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PREVALÊNCIA DA SÍNDROME DE BEHÇET EM PACIENTES PORTADORES DE ULCERAÇÃO AFTOSA RECORRENTE NO BRASIL

Dissertação de Mestrado

Roberto Santos Tunes

Salvador - Bahia
Brasil
2008

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ESCOLA BAHIANA DE MEDICINA E SAÚDE PÚBLICA - EBMSP

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Dissertação apresentada ao curso de Pós-graduação em Medicina e Saúde Humana da Escola Bahiana de Medicina e Saúde Pública para obtenção do título de Mestre em Medicina

Autor:
Roberto Santos Tunes

Orientador:
Prof. Dr. Mittermayer Barreto Santiago

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Prevalência da Síndrome de Behçet em pacientes portadores de Ulceração Aftosa Recorrente no Brasil

Roberto Santos Tunes

Folha de Aprovação

Comissão Examinadora

Profª Drª Silvia Regina Reis
Profª Adjunta do curso de Odontologia da Escola Bahiana de Medicina e Saúde Pública (EBMSP).
Profª Adjunta da faculdade de Odontologia da Universidade Federal da Bahia (UFBA)
Doutora em Patologia pela Universidade de Berlim (Alemanha)

Profª Drª Viviane Almeida Sarmento
Profª Adjunta da faculdade de Odontologia da Universidade Estadual de Feira de Santana (UEFS)
Profª Adjunta da faculdade de Odontologia da UFBA
Doutora em Estomatologia pela Pontifícia Universidade Católica do Rio Grande do Sul (PUC-RS)

Prof. Dr. Armênio Guimarães
Livre Docente da Faculdade de Medicina da UFBA
Vice – coordenador da Pós-Graduação em Medicina e Saúde Humana da EBMSP

"Aprender é a única coisa de que a mente nunca se cansa, nunca tem medo e nunca se arrepende."

(Leonardo da Vinci)

A Deus, por conceder-me a serenidade
para aceitar as coisas que não posso mudar;
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E a sabedoria para saber a diferença
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Equipe

Prof. Dr. Mittermayer B. Santiago – Prof. Adjunto da Escola Bahiana de Medicina e Saúde Pública (EBMSP). Chefe do serviço de Reumatologia do Hospital Santa Izabel.

Prof[a] Dr[a] Gabriela B. Martins – Prof[a] Adjunta do curso de Odontologia da EBMSP. Prof[a] Adjunta da faculdade de Odontologia da UEFS.

Tiago C. Anjos – Aluno de graduação do curso de Odontologia da EBMSP. Bolsista PIBIC (FBDC).

Renata Amorim – Aluna de graduação do curso de Medicina da EBMSP. Colaboradora do serviço de Reumatologia do Hospital Santa Izabel.

Funcionários e colaboradores – Serviço de Reumatologia do Hospital Santa Izabel e da disciplina de Estomatologia da EBMSP.

