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MEDICINE
Research article

ASSOCIATION OF ORAL LICHEN PLANUS WITH CHRONIC HEPATITIS B AND C VIRUS INFECTION: A CASE-CONTROL STUDY

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Accepted October 6, 2017

The study aims to investigate the epidemiological association between oral lichen planus (OLP) and chronic hepatitis B and C virus infection. The study group consisted of 551 patients diagnosed with OLP based on clinical and histological criteria and was divided according to the determination of serum levels of antibodies of hepatitis C (anti-HCV) into two subgroups with positive values and negative (absence of the anti-HCV). Having diagnostic support and the results of other laboratory investigations, the patients of the first subgroup were classified as carriers of the chronic hepatitis C and OLP association. The study analysis was based on the comparison of the two subgroups results with reference to a control group consisting of patients without OLP, chronic liver disease or dermatological disorders recognized with autoimmune etiology. Conclusions of the study resulting from the prevalence of association lead to the mandatory setting in the medical practice of monitoring both patients with OLP only and those suffering only from chronic hepatitis C because their pathogenic association influences the therapeutic success.

Key words: Oral lichen planus (OLP), hepatitis B virus, chronic hepatitis C virus (HVC), anti-HCV antibodies, sero-prevalence.

INTRODUCTION

Lichen planus (LP) is a chronic dermatosis with complex and multifactorial etiology, manifested on the skin and/or oral mucosa, with characteristic clinical and histopathological aspects[1,2]. Oral manifestations are a frequent localization. Although there are few studies on the prevalence of OLP in the general population, the average of 1.27%[3] with variations depending on the studied geographic area: 0.1–4%[4,5], 0.1–2.2%[6], 2%[7], but also by the patients gender (men: 0.96%, women: 1.57%)[3]. Published studies have shown that OLP patients frequently associate general disorders such as chronic hepatopathies, such as those with C virus (HVC), diabetes mellitus and autoimmune diseases[4,8]. The identification of such associated conditions is a necessity as they influence the evolution and prognosis of OLP, as it is known that an acute episode of systemic disease also aggravates oral lesions[8].

MATERIAL AND METHODS

The study covers a period of 10 years (2005–2014) for investigating 767 patients selected from those who attended the Clinical Department of Oral Medicine Discipline of the Faculty of Dentistry, "Carol Davila" University of Medicine and Pharmacy, from Bucharest. The patients were outpatients with clinical observation forms filled in. The research was conducted on the basis of a protocol approved by the Ethics Committee of the University's Scientific Research. The whole study was conducted in accordance with the Helsinki Declaration.

The patients included in the present study, depending on the clinical oral examination of the presence or absence of characteristic OLP lesions, were divided in:

1. The group consisting of those presenting the oral condition: 551 cases (referred to as follow-up **study group**). The OLP diagnosis was established following the 1978 WHO criteria and the van der Meij and van der Waal recommendations from 2003[9,10].

A. In the study group, for the determination of positive diagnosis and clinical forms we used the Andreasen's OLP classification[11]. Thus, the positive diagnosis of OLP was established by the existence of at least the minimal criteria (symmetrical reticular keratosis located, bilaterally on the buccal mucosa in the posterior areas, associated or not with other types of lesions), although most of the analysed cases presented characteristic oral lesions[8,10,12] (Figure 1).

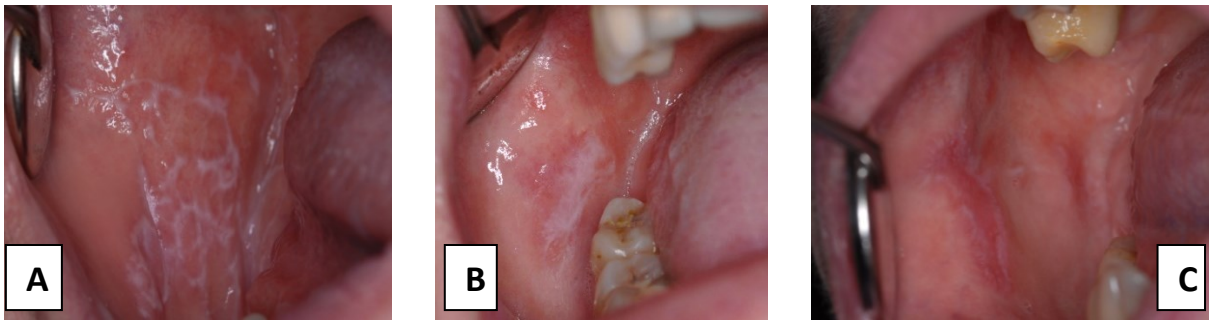

Figure 1. Clinical appearance in OLP (A: reticular keratosis, B: plaque-like keratosis and atrophy, C: keratosis and atrophy involving oral mucosa).

