Behcet's disease: A national casuistic

National Group for the Study of Behcet's Disease*

Jorge Crespo**

Abstract

Since January 1993, a National Study Group from Portugal has gathered physicians from different specialties sharing a common interest in this clinical syndrome. Therefore it was possible to obtain a population of 241 patients from the whole country (121 males/120 females, average age = 38.6 ± 11.8 years) with diagnostic criteria as defined by ISGBD.

The following conclusions were reached:

BD is a condition of early onset, usually between the 2nd and 4th decades of life (average age of onset from first symptom = 25.8 ± 11.1 years). Recurrent episodes of oral ulceration are the presenting manifestation in 78% of cases. Ocular involvement is the most disabling complication, being observed in 74% of cases. From these 80% show bilateral involvement with permanent sequels in 52%. Cutaneous findings are observed in 82%, with pseudo folliculitis found in 62% of the total. Genital aphtha were observed in 80% of cases. A positive pathergy test was displayed in 40%. Joint dysfunction, not a diagnostic criterion, was the first clinical finding in 7% of all cases. As a whole, 85% of patients showed some joint involvement. BD clinical diagnosis is late (7.0 ± 7.5 years), but there is an inevitable delay in diagnosis of 4.0 ± 4.7 years (range: 0-21) due to the need of obtaining and associate the necessary diagnostic criteria. Recurrent oral ulceration is a frequent finding in family members of BD patients, being observed in 42% of first and second degree relatives. HLA B5 is found positive in 60% of cases, defining a relative risk of 8.5. In all B5 positive cases, in whom B 51 was tested, 100% had a positive result.

Key words: Behcet's disease, epidemiology, Portugal.

Introduction

Behcet's Disease (DB) is a systemic vasculitis of unknown nature, characterized by the very specific way in which it affects the organism, particularly the mucocutaneous and ocular structures.

Its diagnosis is based on exclusively clinical criteria which, according to the International Study Group for Behcet's Disease (ISGBD), are defined by the indispensable presence of recurrent oral aphthous ulcers (ROAU), associated with two of the following four criteria: genital ulcers, ocular lesions (inflammation of any segment of the ocular globe or retinal veins), skin lesions (pseudofolliculitis, erythema nodosum, papules and pustules) and a positive pathergy test (appearance of a papule or pustule around 48 h. after pricking the skin with a sterile needle).[1]

Other symptoms are also found, with variable expression, but do not constitute diagnostic criteria. These include Joint symptoms (mechanical, inflammatory or mixed, with variable locations and forms of expression), vascular (thrombophlebitis, thrombosis and others), central nervous system, gastrointestinal, and pulmonary symptoms, and those affecting other apparata and systems of the body, as well as general signs and symptoms.[2]

This work outlines the results of a nationwide survey carried out by the Behcet's Disease Study Group. This is an intra-hospital and multidisciplinary cooperative group which, under the aegis of the Center for the Study of Auto-Immune Diseases of the Portuguese Society of Internal Medicine, brings together physicians in the area of Internal Medicine, Ophthalmology, Rheumatology, Dermatology and Immunology who have a manifest interest in this clinical condition.

The first specific case of BD described in Portugal was in 1946 (Moreira Monteiro[3]). Several years later, two more references emerged, at the initiative of Artur Pina, Fernando Fonseca and Francisco Branco.[4,5] Souza Ramalho presented his first personal cases in 1969, subsequently offering, with Guerra Rodrigo and others, an excellent divulgation of BD and the cases referred to him.[6,7,8,9,10] Later, he presented the

*The doctors and hospitals participating in this Study Group are listed at the end of the article.

**Group Coordinator. Medicine Service III of the Hospitals of the University of Coimbra

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first nationwide panoramic overview of this disease, giving a purely numerical analysis of some of the cases identified outside the South area, and arriving at an initial estimate of the prevalence of BD in Portugal of 1.3 patients per 100,000 inhabitants.[11]

Other works emerged, presented by Portuguese groups of the main medical centers, demonstrating the interest that this disease continues to attract among us.[12,13,14,15,16,17,18,19,20,21,22,23,24,25]

With this widened individual investigation work, we think we have achieved a good overview of the national scenario in this field, in view of the balance shown in the evaluations of the North, Center, South and Madeira zones.