Instituições Envolvidas

EBMSP – **Escola Bahiana de Medicina e Saúde Pública**

FBDC – Fundação Bahiana para Desenvolvimento das Ciências

HSI – Hospital Santa Izabel

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SUMÁRIO

LISTA DE SIGLAS E ABREVIATURAS

AC	Antes de Cristo
EBMSP	Escola Bahiana de Medicina e Saúde Pública
CEP	Comitê de Ética e Pesquisa
EUA	Estados Unidos da América
FAPA	Periodic Fever with Aphtous Pharyngitis and Adenitis (em português, febre, aftose, faringite e adenite)
FBDC	Fundação Bahiana para Desenvolvimento das Ciências
FIOCRUZ	Fundação Oswaldo Cruz-Centro de Pesquisa Gonçalo Muniz
HLA-B51	Human Leukocyte Antigen B51 (em português, Antígeno Leucocitário Humano B51)
HSI	Hospital Santa Izabel
ISGBD	International Study Group for Behcet´s Disease (em português, critérios internacionais do grupo de estudo da doença de Behçet)
KCl	Cloreto de Potássio
M:F	Masculino:Feminino
MAGIC	Mouth and Genital Ulcers with Inflamed Cartilage (em português, úlceras orais e genitais com inflamação de cartilagem)
MIC	MHC class I chain-related gene (em português, gene ralacionado ao complexo de histocompatibilidade classe I)
$NaHCO_3$	Bicarbonato de sódio
NHANES III	Levantamento Nacional de Saúde e Nutrição de 1988-94 (EUA)
p	Valor de probabilidade
IC	Intervalo de confiança
PEPI	Computer Programs for Epidemiologists
SB	Síndrome de Behçet
SIDA	Síndrome da Imunodeficiência Adquirida
SNC	Sistema Nervoso Central
SPSS	Statistical Package for the Social Sciences
UAMa	Ulceração Aftosa do tipo Maior
UAMe	Ulceração Aftosa do tipo Menor
UAR	Ulceração Aftosa Recorrente
UH	Ulceração Herpertiforme

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RESUMO

PREVALÊNCIA DA SÍNDROME DE BEHÇET EM PACIENTES PORTADORES DE ULCERAÇÃO AFTOSA RECORRENTE

Introdução/Objetivos. A síndrome de Behçet (SB) é uma entidade clínica caracterizada pelo aparecimento de úlceras orais e genitais recorrentes, além de um amplo espectro de manifestações clínicas. Tem sido mais freqüentemente vista em países como Turquia e Japão, mas também no Brasil, embora não existam dados epidemiológicos consistentes no nosso país. O objetivo do presente estudo é avaliar a prevalência da SB em pacientes portadores de ulceração aftosa recorrente (UAR), testando-se a hipótese de que a SB poderia estar sendo subdiagnosticada no nosso meio. **Material e Métodos.** Esta é uma investigação transversal da prevalência da SB em pacientes portadores de UAR atendidos no serviço de Estomatologia da Escola Bahiana de Medicina e Saúde Pública (Salvador-Bahia) entre agosto de 2006 e agosto de 2007. O primeiro estágio identificou os indivíduos com UAR dentre todos os pacientes examinados no ambulatório; o segundo estágio examinou criteriosamente os pacientes com UAR para identificar os pacientes com a SB. **Resultados.** Foram atendidos 306 pacientes no ambulatório, no período do estudo, mas o questionário padrão foi aplicado em 50 (16,6%) pacientes, 29 homens e 21 mulheres, identificados como portadores de UAR. Apenas um paciente preencheu os critérios internacionais para diagnóstico da SB [*International Study Group for Behcet´s Disease (ISGBD)*], apresentando UAR do tipo menor e complexa, úlceras genitais recorrentes, manifestações cutâneas, articulares, oculares, vasculares, hipoacusia e febre, definindo-se uma prevalência de 2% de SB nesse subgrupo de pacientes. ***Conclusão.*** No

Brasil não existem dados relativos à prevalência ou incidência da SB, porém a doença tem sido observada em diferentes regiões do país. No presente estudo, a freqüência de 2% SB nos portadores da UAR demonstra a necessidade de que outros estudos de base populacional sejam desenvolvidos no nosso meio para que a real prevalência dessa condição seja definitivamente estabelecida.

Palavras-chave: 1. Síndrome de Behçet; 2. ulceração aftosa recorrente; 3. prevalência.

I INTRODUÇÃO

I. **INTRODUÇÃO**

A ulceração aftosa recorrente (UAR), também denominada estomatite aftosa, é uma doença inflamatória da mucosa bucal cuja prevalência na população mundial é de cerca de 5-25%, chegando a até 60% em grupos específicos[1,2]. A afecção caracteriza-se pelo aparecimento de ulcerações dolorosas e recidivantes, únicas ou múltiplas, que acometem preferencialmente a mucosa bucal não-ceratinizada[3]. Considerações importantes devem ser realçadas quanto ao diagnóstico diferencial que inclui as estomatites aftosas complexas e as variantes relacionadas com manifestações sistêmicas como aquelas associadas a alterações hematológicas, hormonais, nutricionais e gastro-intestinais[4]. Diante desses fatores, o clínico, através de uma anamnese e um exame clínico bem elaborado, necessita estar preparado para o diagnóstico de condições clínicas que envolvam a UAR e outros sistemas, como a síndrome de Behçet (SB)[3].