B. Although in terms of cost / effectiveness it would have been required to perform a histopathological examination only in cases of atypical forms of OLP in order to eliminate the possibility of an error, we decided to carry out this investigation by all patients in the study group.

The presence of characteristic features of OLP: chronic, dense, predominantly lymphocytic inflammatory "band-like" infiltration located in the superficial chorion, vacuolisation of basal keratinocytes and absence of epithelial dysplasia[10] (Figure 2).

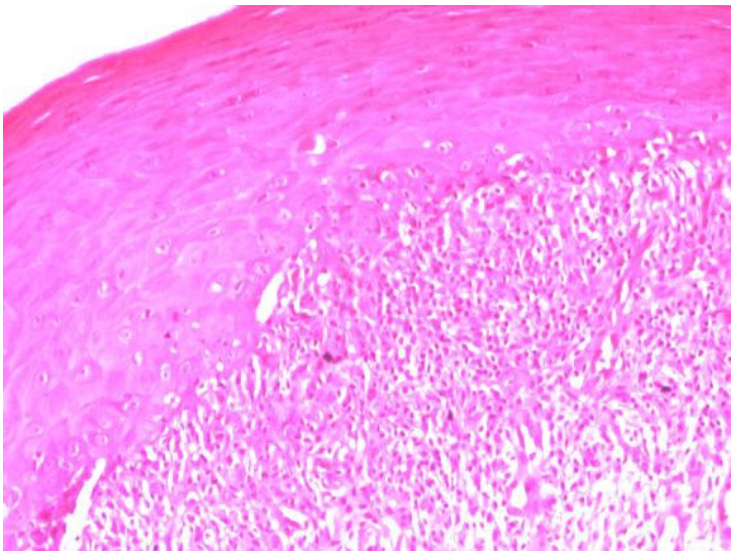

Figure 2. Histological appearance of OLP: absence of basal cell layer, small cleft between epithelium and chorion, Civatte colloidal corpuscles, aspect of exocytosis of lymphocytes in the deep epithelium, (HE, 100×).

2. In order to constitute **the control group**, comprising 216 patients without OLP and having considered any possible sources of error in interpreting the results, we included only those who:

– at the time of the clinical examination, presented no oral mucosal lesions;

– denied the existence of a medical history of any oral disease as well as dermatological diseases with immune / autoimmune etiology.

All the patients have been examined by an oral medicine specialist and a dermatologist.

General and demographic characteristics (age, gender, profession, domicile – rural / urban), personal medical history and drug intake were analysed for patients of both groups. Laboratory investigations included:

A. Compulsory tests to be performed on any patient regardless of the symptomatology presented: a complete blood count, blood glucose;

B. The level of serum transaminases (ALT and AST)-tests that exploit the hepatic function, in particular, those that reveal the existence or not of hepatocitolysis, hepatopriviality, excreta-biliary and mesenchymal activity;

C. Tests that investigated the circulatory presence of anti-virus antibodies with hepatic tropism. To investigate the association of OLP with viral hepatitis B, specific tests were performed to detect the presence of HBsAg by the MONOLISA reaction. To determine the presence of serum levels of antibodies of hepatitis C (anti-HCV) laboratory test ELISA of the 2nd generation (MONOLISA anti-HCV PLUS) were performed, and the reactive results were confirmed by a recombinant RIBA-type immuno-blotting reaction.

The study group of patients with OLP was divided into two subgroups: **subgroup A** – composed of patients with chronic C virus associated hepatopathy and **subgroup B** consisting of patients presenting only OLP lesions.

The analysis of the collected data was performed using the StataIC 11 program (StataCorp, 2009. Stata: Release 11. Statistical Software, College Station, TX, USA). Possible associations between the variables were tested using the Pearson Chi-squared test. The Fischer's test was used when the number of observations corresponding to a cell in the contingency table was less than 5. The level of statistical significance was set at 0.05.