Patients and methods

The current investigation was based on an individual protocol, which resulted in a consensus of various hospital clinics of Lisbon, Porto, Coimbra, Almada and Viseu, which initially demonstrated most interest in this subject. The study was then proposed, seeking to be as inclusive as possible, to various work groups of central and district hospitals, in the multidisciplinary scope described above.

It covered 241 patients with confirmed diagnostic criteria, according to the classification of the ISGBD, in which clinical parameters (diagnostic and non-diagnostic) of their current history were evaluated, as well as the personal and family history. The patients were also asked about the treatment used, and its efficacy was evaluated.

It was advised that the pathergy test be performed by pricking the back of the forearm with a non-disposable needle.

In some patients, we were able to use the evaluation of class I HLA antigens. To establish its correlation with the normal population, 2144 apparently healthy individuals were used, from the North, Center and South regions of the country, typed for HLA at the respective Histocompatibility Centers– Lusotransplante (see reference at the end). This group was comprised mainly of families of bone marrow transplant candidates and donors of the local cell panels. The HLA antigen phenotyping was performed by serological methods, using the micro-lymphocytotoxicity test (Terasaki and McClelland, 1964), with specific antiserums.

The antigen frequencies (af) presented were obtained by direct counting. The genetic frequencies (gf) resulted from the application of the formula: gf = 1-af. In the statistical analysis, the Student t test was used to evaluate the differences in mean quantitative values between the two groups, and the Chi squared test was used to evaluate the incidence of discrete (nominal) variables between two groups. The relative risk was defined by the Haldane formula: (positive patients + 1) x (negative controls + 1) / (negative patients + 1) x (positive controls + 1).

At the end of the article, besides the physicians involved in this investigation, the number of patients studied by the various working groups is also given.

TABLE I

Distribution of the population studied, by geographic area and gender

	Male	Female	Total	M / F
North	42	26	68	1.6/1
Center	35	45	80	0.8/1
South	38	47	85	0.8/1
Islands (Madeira)	6	2	8	3.0/1
Total	121	120	241	1.0/1

TABLE II

Distribution of mean ages and their variation in relation to the total

North	37.9 ± 13.0	(n.s.)*
Center	37.8 ± 11.4	(n.s.)*
South	38.9 ± 11.9	(n.s.)*
Islands (Madeira)	41.0 ± 11.3	(n.s.)*
Total	38.6 ± 11.8	

Results

The population studied was distributed by sex and age, as shown in *Tables 1 and 2*.

The mean age at the start of the first clinical symptom was 25.8 ± 11.1 years, with 25.1 ± 11.9 years for males and 26.5 ± 10.4 years for females, values that are simil*ar to the global average (Table 3)*.

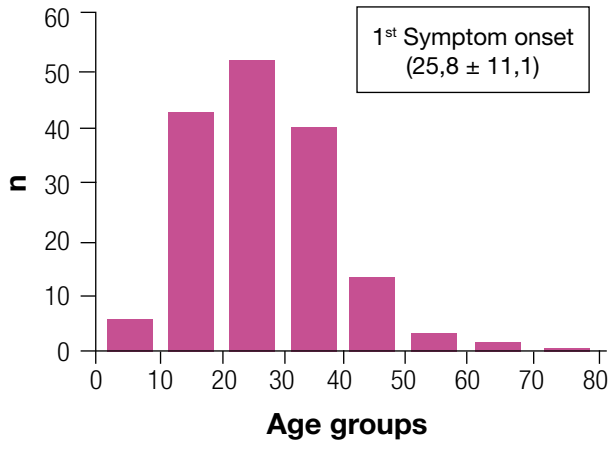
Fig. 1 sample of clear form and of dispersion of the start of the first symptoms, regardless of their type.

