Digestive and Liver Disease 51 (2019) 669–674

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Characteristics of inflammatory bowel disease in patients of Roma/Gypsy ethnicity. A case-control study

Eduard Cabré[a,h,*], Míriam Mañosa[a,h], Ignacio Marín[b], Rosa Martín-Mateos[c], Eva Iglesias-Flores[d], Manuel Barreiro-de-Acosta[e], Pilar Nos[f,h], David Busquets[g], Luis A. Menchén[b,h], Antonio López-Sanromán[c], Eugeni Domènech[a,h]

[a] IBD Unit, Department of Gastroenterology, University Hospital «Germans Trias i Pujol», Badalona, Catalunya, Spain
[b] Department of Gastroenterology, University Hospital «Gregorio Marañón», Madrid, Spain
[c] Department of Gastroenterology, University Hospital «Ramón y Cajal», Madrid, Spain
[d] Department of Gastroenterology, University Hospital «Reina Sofía», Córdoba, Andalucía, Spain
[e] Department of Gastroenterology, University Hospital, Santiago de Compostela, Galicia, Spain
[f] Department of Gastroenterology, University Hospital «La Fe», València, Spain
[g] Department of Gastroenterology, University Hospital «Dr. Josep Trueta», Girona, Catalunya, Spain
[h] Centre for Network Biomedical Research in Liver and Digestive Diseases (CIBEREHD), Madrid, Spain

ARTICLE INFO

Article history:
Received 26 September 2018
Accepted 10 December 2018
Available online 19 December 2018

Keywords:
Crohn's Disease
Inflammatory Bowel Disease
Roma/Gypsy ethnicit
Ulcerative Colitis

ABSTRACT

Background: Peculiarities of inflammatory bowel disease (IBD) have been explored in ethnic groups, such as Asians, Hispanics, and Afro-Americans, but not in other ethnic minorities, such as Roma/Gypsies.
Methods: In a retrospective, hospital-based study, all adult Roma/Gypsy patients included in the IBD databases of seven Spanish centres were identified as cases. For each Roma/Gypsy patient, a Caucasian patient, matched for several demographic features, was searched as a control. Data on phenotypic features, therapeutic requirements, and familial aggregation were recorded.
Results: Sixty-eight Roma/Gypsy patients were identified, 29 of them being women. The mean age at diagnosis of IBD was 24.9 ± 9.5 years, and the mean time elapsed since diagnosis was 96.6 ± 72.2 months. Roma/Gypsy IBD patients showed a significantly higher rate of familial aggregation (43%) than their Caucasian controls (9%) (p = 0.00001). CD in Roma/Gypsies had more often a complicated pattern (mainly penetrating) while UC patients showed a marked trend to more often developing extraintestinal manifestations. In addition, Roma/Gypsy IBD patients had a somewhat greater need for immunosuppressants, biological agents or surgery.
Conclusions: These are the first data on IBD in Roma/Gypsy patients. Familial aggregation is the most prominent feature in these patients, suggesting a predominant role of genetics in its pathogenesis.

1. Introduction

Inflammatory bowel disease (IBD) –Crohn's disease (CD) and ulcerative colitis (UC)– are chronic immunologically mediated disorders traditionally thought of as affecting individuals of European or Ashkenazi Jewish origin [1]. However, in the last decades IBD has emerged as a global disease affecting individuals of every ethnicity and geographic region, with a rapid rise in incidence in regions undergoing urbanization and "westernisation" of the lifestyle [2,3]. The global emergence of IBD offers the possibility of exploring similarities and differences in disease presentation and outcomes across different geographic regions and ethnic groups. To date, such an exploration has focused on disease peculiarities of Asian, Hispanic, and Afro-American patients as compared to Caucasian ones [4–6]. However, to our knowledge, the characteristics of IBD presentation and outcome in other ethnic minorities, such as Roma/Gypsy individuals, have not been studied at all.