RESULTS

The average age of all 767 patients constituting the study group and control group is as shown in the following table.

The average gender correlation in the OLP group showed a 3.6 / 1 ratio for women (n = 432/ 78.4% women and n = 119/ 21.6% men) and an average age of: 58.32 ± 13.06 years in females and 52.50 ± 16.25 years in males (Figure 3).

Table 1

Age range of the two groups of patients included in the present study

	Patients (n)	Average age (years)	Standard deviation	Confidence interval
Study group	551	57.06	14.00	55.89–58.23
Control group	216	57.09	14.99	55.08–59.10

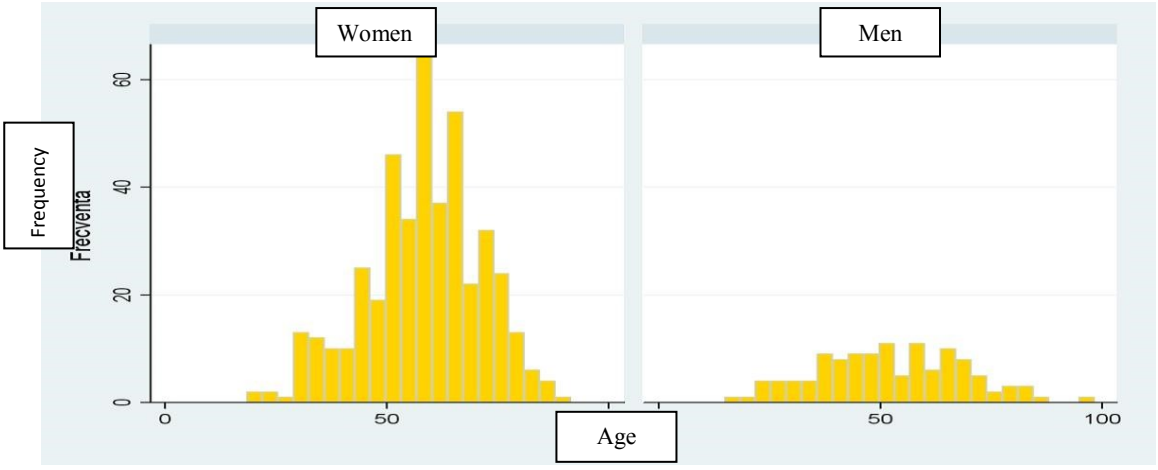

Figure 3. Histogram of patients distribution in the study group by age and gender.