The frequency with which the different diagnostic criteria are verified is presented in *Fig. 2*. The most

TABLE III

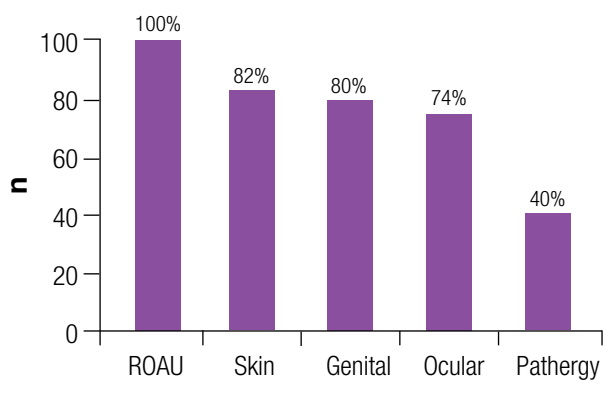
Distribution by sex of the mean ages at the start of the first symptom

Male	25.1 ± 11.9	(n.s.)*
Female	26.5 ± 10.4	(n.s.)*
Global	25.8 ± 11.1*	



Dispersion relating to the start of the 1st symptom.

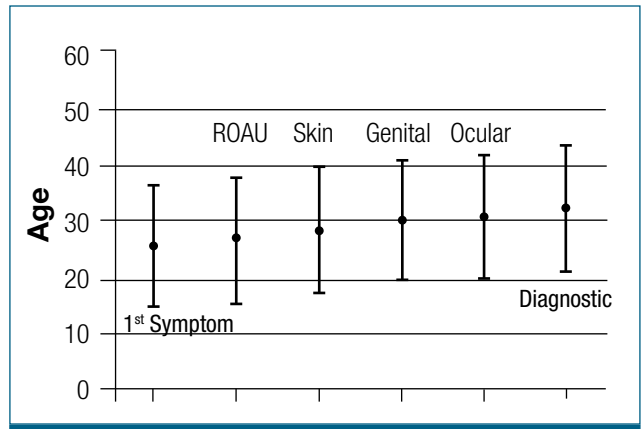
FIG. 1



Frequency of appearance of the diagnostic criteria.

FIG. 2

frequent inaugural symptom found was ROAU (78%), followed by ocular (15%), genital (13%) and cutaneous (12%) symptoms (*Table 4*).



Mean age at start of diagnostic criteria.

FIG. 3

TABLE IV

First symptom: relative percentage

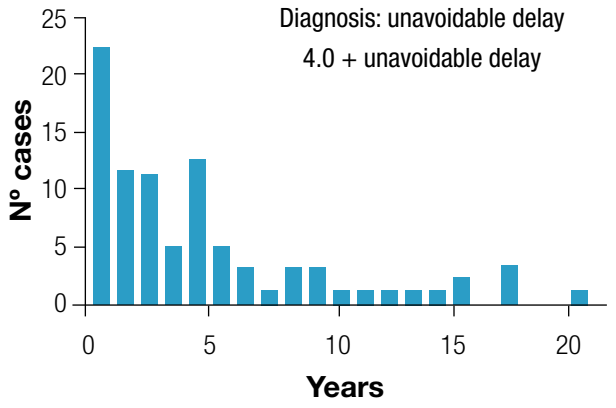
1st Symptom	
Oral aphthous ulcer	78%
Ocular symptoms	15%
Genital ulcer	13%
Skin symptoms	12%
Arthralgias (n.s.)*	7%

Wherever possible, the patient's age at the start of each symptom was evaluated, and it was observed that ROAU was the first symptom to appear (26.5 ± 11.3 years), followed by skin (28.3 ± 11.3 years), genital (30.0 ± 10.9 years) and ocular (31.0 ± 11.0 years) symptoms - *Fig. 3*.

The patients were also questioned about the date of diagnosis, corresponding to the time they were told clearly that they had BD; it was seen that there was a delay in diagnosis of 7.0 ± 7.5 years (limit of 0 - 32).