The Roma/Gypsy population is characterized by a lack of reliable records, a nomadic tradition, and dispersal as an underprivileged ethnic minority in numerous countries. Cultural anthropology, linguistics, and limited historical records from the surrounding majority populations describe the Roma/Gypsies as a population of Northwest Indian origin –in contrast to other hypotheses about their origin (e.g. being the lost descendants of the Jewish tribe of

* Corresponding author at: IBD Unit, Department of Gastroenterology, Hospital Universitari «Germans Trias i Pujol», Badalona, Catalunya, Spain.
E-mail address: ecabre.germanstrias@gencat.cat (E. Cabré).

https://doi.org/10.1016/j.dld.2018.12.004
1590-8658/

Simeon), this has been recently proven by genetic studies [7]–, with their exodus from India dated to approximately the 5th–10th century, their arrival in Byzantium dated to the 11th or 12th century, and their dispersal throughout Europe documented by the end of the 15th century [8]. Upon arrival in Europe, a large fraction of the initial migrant population settled permanently in the Balkans south of the Danube, others moved north into Wallachia (nowadays Romania), while the remainder continued the journey to all parts of the continent, including Spain [8].

Spain is the Western European country with the greatest number of Roma/Gypsy individuals who represent about 1.6% of the total Spanish population. Most of them concentrate in Andalusia, Catalonia, Valencian Community, and Madrid's Community (Fig. 1). Therefore, we were interested in exploring the peculiarities of IBD in this ethnic minority, as compared to patients from the majority Spanish population of Caucasian origin, by means of a case-control study.

2. Patiens and methods

All adult patients of the Roma/Gypsy ethnicity included in the IBD databases of seven Spanish reference centres –six of them from areas with a high number of Roma/Gypsy population– were identified as cases (G group). For each Roma/Gypsy patient, a patient of Caucasian ethnicity, matched for centre, gender, disease type, year of birth, year of IBD diagnosis, and smoking habit at diagnosis, was searched to be used as a control (C group). In the event that more than one control matched for a case, the former was chosen at random. If no patient met for all matching variables for a case, that with more coincidences was chosen.

In all cases and controls, the following data were recorded: (1) Phenotypic features including UC extent and CD location and behaviour –all of these according to the Montreal classification [9]–, UC proximal progression, perianal disease, development of intestinal complications (toxic megacolon, intestinal perforation, intraabdominal abscesses), extraintestinal manifestations, thromboembolic events, and dysplasia or colorectal cancer; (2) Therapeutic requirements including steroids (and the development of steroid refractoriness or dependence), immunosuppressants, biological agents, and surgery procedures; and (3) Familial aggregation. In addition, the disease was arbitrarily defined as "aggressive" (with the meaning of "roughly being somewhat more difficult to manage") when the patient required at least one of these treatments: immunosuppressants, biological agents, or colectomy, in the case of UC; and biological agents or bowel resection, in the case of CD. We did not consider the need for immunosuppressants as a criterion of aggressiveness of CD because the vast majority of these patients require such a therapy sooner or later.

2.1. Statistics

Quantitative and qualitative variables are expressed as mean ± SD and frequencies, respectively. Comparison of quantitative variables between cases and controls was performed with the Student-t-test for paired data. Differences in the frequency of qualitative variables in pairs of cases and control were assessed by means of the McNemar test. In all instances, statistical significance was set up at $p < 0.05$.

All statistical procedures were performed using the SPSS v19 software (Chicago, IL, USA).

2.2. Ethical issues

The study was approved by the Ethics Committee of the steering centre (Hospital Universitari «Germans Trias i Pujol»), and has been performed in accordance with the ethical standards laid down in the 1975 Declaration of Helsinki and its later amendments.

Table 1
Demographic variables in Roma/Gypsy and Caucasian patients.

