BEHÇET'S DISEASE IN PORTUGAL

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SUMMARY

During the last decades 156 patients with Behçet's disease were diagnosed and studied in Portugal. Until 1966 only two cases were referred in Portugal. In 1978 we reported 23 cases (18 males and 5 females) with multisystemic involvement, not different from that reported in other publications elsewhere. In 1987, 17 cases were reported from the Oporto region, diagnosed during a period of 5 years. In the region of Coimbra 15 cases were diagnosed (6 males and 9 females). In the Lisbon area from 1969 until 1990, 123 cases were studied altogether, 76 during the last decade (35 males and 41 females). All the cases studied had oral ulcerations and a high incidence of ocular involvement (clinical and sub-clinical, 87%). HLA-B5 was detected in 50% of the patients. At least four cases were fatal, three died with neuro-Behçet. Steroids, colchicine and thalidomide were the main form of treatment, for the patients in the Lisbon area, but in some cases chlorambucil, cyclophosphamide, azathioprine, cyclosporine-A, fibrinolytic therapy, plasmapheresis and isovolemic hemodilution were also used.

RESUMO

Doença de Behçet em Portugal

Nas últimas décadas foram diagnosticados e estudados em Portugal 156 doentes com Doença de Behçet. Até 1966 apenas dois casos tinham sido referidos em Portugal. Em 1978 descrevemos 23 casos (18 homens e 5 mulheres) com envolvimento multisistémico, envolvimento esse que não diferia do descrito por outros autores. Em 1987 foram apresentados 17 casos provenientes da região do Porto, diagnosticados num período de 5 anos. Na região de Coimbra foram diagnosticados 15 casos (6 homens e 9 mulheres). Na região de Lisboa, entre 1969 e 1990 foram estudados no conjunto 123 casos, 76 dos quais durante a última década (35 homens e 41 mulheres). Todos os casos estudados apresentavam ulcerações orais e uma elevada incidência de envolvimento ocular (clínico e subclínico, 87%). O HLA-B5 foi detectado em 50% dos doentes. Pelo menos quatro casos foram fatais, tendo três falecido com neuro-Behçet. Os doentes da região de Lisboa foram tratados sobretudo com corticóides, colchicina e talidomida, mas nalguns casos utilizou-se também clorambucil, ciclofosfamida, azatioprina, ciclosporina-A, fibrinolíticos, plasmafereses e hemodiluição isovolémica.

INTRODUCTION

Behçet's disease [1] is not a rare condition in Portugal, although its incidence is not as high as in some Mediterranean countries and in Japan. The diagnosis remains clinical in the absence of specific abnormal laboratory data, and it is sometimes difficult to establish because of the delay between the first symptom (oral ulceration as a rule) and the other manifestations.

Until 1966, only three papers on the syndrome were published in Portugal [2-4], and the first case was published in 1946 [2]. In 1969 we reported our first two cases to the meeting of the Portuguese Ophthalmological Society, held in Lisbon, and in 1972 [8,12], 13 cases with multisystemic involvement and fulfilling Mason and Barnes criteria [5] were published. In 1973 we presented our material to the International Symposium *Eye and Systemic Disease* held in Iowa (U.S.A.) [6] and in 1977, 17 more cases were presented to the International meeting in Istambul [7]. Another 23 cases (18 males and 5 females) were investigated, in 1978 [6,8], showing some special features, described earlier in 1972, such as early hyperpermeability of retinal blood vessels to fluorescein contrast in microangiography, during acute phases of the disease and before clinical involvement of the eye [8,9]. We observed ovarian disfunction in the first female cases studied [10] and immunological activity in CSF [10]. Since then, there have been others reports in Portugal [11,12,13,14,15] from Lisbon area, the Oporto region [16,17] and Coimbra area [18].

MATERIAL AND METHODS

We reviewed the reports of the last decades from various main hospitals in the country, related to Behçet's disease. We looked for references in Portuguese medical literature and we sent inquiry letters to different district hospitals in the country and to some members of the Ophthalmological, Dermatological, Neurological and Rheumatological Societies.