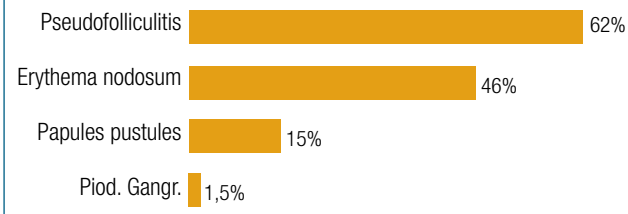
However, this delayed diagnosis was not always the result of a difficulty in recognizing the clinical entity that goes by the name of BD. In fact, from the appearance of the first symptom to the moment when, due to an association of the necessary diagnostic criteria, it became possible to clearly define it, there was a period of 4.0 ± 4.7 years (limits of 0 – 21). This unacceptable delay is clearly expressed in *Fig. 4*.

Analyzing each of the diagnostic criteria, we



Inevitable delay in diagnosis.

FIG. 4



Skin symptoms.

FIG. 5

observed that there were no significant differences between the three major zones (North, Center and South) whether in relation to age on appearance of the ROAU, or in relation to the incidences of skin, genital or ocular symptoms (*Table 5*). Only the positivity of the pathergy test was significantly lower in the North than in the other regions of the country (p<0.001).

The skin symptoms most commonly found were pseudofolliculitis and erythema nodosum (*Fig. 5*), while the ocular symptoms were located mainly in the anterior chamber (*Fig. 6*) and both eyes were affected in 80% of the cases, with complications recorded in 52% of those affected.

The pathergy test was considered positive in 40% of the 118/241 patients on whom it was performed.

In relation to the non-diagnostic symptoms, the joints were affected in 85% of the cases (*Fig. 7*). In cases where it was possible to characterize their clinical nature, these were mainly peripheral and involved multiple joints, with a similar division between those of the inflammatory and mechanical types (*Table 6*). It should be highlighted that in 7% of the patients, arthralgias were the first clinical symptom of BD, before the appearance of any of the criteria considered diagnostic (*Table 4*).

Of the vascular symptoms, the main one was surface thrombophlebitis (*Table 7*) and of the CNS symptoms, headaches were the most common (*Table 8*). The gastrointestinal symptoms, in a context not attributable to therapeutic complications, were insignificant: peptic ulcers in 2% and diarrhea in 1%.

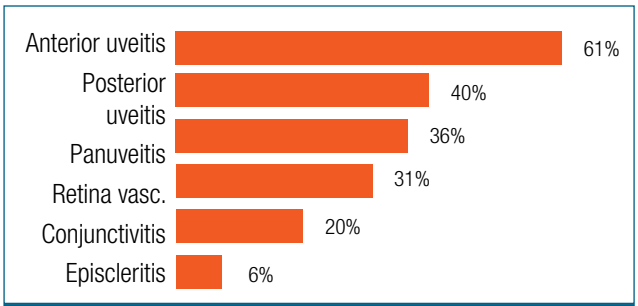
We had a particular interest in evaluating the incidence of the family history of ROAU (understood as the number of episodes of oral aphthous ulcers >3/year) in close members of the family (up to grade 2) of patients with BT. In the 94 cases in which it was possible to answer this question, it was positive in 42% (*Table 9*). This number is particularly significant

TABLE V

Regional differences in the diagnostic criteria

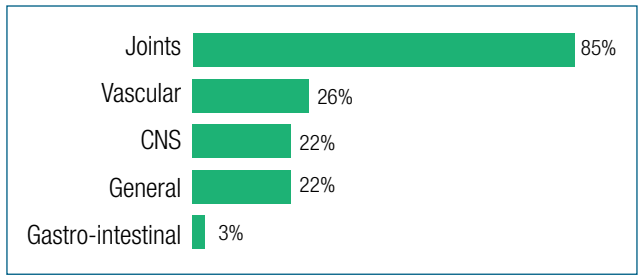
	ROAU (start age)	Skin symp. (% incidence)	Genital Symp. (% incidence)	Ocular Symp (% incidence)	Pathergy (% positivity)
North	28.4 ± 13.2 *	91.2 *	78.0 *	73.5 *	17**
Center	24.1 ± 11.0 *	82.9 *	71.4 *	72.7 *	47 *
South	27.5 ± 11.1 *	74.4 *	90.5 *	76.2 *	37 *
Total	26.4 ± 11.3	82.1	80.6	74.3	40

*not significant; **p<0.001



Ocular symptoms.