Ulcerative Colitis			
	Group G (n = 24)	Group C (n = 24)	P[a]
Gender (M/F)	15/9	15/9	1.000
Age (y) at diagnosis	26.3 ± 11.9	26.6 ± 12.6	0.853
Months elapsed from diagnosis	86.6 ± 61.1	87.2 ± 64.9	0.881
Active smoking (Y/N)	6/18	7/17	1.000
Crohn's disease			
	Group G (n = 44)	Group C (n = 44)	P[a]
Gender (M/F)	24/20	24/20	1.000
Age (y) at diagnosis	24.2 ± 8.0	25.1 ± 8.1	0.773
Months elapsed from diagnosis	102.0 ± 77.7	104.2 ± 65.4	0.825
Active smoking (Y/N)	24/20	23/21	1.000

[a] McNemar's test for qualitative variables, Student-t-test for paired data for quantitative variables.

3. Results

3.1. Demographic data

A total of 68 Roma/Gypsy patients were identified (24 with UC, 44 with CD), 29 of them (42%) being women (9 with UC, 20 with CD). The mean age at diagnosis of IBD was 24.9 ± 9.5 years, and the mean time elapsed since diagnosis was 96.6 ± 72.2 months. Six UC (25%) and 24 CD patients (54%) were active smokers at IBD diagnosis. Table 1 describes de degree of matching for demographic variables between groups G and C.

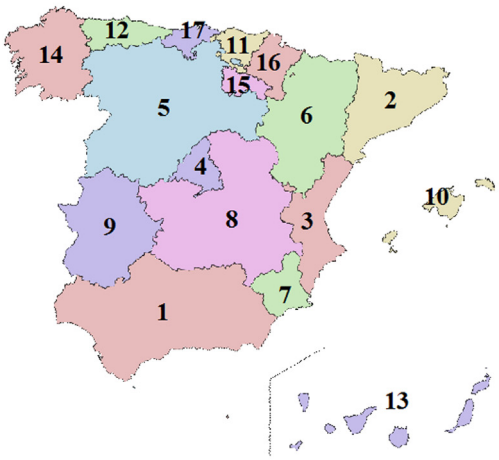
3.2. Phenotypic characteristics

3.2.1. Ulcerative Colitis (Table 2)

There were no differences in the extent of the disease between groups G and C. Extensive colitis predominate in both groups (15/24 in group G, 13/24 in group C), while proctitis was only present in three patients of group G and one of group C. There was no case of toxic megacolon, intraabdominal abscess, colon perforation, or proximal progression of the disease in both G and C groups, and only a single instance of thrombotic complications in a G patient, as well as a colorectal cancer in a patient of the group C. Finally, there was a marked but non-significant trend ($p = 0.07$) to a greater incidence of extraintestinal manifestations –mainly rheumatologic and cutaneous– among Roma/Gypsy patients, as compared to the Caucasian ones.

3.2.2. Crohn's disease (Table 3)

No differences in the location of disease between both groups were found. Ileal disease –present in 18/44 G cases, and 22/44 C controls–, and ileo-colic involvement –occurring in 23/44 G patients, and 20/44 C patients– were the most frequent localizations of the disease, whereas the isolated involvement of the colon was rare. In contrast, at the end of follow-up, complicated disease –mainly penetrating pattern– was significantly more frequent among G than C patients ($p = 0.035$). In spite of this, no differences were observed regarding the development of intestinal perforation or intraabdominal abscesses. Also, the incidence perianal disease and extraintestinal manifestations were similar in both groups. No case of thrombosis, toxic megacolon or colorectal cancer was found in either group.