In the Lisbon area all the subjects observed by our group were diagnosed by the classical criteria of Mason and Barnes [5]: major criteria were buccal ulceration, genital ulceration, eye lesions and skin lesions; minor criteria were gastrointestinal lesions, thrombophlebitis, cardiovascular lesions, arthritis, central nervous system lesions and family history. The diagnosis was made on the basis of three major criteria or two major and two minor criteria. This group of patients was examined by a multidisciplinary team and evaluated regularly by ophthalmologists, dermatologists, neurologists, rheumatologists, internists and biochemists.

During a period of 21 years, with the collaboration of different departments in our hospital and other institutions in the Lisbon area, we investigated various groups of patients with particular objectives. Routine ophthalmological investigations, using fundus contact lens microscopy were carried out periodically. Direct and indirect ophthalmoscopy, fundus, color and fluorescein photography (fluorescein microangiography) were performed in some groups of patients using

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standard techniques. A pathergy test was performed by puncturing the skin of the forearm with a thin needle under asseptic conditions and a positive test was defined as the development of a papular or pustular lesion 24-48 hr after the skin puncture (patients from Lisbon area).

In our hospital, in the last two decades, fasting venous blood samples were obtained from each subject, usually at least twice a year for different determinations. Fibrinolytic activity was studied in 18 patients by euglobulin lysis and in 10 patients by lysis of the total clot [13]. Blastogenic response of the lymphocytes, in the presence of concanavalin A and phytohemaglutinin with autologous or heterologous serum, was studied in 16 patients. Twenty subjects of both sexes (11 males and 9 females) of mean age 35,4 ± 12,7 years were selected for haemorheological studies in the department of biochemistry. Blood viscosity parameters (red cell filterability index and plasma viscosity) and erythrocyte acetylcholinesterase activity were measured and compared to a normal control group of 22 subjects, age and sex matched [19]. Endocrinological and neuroimmunological investigations were performed in some female patients [10].

RESULTS

During the last two decades (1969-1990) 154 cases of Behçet's disease have been diagnosed and studied in Portugal. Seventeen of these cases were reported from Oporto (diagnosed during a period of 5 years), 15 from Coimbra (6 males and 9 females) and 122 from Lisbon. There was a wide range of ages of presentation, age at the first clinical manifestation and date of the diagnosis. The youngest patient was 10 years old and the oldest one was 59 years old. The age at the first clinical manifestation was usually in the second and third decade of life. Out of 115 subects reviewed from our hospital, 85 were male and 70 female. The follow up period of some patients was more than 10 years and we have been following our first patient for over 21 years now; he is blind but otherwise healthy without any symptoms for over 6 years. During the follow up period, 4 cases cured completely without remissions.

In a group of 60 cases (26 males and 34 females), studied by our group, with a follow up of ten years the main clinical features were: oral ulcers 100%, genital ulcers 93%, arthropathy 64%, cutaneous lesions 60%, ocular disease 50%, gastrointestinal symptoms 20%, venous disease 18%, central nervous system involvement 5%, peripheral nervous system involvement 5%, cardiac involvement 5%. There was only one case of two members of the same family being affected but 12 other patients had one or several relatives with recurrent aphtosis.

In a group of 20 patients followed in the department of ophthalmology of our hospital, clinical ocular involvement was observed in 65% of the patients: conjunctivitis 35%, episcleritis 30%, uveitis 65%, retinal vasculitis (hyperfluorescence) 25% and ocular palsies 10%. None of these 20 cases presented severe ocular complications, sequelae or significant reduction of vision. One case that showed microaneurisms and hyperfluorescence of small blood vessels in the retina recently died of neuro-Behçet. In 6 cases intensively investigated with fluorescein angiography of the retina during periods of exacerbation of their symptoms (oral/genital ulcerations), and before any evidence of ocular involvement (*Fig. 1*), optic disc and/or retinal blood vessels (venules) hyperfluorescence showing increased vascular permeability was noticed (*Fig. 2 and 3*). Positive pathergy test was found in 60% of the patients. An increase in the erythrocyte sedimentation rate and occasional leukocytosis were observed during exacerbations of the disease and IgG, IgA and IgM levels were sometimes raised. Decreased fibrinolytic activity was detected in 11 of the 18 patients studied by euglobulin lysis, and in 8 of the 10 patients studied by lysis of the total clot. HLA-B5 was detected in 50% of the patients. No statistically significant differences were observed for blastogenic response of the lymphocytes.