FIG. 6



Other Symptoms (non-diagnostic).

FIG. 7

TABLE VI

Joint symptoms

Type	Location	Distribution
Mechanical 36%	Peripheral 68%	Multiple joints 68%
Inflammation 33%	Axial 14%	Single Joint 2%
Mixed 10%		

TABLE VII

Vascular symptoms

· Superficial thrombophlebitis		**18%**
recurrent	12%	
Isolated	6%	
· Deep Thrombosis		**7%**
Veins	6%	
Arterial	2%	
· Aneurisms		**1%**

TABLE VIII

CNS symptoms

· Headaches	12%
· Stroke	5%
· Aseptic meningitis	4%
· Meningoencephalitis	3%

TABLE IX

BD and recurrent oral aphthous ulcers in the family

	n	ROAU in the Family	
BD	94	42 %	
Control*	200	17 %	p < 0.0001

*Medicine 3 – H.U.C.

when compared with the 17% seen in the general population. [26]

The phenotypical expression of HLA B5 is associated with BD in 63.7% of cases, vs. 28.2% of the controls, which defines a relative risk (RR) of 4.5. The growing regional variations between North and South are emphasized (RR North = 3.3; RR Center = 3.7; RR South = 7.7 - *Table 10*).

In molecular studies, it is commonly observed that the association between HLA and the disease is primarily due not to any HLA antigen in particular, but to a family of antigens with common structural characteristics – or "cross reactive groups" (CREG). Thus, the CREG B5 was analyzed, which is comprised of the antigens HLA B5, B15, B18 and B35. At national level, an association is also found with this CREG B5 and BD (RR = 3.2).

In relation to the HLA A3 antigen, which was reported to be associated with a protective effect against ocular symptoms 16, we found an RR of 0.4 when compared with patients without these symptoms (A3 in 21.7%) and with them (A3 in 10.1% - *Table 11*). Despite confirming some effect of this nature, cases continue to occur with manifest ocular expression, sometimes severe, in A3 positive patients.

Analyzing the phenotypical differences in the clini-

TABLE X

Prevalence of HLA in view of the clinical symptoms and family history

HLA	North Region			Center Region			South Region			National		
	Behcet	Control	RR	Behcet	Control	RR	Behcet	Control	RR	Behcet	Control	RR
HLA-A3	20.8	20.4	1.0	12.5	17.9	0.7	10	23	0.4	14.4	20.4	0.7
HLA-B5	62.5	33.7	3.3	57.1	26.4	3.7	71.4	24.4	7.7	63.7	28.2	4.5
CREG B5	70.8	52.9	2.2	84.9	55.6	4.5	81	52.6	3.8	78.9	53.7	3.2

TABLE XI

Prevalence of HLA in view of clinical manifestations and family history

National	Genital Aphthosis			Ocular Manif.			Skin Manif.			Pathergy			Family History		
	s/	c/	RR	s/	c/	RR	s/	c/	RR	s/	c/	RR	s/	c/	RR
HLA-A3	0.0	16.7		21.7	10.1	0.4	14.3	14.3	1.0	15.6	11.8	0.7	12.1	15.4	1.3
HLA-B5	48.4	59.4	1.6	52.8	57.3	1.2	57.7	64.2	1.3	56.4	57.1	1.0	50.9	53.8	1.1
CREG B5	58.1	85.9	4.4	85.7	76.1	0.5	86.4	85.1	0.9	84.1	86.4	1.2	71.1	73.1	1.1

cal symptoms of BD, it was observed that 85.9% of the patients with genital ulcers presented one of the CREG B5 antigens, compared with 58.1% of those without this symptom, representing an RR of 4.4. No other symptom appears to present vaporizable RR, in association with the B5 or CREG B5 antigen.

In all the B5 positive patients in whom it was possible to evaluate their B51 split, this was also positive.