A SB é uma condição inflamatória, complexa e multissistêmica caracterizada classicamente por ulcerações orais recorrentes, ulcerações genitais e alterações oftalmológicas, mas que pode afetar qualquer sistema, incluindo o músculo-esquelético, vascular, neurológico, respiratório e gastro-intestinal[5]. Sua patogenia permanece incerta, mas dados epidemiológicos sugerem uma interação entre fatores genéticos, imunológicos e infecciosos[6]. Tem distribuição geográfica universal, embora seja mais freqüente na bacia do Mediterrâneo, Japão e Oriente médio, alcançando até 420 casos por 100 mil habitantes[7]. Tendo em vista a alta prevalência de 90-100% de estomatite aftosa em pacientes portadores da SB e a não existência de dados substanciais na literatura quanto à real prevalência e incidência dessa síndrome no Brasil, este

trabalho, pioneiramente, avalia a prevalência da SB em portadores de UAR acompanhados em um ambulatório especializado de uma instituição universitária.

II REVISÃO DE LITERATURA

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II.1. Ulceração Aftosa Recorrente

A Ulceração Aftosa recorrente (UAR) é uma lesão ulcerada que ocorre em áreas pouco queratinizadas da mucosa oral como, por exemplo, mucosa jugal, mucosa labial e assoalho de boca, sendo raramente encontrada no palato duro e gengiva. Esta doença é conhecida desde Hipócrates (460-370 A.C.) que, baseando-se no sintoma prodrômico (sensação de queimadura), chamou-a de *aphthi* ("acender o fogo")[1]. Posteriormente, sua descrição clínica clássica com a apresentação de hipóteses etiológicas e métodos de tratamento foi realizada em 1898 por Mikulicz & Kümmel (1898)[8].

A etiologia da doença ainda é desconhecida, porém são observados alguns fatores desencadeantes como trauma local, tabagismo, estado psicológico, ciclo menstrual, agentes biológicos, fatores genéticos, hipersensibilidade alimentar e quadro imunológico[9]. A UAR, também conhecida como úlcera oral recorrente, estomatite aftosa recorrente, aftas simples ou complexas, caracteriza-se por úlceras localizadas arredondadas ou ovais, dolorosas, rasas a profundas, tendo sempre uma borda eritematosa recoberta por uma base fibrinosa necrótica amarelada ou esbranquiçada[4].

As lesões da UAR são auto-limitadas e persistem entre uma a duas semanas, apresentando resolução com ou sem cicatrizes, além de recorrências após períodos de remissão. Alguns pacientes apresentam períodos de recorrências infrequentes, duas a quatro vezes por ano (aftas simples), entretanto outros pacientes apresentam uma atividade contínua da doença com o aparecimento de novas lesões se desenvolvendo, concomitantemente ao processo de resolução das lesões mais velhas (aftas complexas)[10].