Abnormal red cell deformability and high plasma viscosity were measured in some Behçet's disease patients during the active periods of the disease. A significant increase of erythrocyte acetycholinesterase was also found in this group of patients. Hormonal changes were present in some young female patients with exacerbation of their symptoms during the premenstrual periods. They presented increased urinary excretion of gonadotrophins, higher levels of estrogens and a decrease of progesterone and pregnanediol.

At least four cases were fatal; three died with neuro-Behçet. The treatment was very different from one hospital to another and inside the same hospital, because it was related to the clinical manifestations and also related to the speciality involved in the follow up of the patients. However, in our hospital, steroids, colchicine and thalidomide were the main drugs available for the treatment approach. In some cases, chlorambucil, cyclophosphamide, azathioprine, cyclosporine-A, fibrinolytic therapy, plasmapheresis and isovolemic hemodilution were also used.

In difficult and severe cases of ocular involvement we generally used azathioprine (2 or 3 mg/Kg) or cyclosporine-A low dose (5-8 mg/Kg) besides steroids and hemodilution, when necessary, with good results. Sequelae such as jacksonian epilepsy (one case), hemiparesis (two cases), secondary glaucoma (two cases), cataract (12 cases), optic nerve atrophy (10 cases) and total bilateral blindness (one case) were observed.

COMMENTS

One of the aims of this report was to analyze the prevalence of Behçet's syndrome in Portugal. Some patients were referred from other hospitals. We reviewed 156 subjects with Behçet's disease studied in Portugal during the last decades. In the Lisbon area 123 cases were diagnosed in our hospital and studied during a period of 21 years. In spite of this survey and inquiry letters, we think that these are not the real figures; there are more cases still not reported. Considering our numbers the apparent prevalence in Portugal would be more or less 1.5 per 100 000. In Japan the estimated prevalence is 1 per 10.000. The prevalence of Behçet syndrome is higher in Japan, Korea, China and the Middle East [21], but we find the disease all over the world [22]. Most studies report a male to female ratio of 1-2:1 [22]. A survey in Japan found the male to female ratio to be 0.8:1 [23]. The ratio in our data is 1.2:1. The age at the time of diagnosis is known to be most commonly in the third to fourth decades of life [22]. Our data coincides with this.

The diagnosis of Behçet's syndrome depends on the history and clinical findings. In our multidisciplinary follow up studies, ocular involvement was more frequent than in previous reports but less severe, specially in females. Oral ulcers observed in almost all the patients were the most frequent major symptom, as well as the most frequent initial manifestation, as in other series. The new set of diagnostic criteria [24]: presence of oral ulceration plus any two of genital ulceration, typical defined eye lesions, typical defined skin lesions, or a positive pathergy test is simple to use, and seems to be a good approach to the disease [25]. The incidence of cutaneous involvement was reported to be 48-88% of patients [26,27]. In our series 60% of Behçet's syndrome patients had skin lesions.