Finally, the drugs used in these patients were also evaluated, having obtained 149/241 responses. The following are emphasized: colchicine for treatment of the ROAU, systemic corticoids for control of overall worsening effects, ocular lesions and the CNS, cyclosporine (more than chlorambucil and azathioprine) for the treatment of uveitis, and thalidomide for the treatment of resistant mucocutaneous symptoms.

Discussion

This survey, which cannot be exhaustive, sought to gather around it the main national groups that have been active in the study if this disease.

Not all the data of patients included resulted in the individual filling of the pre-established protocol. Some series had been presented in a bloc, but whenever possible, their global data were included in this study.

The average age at the onset of BD is the same as that reported in other international studies, regardless of the geographical area they come from, or the date on which they were carried out. In relation to gender of the individuals affected, there was also a trend towards equal distribution. It is interesting to note that older studies[27] suggest a higher prevalence among males in the Middle East (3 to 11/1) and Japan (1.7/1), compared with a higher prevalence of females in the western countries (0.4 to 0.6/1). But as the series presented were gaining more significance, and covering the real generality of the population, this tendency for the sexes to be equally distributed has been constant. It is also possible to find this discrepancy in recent studies, but with manifestly reduced series, compared with the analysis of 3153 cases in Iran[28] (1.13/1), 3648 patients in Japan[29] (0.98/1) or 1127 in Turky[30] (1.18/1).

But in marked contrast to the countries of the Middle and Far East, for the western countries, it is a populational prevalence. The correlation of this disease with the Silk Road[31] is well-known, and it is believed that its dissemination from the Mediterranean to China and Japan through the Arabs, Romans, Byzantines and Mongols, who traveled through those regions by land and sea, although it is still not possible to determine their origin, was very similar to that which took place with Portuguese family paramy-

loidosis. The gene (having mutated somewhere) has dissipated along the route, with marked prevalence towards the East. Thus, differences of 15/100,000 inhabitants are included, as verified in Japan, or of 37/100,000 in Turkey, for 0.7/100,000 as seen in Great Britain.[27] Our verified prevalence of 2.4/100,000 inhabitants is close to that of the European countries of the Mediterranean basin.[32]

Skin, genital and ocular symptoms are found with rates within the usual spectrum of its distribution in BD.[28-35]

The pathergy test was considered positive in 40% of the patients, but it was only possible to find reference to its concretization in 49% of cases. The methodology used to carry out this test, as specific as BD, appears to be very important for evaluating its positivity, as it is seen that it depends on the type of needle used. [36,37,38] Dilsen found differences, in the same group of patients, of 40% to 70%, when needles of the disposable or blunt-tip type are used. It was not possible to evaluate any difference between the positivity of the test performed with disposable needles versus the blunt-tip type, due to the fact that the type used cannot be referenced in the majority of cases. Perhaps this is why, among the diagnostic criteria, only the pathergy test has not proven to be uniform for the North and South of the country.

It is interesting to observe the time gap between the various symptoms of BD, what should mean that in the presence of clearer data, such as recurrent ROAU or uveitis, the questioning of other symptoms will not be neglected, as these often end up occurring later, albeit in mild form, or in isolated regions, but capable of establishing a diagnosis. Because it is a rare condition, it is our conviction that many less aggressive forms of BD go unnoticed, precisely due to this relatively delayed appearance of the different symptoms.

In the sense of an earlier diagnosis, we believe that in the absence of a clear and recognizable ocular symptom when two other criteria are present, the observation of a subclinical inflammatory activity in the aqueous media of the eye, made by means of Laser-Flare or fluorophotometry, may constitute an additional piece of information that strongly suggests a diagnosis of BD.[19,20]

We believe that some situations will never develop beyond incomplete forms, in which only clinical sensitivity will lead the physician to consider a disease of this type. The observation of the HLA B5 antigen (or that of another family of CREG B5) in similar cases may be another indicating factor of a form of this disease still in a phase that is not clearly defined.

In fact, as in many other studies, the association of BD with HLA B5 is very clear.[11,25,39]

We would also like to emphasize the frequency of isolated ROAU in the families of patients with BD (42%). Compared with the levels in a normal population (17%), the difference is highly significant ($p<0.0001$), which raises the question of knowing whether ROAU and BD can reflect different forms of expression of the same mechanism of immunological susceptibility.

