wojtara M, Rana E, Rahman T, Khanna P, Singh H. Artificial intelligence in rare disease diagnosis and treatment. Clin Transl Sci. 2023 Nov;**16**(11):2106-2111. doi: 10.1111/cts.13619. Epub 2023 Aug 30.

Corresponding Author: Francesco Donato, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Viale Europa 11, 25121 Brescia, Italy
e-mail: francesco.donato@unibs.it