A UAR é afecção mais comum das lesões inflamatórias orais nas Américas[11,12]. Afeta 0,5-66% da população mundial, variando sua incidência de acordo com as características sociais e populacionais[13,14]. Além disso, pelo fato da doença ter um caráter auto-limitante, a diferença entre a prevalência referida através da história ou da freqüência clinicamente observada, altera drasticamente o cenário epidemiológico da UAR[13]. Embil *et al.*[12] (1975) em estudo clássico de 1975, observaram a seguinte distribuição da UAR entre seis continentes: 30,5% na África; 45,3% na Ásia; 33,1% na Oceania; 36,3% na Europa; 57,9% na América do Norte e 26.2% na América do Sul. Shulman *et al.*[15] (2006) relataram no terceiro Levantamento Nacional de Saúde e Nutrição de 1988-1994 (NHANES III) que a UAR foi a décima terceira lesão oral mais comum e a lesão inflamatória mais prevalente nos EUA. No Brasil, jamais foi realizado um levantamento tão expressivo como o NHANES III, entretanto alguns poucos estudos procuraram mostrar a realidade nacional, principalmente em crianças e idosos. Dentro desse padrão, Mesas *et al.*[16] (2006) observaram em uma amostra de 267 pacientes com uma média de 66,5 anos de idade que as úlceras orais eram as lesões inflamatórias mais prevalentes entre idosos (11,3%). Dos Santos *et al.*[17] (2004) em um corte transversal com 587 indivíduos de uma comunidade indígena na Amazônia Central, que não mantém hábitos de etilismo, fumo ou uso de pacificadores, encontraram uma prevalência de UAR baixa (1,2%) para menores de doze anos, além de uma freqüência geral de 0,9%. Bessa *et al.*[18] (2004), avaliando 1211 crianças entre 0-4 e 5-12 anos, observaram a presença de lesões orais em 27% dos pacientes, sendo que dentre elas a lesão inflamatória mais comum foi a UAR com uma freqüência de 1,47% e 1,72% nos respectivos grupos. Como já

enfatizado, esses dados mostram que estimar a prevalência de UAR apenas na vigência do exame clínico diminui muito a freqüência geral. Dessa maneira, mais estudos são necessários para determinar a real prevalência desta doença no Brasil.

É considerada uma doença típica da infância e da adolescência, porém pode acometer qualquer faixa etária[19]. Motta *et al.*[20] (2003) encontraram no Brasil uma média de aparecimento da doença aos 33 anos, entretanto a literatura enfatiza que a idade da primeira manifestação ocorre de forma bifásica entre 0 e 9 anos e entre 10 e 19 anos. Estudos estimam que 20% da população em geral terá UAR durante sua infância ou no início da vida adulta[11]. As lesões recorrem com menor freqüência e severidade com o aumento da idade[4]. Lin *et al.*[14] (2001), analisando pacientes chineses, corroboram com essa afirmação observando no grupo entre 35 e 44 anos uma prevalência da UAR de 2% contra uma freqüência de 0,6% na faixa etária entre 65 e 74 anos.

A prevalência da UAR nas crianças, como nos adultos, varia muito entre diferentes regiões[21, 22, 23]. Segundo Gándara *et al.*[24] (2002) e Risboo-Crespo *et al.*[23] 2005 essa freqüência intercala-se entre 0,9% a 45%. Crianças de classe social privilegiada podem ser mais comumente afetadas do que aquelas pertencentes às classes sociais inferiores. Crivelli *et al.*[25] (1988) investigando a relação entre os fatores sociais e a UAR, encontraram uma prevalência de 19% em estudantes de classe social elevada contra 12% de estudantes de classe social menos privilegiada.

Alguns grupos populacionais, especialmente os estudantes de medicina, odontologia ou que tenham responsabilidades cobradas acima das expectativas, tem a prevalência de UAR aumentada em 50%, com freqüências

que chegam a 66%[2,12]. Estudo realizado no Kuwait correlacionou a prevalência das UAR entre populações das cidades e do deserto. A freqüência menor foi nos beduínos (deserto) (5%) do que nos habitantes urbanos (22%), que foram considerados mais sujeitos ao estresse no ambiente competitivo das cidades[26]. Mulheres eram acometidas mais comumente que homens e, por isso, acreditava-se em uma correlação entre a UAR e o ciclo menstrual, levando a uma base hormonal para a doença. Entretanto, a distribuição aproximadamente igual da estomatite aftosa nos homens contraria essa idéia[11].