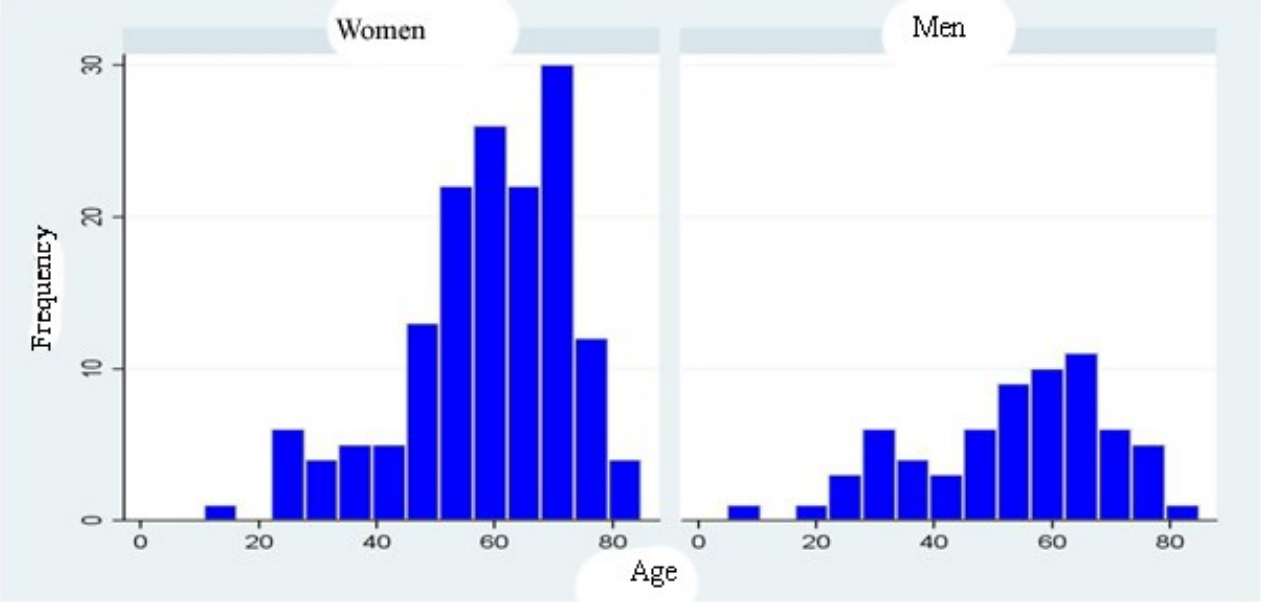

Figure 4. Histogram of distribution of patients in the control group by age and gender.

Table 2

Distribution of clinical forms of OLP manifestations in the study group

Clinical form	**Number of cases**	
	Total number	**%**
Keratotic type	262	47.55
Erosive- ulcerative type	169	30,67
Atrophic type	112	20,32
Bullous type	8	1,45
Total cases	551	100

Analysing the demographic characteristics of OLP patients, we found that most (80% *vs*. 20%) come from the urban environment and two thirds have an average level of education (65.34% *vs*. 34.66%).

The same parameters were also analyzed for the 216 patients in the control group.

The mean age was 57.09 ± 14.99 years with a gender distribution of: 150 (69.44%) women with mean age 58.68 ± 14.02 years and 66 (30.56%) men with mean age 53.48 ± 16.55 years (Figure 4).

The analysis of demographic characteristics of patients in the control group shows almost similarity to the study group. The majority (83.81% *vs*. 16.19%) coming from the urban area, with only the percentage referring to the average level of education being different (77.35% *vs*. 22.65%). That is, over ¾ in this batch compared to the 2/3 existing in the study group.

The incidence of the various clinical forms under which OLP are manifested are presented in Table 2.

Of the 551 OLP patients that consisted of the study group, almost 1/3 (169 cases/30.67%) associated chronic hepatopathy, of which 148 cases (87.6%) were reported with viral etiology (Figure 5).

The results of anti HCV and AgHBs determination in serum of the patients included in the two research groups are summarized in Table 3.

Knowing that the relative risk gives indications of the higher probability of a disease, when exposed, to assess the strength of the epidemiological association, we calculated the odds ratio (OR), and the results are presented in Table 3.

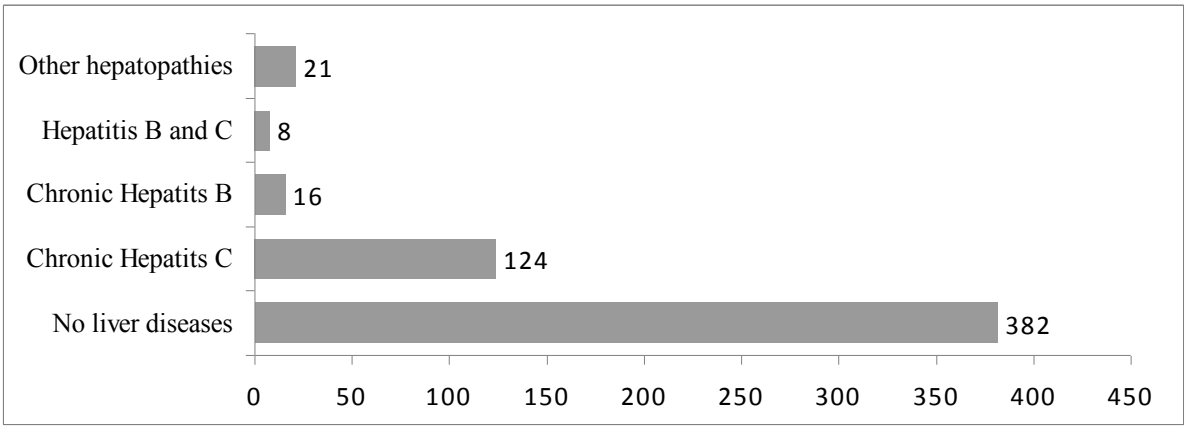

Figure 5. Distribution of patients in the study group after the etiology of associated chronic hepatopathy.