Community	Approximate Gypsy popul.
1. Andalusia	280,000
2. Catalonia	80,000
3. Valencian Community	65,000
4. Madrid's Community	60,000
5. Castilla & Leon	29,000
6. Aragon	21,000
7. Region of Murcia	20,000
8. Castilla-La Mancha	20,000
9. Extremadura	15,000
10. Balearic Islands	13,000
11. Basque Country	13,000
12. Asturias	10,000
13. Canary Islands	9,500
14. Galicia	9,000
15. La Rioja	7,000
16. Navarre	6,000
17. Cantabria	5,000

Fig. 1. Approximate number of Roma/Gypsy people living in the different Spanish Autonomous Communities. (Source: "Foundation for the Spanish Gypsy Secretariat"; https://www.gitanos.org/).

Table 2
Phenotypic features and therapeutic requirements in pairs of G–C[a] UC patients.

Feature	Present in G Present in C	Absent in G Absent in C	Present in G Absent in C	Absent in G Present in C	P[b]
Proctitis (E1)	0/24	20/24	3/24	1/24	
Distal colitis (E2)	2/24	11/24	4/24	7/24	0.542
Extensive colitis (E3)	7/24	3/24	8/24	6/24	
Extraintestinal manifestations	0/24	16/24	7/24	1/24	0.070
Thrombosis	0/24	23/24	1/24	0/24	1.000
Colorectal cancer	23/24	0/24	0/24	1/24	1.000
Need for systemic steroids	14/24	0/24	8/24	2/24	0.109
Steroid dependence[c]	1/14	5/14	6/14	2/14	0.289
Steroid refractoriness[c]	1/14	9/14	3/14	1/14	0.625
Need for immunosuppressants	5/24	5/24	11/24	3/24	0.057
Need for biological agents	1/24	15/24	6/24	2/24	0.289
Need for colectomy	0/24	20/24	2/24	2/24	1.000
"Aggressive" disease[d]	6/24	5/24	11/24	1/24	0.022

There was no case of toxic megacolon, intraabdominal abscess, colon perforation, or proximal progression of the disease in either Gypsy and Caucasian patients.
[a] G = Gypsy patients (cases); C = Caucasian patients (controls).
[b] McNemar's test.
[c] For the 14 pairs with both members needing steroids.
[d] Need for immunesuppressors and/or need for biological agents and/or need for colectomy.

3.3. Therapeutic requirements

3.3.1. Ulcerative colitis (Table 2)

No differences were observed in the need for systemic steroids –and also in the development of steroid refractoriness and dependence–, biological agents or colectomy between G and C groups. However, the use of immunosuppressants (i.e. thiopurines) showed a marked, albeit non-significant, trend to be more frequent among the Roma/Gypsy patients (p = 0.057). As a consequence, and according to the predefined criteria, UC could be more often qualified as "aggressive" among Roma/Gypsy individuals (p = 0.022).

3.3.2. Crohn's disease (Table 3)

Roma/Gypsy CD patients did not have increased needs of systemic steroids, immunosuppressants, biological agent or intestinal resection, as compared to their Caucasian counterparts. There was, however, a non-significant trend to more often develop an "aggressive" disease as defined above (p = 0.064).

3.4. Familial aggregation

Familial aggregation –i.e. having at least one first or second degree relative with IBD– occurred in 29/68 (43%) Roma/Gypsy patients, and only in 6/68 (9%) among their Caucasian counterparts. Paired McNemar's test proved such a difference to be statistically significant both for all IBD pairs, and for UC and CD pairs separately (Table 4). In addition, in those patients showing familial aggregation, the number of affected relatives was greater among Roma/Gypsy (55 relatives, with a mean of two relatives per patient) than Caucasian subjects (6 relatives, one per patient). More than a half (n = 28) of the 55 Roma/Gypsy affected relatives were second degree relatives, while only 2/6 affected relatives were of second degree among Caucasian patients. Forty-seven out of 55 relatives from G group (85%) were concordant with the index case for the type of IBD. This occurred in 5/6 pairs (83%) among Caucasian patients.

Table 3
Phenotypic features and therapeutic requirements in pairs of G–C[a] CD patients.