Cooke[27] (1969), em 1969, classificou as lesões da UAR em três grupos: 1) Úlceras aftosas menores; 2) Úlceras aftosas maiores; 3) Úlceras herpetiformes. A forma mais comum de UAR é a úlcera aftosa menor (UAMe) que acomete entre 75 a 85% dos pacientes de UAR. UAMe são uma ou mais úlceras, pequenas (<1,0 cm), ovais ou circulares, rasas e cobertas por uma camada fibromembranosa de coloração cinzenta e circundada por uma zona eritematosa periférica. UAMe são úlceras moderadamente dolorosas que usualmente resolvem sem cicatrizes entre uma a duas semanas. As lesões podem recidivar com freqüência, entretanto a maioria dos pacientes sofre dois a quatro episódios por ano[10].

Úlceras Aftosas Maiores (UAMa) representam a forma mais severa de UAR. Essas lesões afetam aproximadamente entre 10% e 15% dos pacientes com UAR. UAMa são também conhecidas úlceras de Sutton ou periadenite mucosa necrótica recorrente. Como UAMe, as UAMa quase sempre se iniciam na infância ou adolescência. Essas lesões são morfologicamente parecidas com as UAMe, todavia são maiores (freqüentemente >1cm), e profundas. UAMa resolvem mais lentamente (10-30 dias) e caracterizam-se pela reparação com

cicatrizes. As lesões de UAMa podem causar considerável desconforto, dor oral, febre e mal estar[3].

A terceira variante, úlceras herpetiformes (UH), são as menos comuns, afetando cerca de 5 a 10% dos pacientes com UAR (Rogers, 1998). As lesões das UH são geralmente implicadas como "herpetiformes" por causa da nomenclatura, mas não são resultantes da infecção do vírus da herpes simples. Lesões individuais podem ser numerosas, oscilando entre 10 a 100 úlceras. A lesão elementar é uma discreta pápula de 1 a 2mm que evolui para uma lesão vesículo-bolhosa e posteriormente para uma úlcera. As UH freqüentemente se agrupam, confluentemente, formando grandes placas. Por causa do tamanho e da profundidade, as UH reparam-se em 7 e 30 dias formando cicatrizes[28].

As lesões da mucosa oral podem representar manifestações de doenças dermatológicas, sistêmica, lesões reacionais ou neoplasmas ocultos[11]. O sucesso do manejo de pacientes portadores de lesões de UAR é dependente no diagnóstico precoce, na classificação da doença, reconhecimento dos possíveis fatores causais e da identificação das desordens sistêmicas associada que contribui para a debilidade, tratamento e prognóstico da UAR[3]. Em virtude desta natureza multifatorial, um tratamento da UAR bem sucedido depende de um diagnóstico preciso, classificação da doença e reconhecimento de possíveis fatores ou doenças associadas como a úlcera vulvar aguda, anemia, enteropatia glúten-sensível (doença celíaca), doença inflamatória intestinal, neutropenia cíclica, ulceração aftosa-like a SIDA (síndrome da imunodeficiência adquirida), síndrome MAGIC (úlceras orais e genitais com inflamação de cartilagem), síndrome FAPA (febre, aftose, faringite e adenite),

síndrome de Sweet, síndrome de Reiter e a própria Síndrome de Behçet (SB)[29,30].

II.2. Síndrome de Behçet

A síndrome de Behçet (SB) é uma enfermidade multissistêmica crônica, caracterizada por aftas orais e genitais, artrite, lesões cutâneas, manifestações oculares, gastro-intestinais e neurológicas. Classificada também como uma vasculite sistêmica, a SB pode envolver artérias e veias de qualquer órgão[5]. Foi descrita pela primeira vez pelo oftalmologista grego Benedict Adamantiades em 1931, mas foi em 1937 que o dermatologista turco Hulusi Behçet realizou uma descrição completa da doença, reconhecendo o caráter sistêmico da doença e estabelecendo a tríade clássica composta por úlceras aftosas orais recorrentes, úlceras genitais e "uveíte-hipópio"[31,32,33]. Todavia, desde a sua descrição inicial, o conceito da SB foi expandido e, atualmente, sabe-se que a doença pode afetar qualquer sistema[30].