Table 3

AntiHCV and AgBHS results

Type of the group	Number of patients	Serum levels results for							
		AgHBs				Ac antiVHC			
		Negative		Positive		Negative		Positive	
		No.	%	No.	%	No.	%	No.	%
Study group	551	527	95.64	24	4.36	419	76.04	**132**	**23.96**
Control group	216	209	96.76	7	3.24	206	95.37	**10**	**4.63**
Statistical significance		p = 0.522, Test chi²				**p = 0.001, Test chi²**			
Odds ratio (95%CI)		6.48 (3.34–12.60)							

DISCUSSIONS

1. Comparative statistical analysis of the constituent patients of the two groups confirms that, at least in terms of age, the groups were homogeneous (dif = 0.03, p = 0.97, t test).

2. Legally related to the sex of the patients included in the control group, we also sought to have a homogeneous group. Knowing that in the OLP literature women predominantly affect women, we included predominantly women patients in the control group.

3. In the study group, the analysis of the frequency of clinical manifestations of OLP allows to mention that: one in two patients presents the keratosis form of the disease, one in three has erosive-ulcerative form and 1 in 5 atrophic form. The form of bullous manifestation in the studied group had an insignificant representation (Table 2). In the keratosis form, the reticular and plaque layout prevailed, and in those with a recent onset, the clinical picture was the keratosis papules.

4. Of the nearly 1/3 (N = 169/ 30.67%) cases associated with OLP and chronic hepatopathy, the most common cause is viral etiology (n = 148 cases/ 96,19%), and the HCV infection represents (n = 132 cases/ 89,2%) (Figure 5).

The report value of patients with OLP + HVC / patients with OLP + HVB = 132 (124 + 8) / 24 (16 + 8) shows us a frequency of over 5 times greater for association with C virus than for B virus. Comparison of data allows us to argue that hepatitis C virus is a favourable factor, predisposing to OLP development. An additional argument that cannot be countered results if we exclude the eight patients who recognized both the viruses as the etiology of hepatitis associated with OLP:

Patients with OLP + HCV / patients with OLP + HBV = 124/16 = 22.50% / 2.90%).

In particular, our study is related to the positivity anti-HCV levels that are inferior to those reported by other investigations, such as those in San Francisco, which reported positive results at 45% (14 cases / 31 cases) of patients with OLP[13]. The results of another study, conducted in the Kyushu region of Japan, considered endemic in terms of the prevalence of HCV infection, is the presence of

seroprevalence of anti-HCV in patients with OLP investigated at a rate of 62[14].

In this context, we interpret the results from our study on serum anti-HCV seroprevalence in patients with OLP as explained by the lower incidence of hepatitis C virus in our country, estimated at about 10%.

A number of 27 of the patients of **subgroup A** did not know at the time of inclusion in the study that they are carriers of hepatitis C. This means that in one of four cases with OLP, chronic viral hepatic injury may not be diagnosed, an argument that makes it difficult to detect these.

In order to support the aforementioned, that chronic C virus hepatitis favours immune disorder, OLP grafting, we questioned the remaining 105 patients in **subgroup A** on the moment they found out about the two diseases. In 87 cases (82,8%), hepatitis C virus disease preceded OLP.

From a pathogenic point of view, this percentage allows us to state, that on one side, after infection with hepatic C virus, immunological disorder generates the field of development and OLP and on the other side that only 17–18% of cases with OLP – develops primarily as an independent disease. Subsequent association with chronic C virus hepatitis, exacerbated the progression of oral disease, as well as the dynamics of the cases we follow-up.

On the other hand, these findings may be useful to medical practice because they require the investigation of any OLP patient on the liver function status, including the state of carrying or not the hepatotropic virus C and/or B. In this regard, we mention a 4-year clinical study in Japan, which consisted of periodic examination of oral mucosa in patients diagnosed with chronic hepatitis C. The results showed an annual increase in the number of those developing OLP, the annual incidence of OLP being 12.5%[15]. Opposite to this recommendation to screen all patients with OLP are the results of the studies undertaken in Germany or in the Ohio region of the United States. Thus, in 2003, Friedrich *et al*. studying the prevalence of OLP in a group of 156 patients diagnosed with chronic hepatopathy demonstrated the presence of HCV infection in 75% of them. Oral and histopathological clinical trials showed that only 3 of them had OLP, a prevalence comparable to that in the general population of the country[16]. Following research conducted in the US, Ohio Region in 2002, Eisen found no positive results in anti-HCV determination in any of the patients with OLP. The conclusion of the study was that for North American patients with OLP, routine screening for hepatitis C is not justified[17].