Conclusions

BD is a rare disease, but it exists. It is necessary to consider it, particularly when faced with situations of recurrent uveitis or when complaints of recurrent oral aphthous ulcers begin to be associated with another clinically diagnosed symptom.

Following this study, its prevalence in Portugal (2.4/100.000) appears to be higher than was imagined, and we are certain that these figures represent a reality that is underestimated.

It is essential to bear in mind the inevitable delay of its symptoms, which means the definitive clinical symptoms may not occur until, in some cases, several years after the initial complaint (4.0 ± 4.7 years, with limits of 0 to 21 years). For reasons that are not clear, the ratio of males to females is 1.6/1 in the North and 0.8/1 in the Center and South.

ROAU, present (by definition of BD) in all the patients, was the initial symptom in 78% of cases. Skin symptoms were found in 82% of cases, and genital symptoms in 80% of cases. Ocular symptoms are present in 75% of patients in homogenous geographical form, and are, without doubt, the most incapacitating of the symptoms with 50%, leaving complications of any nature, often taking the form of amblyopia. It is bilateral in 80% of cases, which further highlights this characteristic. The pathergy test was positive in 40%, but was carried out in just under half of the cases. The fact that pain is the first symptom in 7% of cases, and is present in 85% of the total, means that this disease sometimes assumes important rheumatism characteristics, to the point of manifesting the patient's main complaint and sometimes being confused with other pathologies.

The frequency of ROAU in families of patients with BD is highlighted (42%), a fact that should raise questions of immunological susceptibility.

HLA B5 is present, in global form, in 63.7% of cases, demonstrating the importance of this antigen as a marker of susceptibility for BD, in a probable imbalance of linking with the gene for the disease.[40] The relative risk of this association is increasing from North to South. ■

List of physicians and hospitals participating in the National BD Study Group with indication of the number of cases sent

North (68): H. Sto António (24): Barbosa Leão (M), Paulo Torres (O), Carlos Vasconcelos (M), João Correia (M), Elga Freire (M). H. S. João (44): Jorge Palmares (O), Domingos Araújo (R), J. Castro Correia (O), M.F. Coutinho (O), L. Delgado (I), João Pinto (M).

Center (80): H. U. Coimbra (75) Jorge Crespo (M), Rui Proença (O), Borges Alexandrino (M), Manuel Veríssimo (M), João Ribeiro (M), Alves Moura (R), Conceição Reis (R), Armando Malcata (R), Jorge Silva (R), Emanuel Jesus (M), Óscar Mota (M), Carlos Filipe (M), Anabela Sá (M), Armando Carvalho (M), Ermida (M), José Ávila (M), Teresa Veloso (M), Júlia Veríssimo (O), Eduardo Silva (O), Campos Figueiredo (O). H. D. Leiria (4): Amália Pereira (M). H. D. Viseu (1): Marina Bastos (M), Fernando Girão (M).

South (85): H. Sta Maria (48): Viana Queiróz (R), Miranda Rosa (R), J. P. Freitas (D), Paula Alcântara (M). H. Sº Antº Capuchos (19): Santos Castro (M), R. Mesquita da Cunha (M), A. Bayão Horta (M). H. S. Francisco Xavier (11): Luís Campos (M), Ana Lince (M). H. Sª Marta (4): Teresa Eliseu (M), Manuela Coelho (M), Paulo Chinopa (M). H. Garcia de Orta (2): Ana França (M), Álvaro Carvalho (M), Pedro Gonçalves (M), Luísa Sequeira (M). H. D. Santarém (1): Marouço (M), Geraldes Barba (M).

Madeira (8): C. H. Funchal (8): Augusto Barros (M), Herberto T. Jesus (R), Caldeira Ferreira (M), Camacho de Freitas (M), Duarte Correia (M), Herculano Freitas (M), Jorge Martins (M).

Specialties: M – Medicine; O – Ophthalmology; R – Rheumatology; D – Dermatology; I – Immunology.

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