A etiologia dessa síndrome permanece obscura, mas a hipótese mais comumente aceita pela literatura para a sua patogênese é estabelecida quando uma resposta inflamatória profunda é deflagrada por um agente infeccioso num hospedeiro geneticamente susceptível[6,34].

A SB tem distribuição geográfica distinta, com alta incidência em países banhados pelo Mediterrâneo, e Japão, sendo que a Turquia apresenta as maiores prevalências, alcançando até 420 casos por 100 mil habitantes[7,35]. É mais rara no norte da Europa, norte da Ásia, no continente africano não banhado pelo mar Mediterrâneo e nas Américas[31,36,37]. SB afeta mais freqüentemente pacientes jovens (15-45 anos), incidindo igualmente em

homens e mulheres, embora pareça que o prognóstico é pior no sexo masculino[37,38]. No Brasil, Aguiar *et al.*[39] (1997) em um estudo retrospectivo com 22 pacientes portadores da SB, encontraram uma relação homem-mulher de 1:3,4, enquanto que Coimbra *et al.*[40] (1989) e Vitral *et al.*[41] (2000) demonstraram uma prevalência maior de homens portadores da SB com índices de 2:1 e 1,5:1, respectivamente.

A doença apresenta-se mais comumente na forma de ataques recorrentes de inflamação aguda[6]. A principal morbidade sequelar da síndrome é a cegueira que evolui após ataques repetidos de inflamação ocular, mas mesmo que a doença apresente a maioria de suas manifestações benignas, o acometimento do sistema nervoso central (SNC) e de grandes vasos pode ser grave, levando o paciente a óbito[42,43,44,45]. Além disso, tem sido observado um aumento do risco para câncer associado às doenças do colágeno e novos casos de neoplasias malignas relacionadas à SB vêm sendo relatados[46]. O desenvolvimento de métodos internacionais de diagnóstico e prognóstico permitiu que a comunidade médica internacional despertasse um maior interesse na síndrome, principalmente com a introdução de medidas terapêuticas que melhorassem as taxas de co-morbidades e letalidade da doença[47,48]. Dessa maneira, os estudos mais atuais estão direcionados para a elucidação da etiopatogênese da doença e do estabelecimento de uma estratégia terapêutica mais eficaz.

II.3. Epidemiologia da SB

Como citado acima, a SB tem uma maior prevalência e incidência entre a bacia do Mediterrâneo e o leste da Ásia, numa região comercialmente histórica

chamada de "rota da seda"[49]. Esse termo largamente utilizado pela literatura médica, segundo Ohno *et al.*[50] (1982), possivelmente reflete uma predisposição genética da doença que se espalhou entre as tribos e comerciantes que viajavam entre o mundo Arábico e o Oriente. Verity *et al.*[51] (1999) corroboraram esses achados quando compararam a distribuição mundial do HLA-B51 e a migração do *Homo sapiens* entre 300.000 e 10.000 anos atrás. Entretanto, esses autores evidenciaram que a alta prevalência do gene HLA-B51 em certas regiões do globo, como na própria América (prevalência de 11.1% do HLA-B51 na Amazônia), pode não estar relacionado exclusivamente com uma alta incidência da SB. Isto evidencia a característica multifatorial da SB e uma possível influência de fatores ambientais na realidade epidemiológica da doença.

Quando se estabelece uma correlação geográfica com a prevalência da SB nos países em que os dados são disponíveis, verifica-se que existe uma relação entre a latitude e prevalência da doença (tabela I)[51]. Assim, em pacientes com a mesma origem étnica, a prevalência da síndrome parece também ter uma relação forte com latitude e longitude. A prevalência na população turca diminui com o aumento da distância do leste da Turquia para a direção oeste. Por outro lado, no Japão, a prevalência tem uma tendência a diminuir quando se move do norte para o sul, chegando a zero em japoneses vivendo nos Estados Unidos da América (EUA) e Havaí[52]. Poucos pacientes de origem japonesa foram relatados como portadores da SB no Brasil[53].