By comparison, the results of Ac anti-HCV levels in patients of both study and control groups were positive 132 = 23.96% of those in the study group and only 10 = 4.63% of the control group. Thus, statistically, we found a strongly significant association of test positivity in OLP patients of the study group (23.96% *vs*. 4.63%, $p < 0.001$, chi² test) (Table 2). Our results suggest that OLP develops nearly 6 times more frequently in patients with hepatitis C than in those who are not infected with hepatic C virus, a prevalence value similar to the results of a meta-analysis of the most important retrospective studies performed on this topic, which showed that the prevalence of HCV infection in OLP patients with OLP is 3 to 9 times higher than in the control groups[18]. In our study, the prevalence of the OLP-hepatitis B virus-associated association was 5.5 times lower than for the association of OLP-chronic hepatitis with C virus (Table 3): no. OLP cases + chronic C virus hepatitis C / OLP cases + chronic hepatitis with virus B = 132/24 = 23,96/4,36 = 5,5.

Results may be considered superposable to those of other studies that have highlighted that the incidence / prevalence values of the chronic hepatitis C + OLP association should be related to the incidence / prevalence of hepatitis with viral etiology in the respective geographic region. An argument in this respect is the results of research carried out in regions such as northern France, England, Brazil and Canada, which highlighted the high prevalence of viral hepatitis C in OLP patients compared to those of the general population[19-21].

Opposite, there are results of the study in 2000 in the Netherlands, which investigated the prevalence of hepatitis C in a group of 55 OLP patients. As there was no positive outcome, the study findings invoked the low prevalence of chronic HCV infection in this country[22].

The relative risk rate (OR) ratio in patients in our study revealed a value of 6.48, almost double the one determined in 2004 by Chung *et al*., in a study conducted in Southern Taiwan, a region known for increased hepatitis C prevalence (OR = 2.05)[23].

The studies that support the involvement of HCV in the pathogenic mechanism of OLP lead to two possible hypotheses: oral lesions occur as a result of direct virus replication in basal keratinocytes or repeated activation of local immune cells owed to an expression of the high rate of virus multiplication. This would lead to the

likelihood of cross reaction with their own tissues, causing autoimmune lesions[24,25].

According to other authors, the predisposition for a certain type of HLA genotype specific to certain populations is the cause of extrahepatic manifestations of chronic HCV infection, since it is possible to influence cross-reactivity[12,26].

CONCLUSIONS

The results of the present study showed a higher prevalence of anti-HCV seroprevalence in patients with OLP versus the control group. The high prevalence of chronic hepatitis with HCV in patients with OLP recommends the serological determination of Ac anti HCV in all OLP patients.

Based on the results of our study, we consider that it is a pertinent requirement to investigate the functional liver state and the possible status of carrier of hepatitis B and / or C viruses in all OLP patients because by the possible identification of these chronic hepatopathies which allows appropriate therapy, useful for the favourable evolution of both coexisting diseases.

The main conclusion of this study is that in certain geographical areas of our country there is a higher prevalence of HCV chronic infection in OLP patients compared to the general population. This observation recommends the routine determination of anti-HCV in all patients diagnosed with OLP. On the other hand, OLP is considered an extrahepatic dermatological manifestation of chronic persistent HCV infection which suggests the need for routine examination of the oral mucosa of patients diagnosed with this liver disease.

In daily dental medical practice, the results of the present study allow to recommend compulsory screening for OLP patients to identify the coexistence of other systemic conditions, useful recommendation and doctors in other specialties, from the general medical profile to include in the general clinical examination, as a mandatory point an oral mucosal examination.

AKNOWLEDGEMENTS

This work was supported by the Sectorial Operational Program Human Resources Development (SOP HRD) 2007–2013, financed from the European Social Fund and the Romanian Government under the contact number POSDRU/107/1.5/S/82839.

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