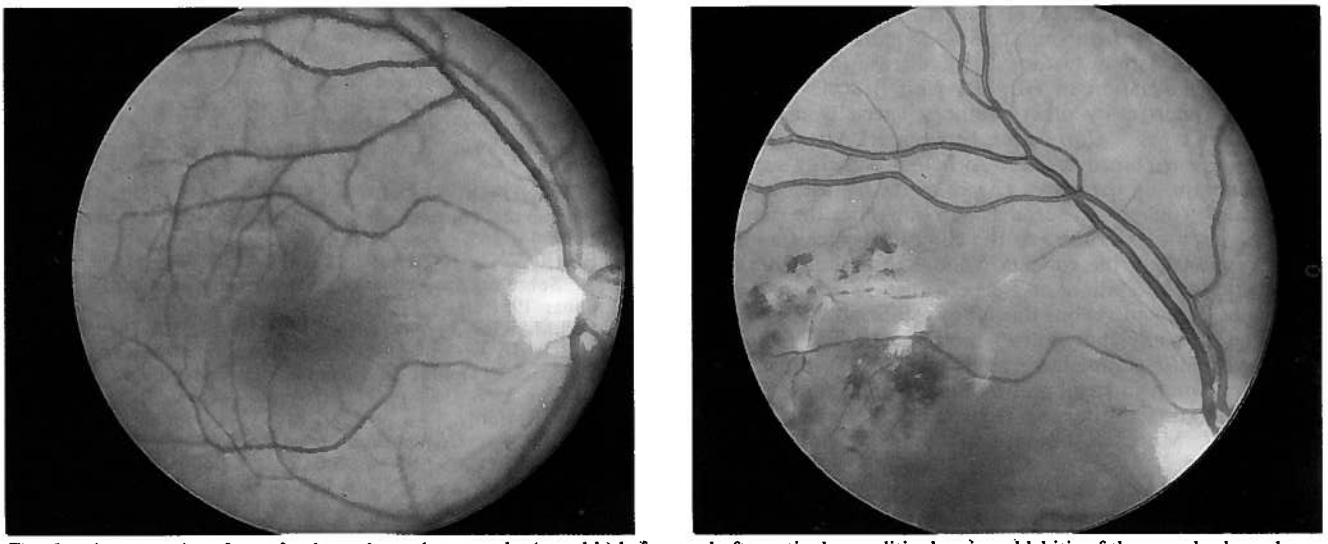

Fig. 1 — A composite of two fundus colour photographs (a and b) before and after retinal vasculitis showing phlebitis of the macular branch of superior temporal venule in the right eye of a Behçet's patient. (Photographs taken with two week interval).

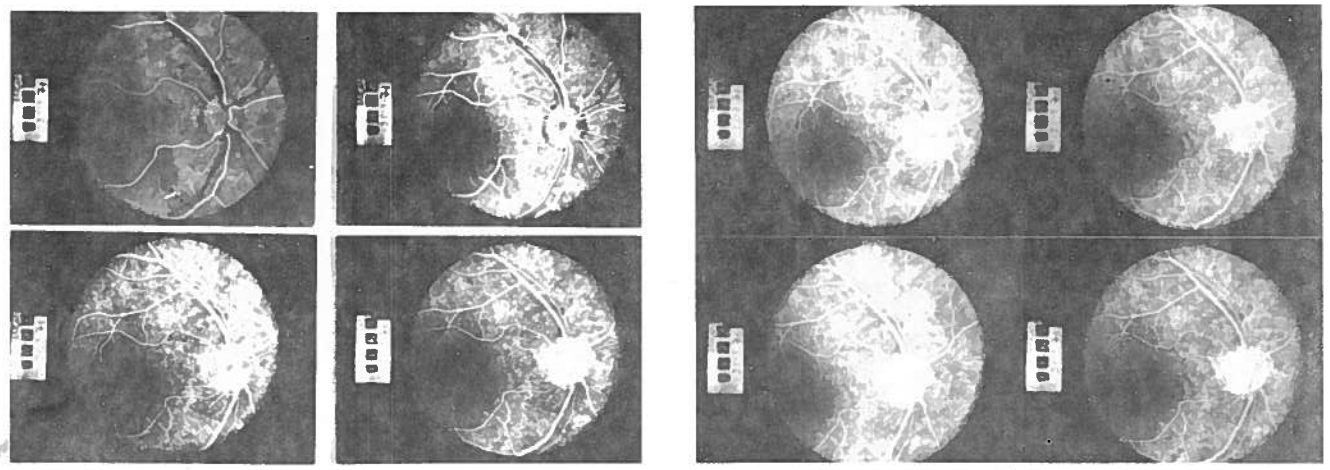

Fig. 2 — Showing 8 phases of fluorescein fundus angiography of the same eye as in the Figure 1a, two weeks before phlebitis of the right superior temporal venular branch, showing different phases of the transit of fluorescein with hyperfluorescence of disc area (abnormal vascular permeability before eye involvement two weeks before thrombophlebitis).