Tabela I. Distribuição mundial da síndrome de Behçet

País	Ano	Latitude (°N)	HLA-B51	Prevalência da SB por 100.000 habitantes
ÁSIA				
Turquia[7,35,54,55,56]	1981-2004	39	26,3	20-420
Japão[57]	1991	36	22,3	0,99-30,50
Israel[58,59]	2002-2007	31	81	8,6-146,4
Irã[60]	2005	32	34	16,7
China[52,61]	1998-2002	32	56	2,62-14
Coréia[62]	2001	35	13	109,2*
Arábia Saudita[52,63]	1997	26	72	20
ÁFRICA				
Egito (Alexandria)[52]	1997	30	---	7,5
EUROPA				
Espanha[64,65]	1998	41	6,1-24,5	0,32-10,8
Itália[36]	1988	42	17,4	2,5
Portugal[66]	1991	17	53	1,53
Suécia[67]	1990	60	3	1,18
Suíça[68]	1991	52	66	0,65
Inglaterra[36]	1977-1992	52	25	0,27-0,64
Alemanha[36]	1994	52	36	0,55-20,75
AMÉRICA				
EUA[52]	1975-1985	46	13	0-0,33

*Primeiro estudo multicêntrico na Coréia, observando uma prevalência de 109,2/100.000 habitantes.

Segundo Azizlerli *et al.*[7] (2003), a Turquia é o país de maior prevalência mundial da SB com uma razão que se estende de 20-420/100.000 habitantes. Num estudo realizado em Istambul (a maior e mais cosmopolita cidade da Turquia) foram encontrados 101 casos da SB para 23.986 indivíduos, evidenciando uma prevalência de 42/10.000 habitantes. Essa discrepância da prevalência entre as diferentes regiões da Turquia pode ser explicada através da diversidade étnica e racial da região, além de um menor ou maior acesso a cuidados médicos entre essas comunidades. A imigração e emigração, principalmente nos países de maior prevalência e incidência, suportaria a

hipótese da provável mistura de material genético ou da transferência de um agente exógeno associado, o que estaria relacionado com a crescente expansão da SB no mundo atual[36].

Em 1981, Dimirhindi *et al.*[69] (1981), conduzindo o primeiro estudo de prevalência da SB na Turquia, através de uma amostra de 4940 habitantes de 9 vilas, encontraram uma prevalência de 80/100.000. Em seguida, Yurdakul *et al.*[35] (1988) avaliaram 5131 habitantes, maiores de 10 anos, de uma vila no norte da Turquia, evidenciando uma prevalência de 38/10.000, parecida com o estudo mais recente de Azizlerli *et al.*[7] (2003). Os autores também descreveram uma maior prevalência do HLA-B5 em pacientes com a SB hospitalizados.

Idil *et al.*[55] (2002), em um estudo de prevalência de base populacional em Ankara na Turquia, mostraram uma prevalência de 0,11%, ou seja, 16 pacientes dos 17.256 participantes eram portadores da SB, sendo 11 do sexo feminino e 5 do sexo masculino (feminino/masculino = 2,2:1). Nove pacientes dos 16 já eram previamente diagnosticados e 5 obtiveram o seu diagnóstico durante a pesquisa. Os autores discutiram que mesmo observando uma prevalência mais baixa na região em comparação com os estudos prévios, é possível que existam muitos casos subdiagnosticados da doença, o que remete a um número muito mais alto da SB na Turquia.