Feature	Present in G Present in C	Absent in G Absent in C	Present in G Absent in C	Absent in G Present in C	P[b]
Ileal (L1)	7/44	11/44	11/44	15/44	
Colic (L2)	1/44	40/44	2//44	1/44	0.644
Ileo-colic (L3)	9/44	10/44	14/44	11/44	
Upper G-I tract (L4)	0/44	37/44	3/44	4/44	1.000
Inflammatory (B1)	12/44	12/44	8/44	12/44	
Stricturing (B2)	5/44	24/44	7/44	8/44	0.035
Penetrating (B3)	0/44	25/44	12/44	7/44	
Perianal disease	2/44	27/44	11/44	4/44	0.118
Extraintestinal manifestations	3/44	27/44	7/44	7/44	1.000
Intraabdominal abscess	1/44	34/44	6/44	3/44	0.508
Intestinal perforation	0/44	38/44	4/44	2/44	0.687
Need for systemic steroids	28/44	4/44	8/44	4/44	0.388
Steroid dependence[c]	11/28	4/28	8/28	5/28	0.581
Steroid refractoriness[c]	1/28	17/28	5/28	5/28	1.000
Need for immunosuppressants	31/44	0/44	9/44	4/44	0.267
Need for biological agents	9/44	13/44	14/44	8/44	0.286
Need for bowel resection	8/44	14/44	14/44	8/44	1.000
"Aggressive" disease[d]	18/44	2/44	17/44	7/44	0.064

There was no case of thrombosis, toxic megacolon or colorectal cancer in either Gypsy and Caucasian patients.
[a] G = Gypsy patient; C = Caucasian patient (controls).
[b] McNemar's test.
[c] For the 28 pairs with both members needing steroids.
[d] Need for biological agents and/or need for bowel resection.

Table 4
Familial aggregation in pairs of G–C[a] Inflammatory Bowel Disease patients.

Familial aggregation in...	Present in G Present in C	Absent in G Absent in C	Present in G Absent in C	Absent in G Present in C	P[b]
...All patients	3/68	36/68	26/68	3/68	0.00001
...UC patients	1/24	12/24	11/24	0/24	0.001
...CD patients	2/44	24/44	15/44	3/44	0.008

[a] G = Gypsy patients; C = Caucasian patients (controls).
[b] McNemar's test.

4. Discussion

In the last years, attention has been paid to disclose the possible differences in the presentation and outcome of IBD in some non-Caucasian ethnic groups, mainly Asians [3] as well as Hispanics and Africans living in North America [4–6]. As far as we know, the present paper is the first attempt to describe the peculiarities of IBD affecting one of the most numerous ethnic minorities in Europe such as the Roma/Gypsies.

The most remarkable finding in this study is the very high rate of familial aggregation in Roma/Gypsy patients (43%) –with also a high concordance for IBD type– as compared with that found in their Caucasian counterparts. Such a figure is higher than that reported in a large Spanish hospital-based series of IBD patients [10], and exceeds by large the prevalence described in population-based studies from Western [11–13] and other Mediterranean countries [14,15], which vary from 4.5% to 11.5%.