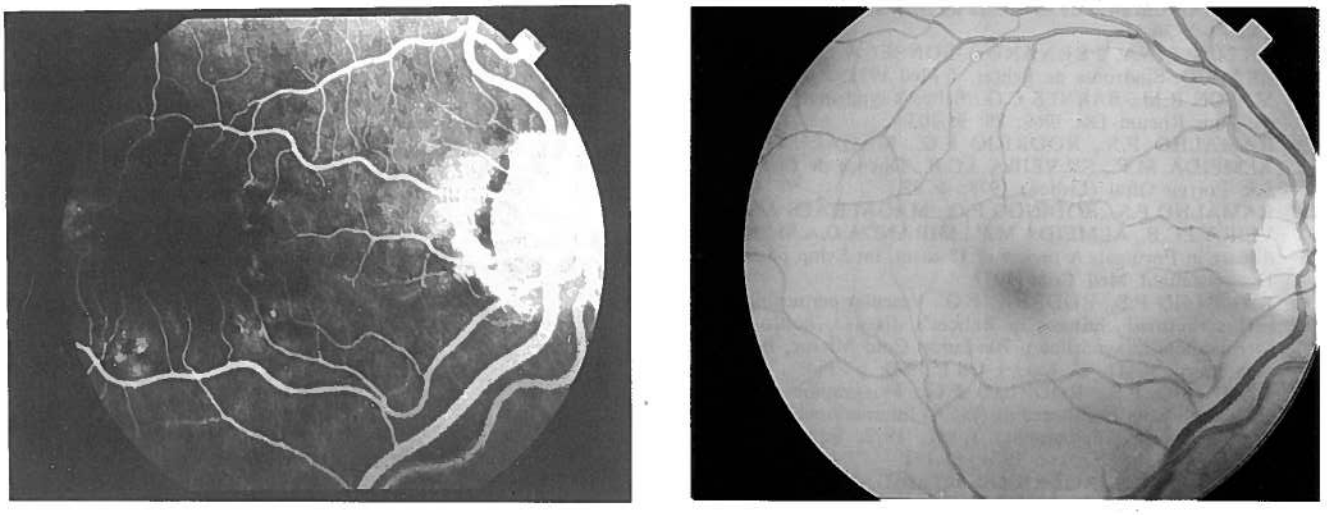

Fig. 3 — Fundus photograph (Top) and fluorescein angiography (Bottom) of the same eye showing leakage at macular area during acute phase of evolution of a Behçet's disease in a male patient; no visible clinical involvement of the eye was present and the vision was 20/20 in both eyes. (Notice leakage in the lower photograph).

The familiar occurrence of Behçet's syndrome has been rarely reported [5,28,29]. In our studies, a small number of the patients had a family history of the disease (4 families). A significant association of HLA-B5 with Behçet's syndrome has been reported by others authors, specially in patients with ocular types [30]. Correlation between HLA-antigens and pathogenesis is controversial [31]. Although pathergy seems to occur only during the active phases of the disease, it is characteristic of Behçet's syndrome [32]. In our series the pathergy test was used as a criteria to the clinical diagnosis and was positive in 60% of the patients. Venous thrombosis is a characteristic manifestation of Behçet's disease [33,34]. In one of our series 21% had venous thrombosis. Fibrinolysis might be impaired in many, but not all the patients. The abnormal blood viscosity parameters could have some influence on microcirculation in small and terminal blood vessels such as CNS and retina during the recurrent active phases of the disease [19,20]. More studies are necessary to support this hypothesis.

The decision to treat Behçet's disease must be based on a sound clinical diagnosis. The diagnosis depends on the documentation of the criteria for the disease. We think that the most appropriate management of Behçet's disease must include a multidisciplinary approach. The team may consist of an ophthalmologist, dermatologist, neurologist, rheumatologist, internist and vascular surgeon. Errors in diagnosis are minimized by this team approach and the therapy and follow up will certainly be more effective.

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