Although sharing both susceptibility genes and/or environmental factors by members of the same family may result in familial aggregation for IBD [16–19], there are reasons that favour a predominant role of genetics as the cause of the high familial aggregation occurring in IBD Roma/Gypsy patients, the strongest one being the high rate of endogamy –and, therefore, consanguinity– that exists within the communities of this ethnic group [20]. Although the presence of endogamy was not available in the medical records of our patients, this is a well known characteristic of Spanish gypsies [21]. In the context of endogamy, Roma/Gypsy ethnicity is viewed as founder of a number of private gene mutations related to Mendelian inherited diseases [22–24]. Similarly, it could be hypothesized the gypsies as being founders of some mutations for complex polygenic diseases such as IBD but, to prove that, specific studies are required. Indeed, some data are already available that indicate a different distribution in the frequency of haplotypes of the IL23 receptor gene [25], the cytochrome P450 genes [26,27], and the genes involved in the response to steroids [28] between Roma/Gypsy and Caucasian individuals. The existence of families with more than two members affected with the disease, as well as the high proportion (more than 50%) of second-degree relatives sharing the disease, also argue for genetic rather than environmental factors leading to familial aggregation among Roma/Gypsies. Moreover, the marked trend to develop extraintestinal manifestations (mainly in UC cases) in these patients also suggests inheritance of shared pathogenic mechanisms between intestinal and extraintestinal diseases, as has already been proposed for other ethnic minorities with IBD [29]. In the setting of a predominant role of genetics, some degree of diagnostic anticipation should be expected among Roma/Gypsies. However, the design of the study –where both the year of birth and the year of diagnosis were criteria for matching– does not allow to assess this issue. Finally, the marked predominance of CD –in spite of being in part due to a bias as the study was hospital-based– also favours a predominant role of genetics, which appears to be more marked in CD than UC, as suggested by twin studies [18].

The only phenotypic characteristic found to be differential between Roma/Gypsy and Caucasian patients was the greater frequency of complicated (i.e. structuring, and mainly penetrating) CD, although this was not accompanied by a higher frequency of abdominal catastrophes such as intestinal perforation or intraabdominal abscesses. Again, this finding could rely on a genetic basis, since some candidate genes and polymorphisms have recently described as associated to the CD progression from inflammatory to complicated forms [30,31].

In spite that no clear-cut differences in therapeutic requirements for specific drugs or surgery were found between Roma/Gypsy and Caucasian patients, the composite variable of need on any of these (so called "aggressive disease") was found the occur more often among Roma/Gypsy patients (mainly those with UC). In the absence of a clearly more aggressive disease phenotype, this finding could be interpreted as a result of the poor adherence of these patients to maintenance therapies which would lead them to more severe flares requiring more potent/complex treatments [32]. Although difficulties for accessing healthcare facilities have been reported for Roma/Gypsies [33–35] and other ethnic minorities [36], this does not seem to be the case for Spanish gypsies, since in Spain universal free access to the National Healthcare System does exist. However, poor adherence to therapies and lack of engagement to medical control are frequent in these patients [33,35], resulting in worse health issues as compared to the non-Gypsy surrounding population [37,38]. Although most of the Spanish gypsies are no longer nomadic but permanently settled in proper houses, marginality and idiosyncratic cultural issues could account for such a behaviour [39]. Unfortunately, we could not investigate on the adherence of our patients to therapy because of the lack of objective registry of patients' drug dispensation in the pharmacies, but the recent implementation of hospital administration of treatments on an out-patient basis (e.g. for biological agents) has confirmed a suboptimal adherence among gypsies in our centres. Other plausible reason accounting for a greater need for therapies among gypsies could be a delay in seeking medical advice before diagnosis. This aspect could not be assessed because of the retrospective nature of the study.

It has to be acknowledged that the present study has two main limitations; namely, its retrospective nature and the fact of being hospital-based. The last characteristic may favour a bias towards more severe cases and to patients with better engagement with medical control as well. In addition, it is not useful to assess either the real prevalence and incidence or the demographic features (e.g. UC extent, CD location or behaviour) of IBD in the Roma/Gypsy community. These items should be answered by well designed population-based studies. Such studies can be difficult to perform at least in Spain where data on race or ethnicity are not included in the official registration records of citizens (in order to avoid any discrimination on these grounds). Anyway, the present study provides valuable data that should prompt specific studies on IBD genetics in this ethnic group.

In conclusion, these are the first data on IBD in Roma/Gypsy patients. Familial aggregation is the most prominent feature in these patients, suggesting a predominant role of genetics in its pathogenesis. In this sense, GWAS studies comparing cohorts of Roma/Gypsy and Caucasian patients seem to be warranted.

Conflict of interest

None declared.

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