Em outro estudo realizado em 7 vilas da zona rural do oeste da Turquia, Cakir *et al.*[54] (2004) observaram que dos 5203 indivíduos participantes (4861 maiores de 10 anos de idade), 124 (2,3%) apresentavam ulceração oral recorrente (UOR), 4/124 obtiveram o teste de patergia positivo e apenas 1 (0,02%) indivíduo completou os critérios da *International Study Group for Behcet´s*

Disease (ISGBD). Com isso, a prevalência relatada foi de 20:100.000 indivíduos, a mais baixa dentre todos os estudos previamente conduzidos naquele país.

O segundo país de maior prevalência da SB é o Japão com uma prevalência que varia de 0,99-30,5/100.000 indivíduos. A maior prevalência naquele país foi encontrada na região de Hokkaido, onde há 30,5 casos por 100 mil pessoas, enquanto que a menor freqüência foi encontrada na região de Kyushu com 0,99/100.000[57]. Dados mais recentes sugerem uma estimativa que 16.750 indivíduos são portadores da doença no Japão, evidenciando uma prevalência de 13.5/100.000[70].

Além da Turquia e do Japão, a Coréia do Sul também é um país da "rota da seda" com uma prevalência altíssima, sendo esta demonstrada por Bang *et al.*[62] (2001) num estudo retrospectivo multicêntrico de cunho nacional. Os autores analisaram dados epidemiológicos em 20 hospitais entre 1997 e 1999, encontrando 382 portadores da SB completa num universo amostral de 3497 pacientes. Dessa maneira, os autores demonstraram uma excepcional prevalência de 10,9%. Porém, Davatchi *et al.*[60] (2005), em sua revisão de 2005, relata que os dados coreanos ainda são pouco consistentes, não colaborando para uma exatidão do cenário epidemiológico daquele país.

Quando comparamos os países de maior com aqueles de menor prevalência observa-se uma diferença importante. Países como a Suíça, Grã-Bretanha, Alemanha, Portugal, Espanha, Polônia, Itália e EUA (Havaí) evidenciam uma prevalência entre 0-2.5/100.000, enquanto que no norte da China, Irã e Arábia Saudita, demais países que compõem a "rota da seda", ela varia entre 13,5 a 20 casos por 100 mil habitantes. Freqüência intermediária se comparada com a

Turquia e o Japão (tabela I)[36,37,62,64]. Vale ressaltar que em algumas regiões de países onde a doença é rara, a prevalência pode ser alta, tendo em vista um número maior de descendentes e imigrantes de países de maior prevalência como a própria Turquia[36,37,71].

Em um estudo de prevalência em uma vila árabe de Israel em que 44% dos casamentos são consangüíneos, os autores observaram uma prevalência de 12/10.000 após avaliarem 4876 indivíduos. Esse trabalho seguiu uma metodologia quase que padrão para a descrição da prevalência da SB, baseando-se sempre na busca de paciente com UOR. De todos participantes avaliados, 849 apresentavam UOR e apenas 6 adultos preencheram os critérios da *ISGBD* (5 mulheres e 1 homem)[58]. Krause *et al.*[59] (2007) observaram uma prevalência consideravelmente menor no norte de Israel de 15,2/100.000. Notadamente nesse trabalho, os autores relataram uma prevalência ainda mais alta de 26,2/100.000 na comunidade Arábica e de 146,4/100.000 para uma comunidade islâmica de Israel (os Druzes)[59]. Dessa maneira, observa-se que a SB é acentuadamente prevalente em Israel, mas que as taxas de prevalência podem variar acentuadamente entre as diferentes regiões do país.

Como descrito previamente, o inverso também pode ocorrer quando, por exemplo, na China, país que compõe a "rota da seda", existe uma contradição nas taxas de prevalência entre a região norte e sul. Em Hong Kong, cidade sulista, num estudo de 22 anos que avaliou a prevalência da SB nos quatro maiores hospitais da cidade, observou-se que de uma base populacional de 1,41 milhões de habitantes, apenas 37 pacientes completaram os critérios da ISGBD, estimando uma prevalência de 2,62/100.000. Segundo os autores,

essa baixa prevalência poderia estar relacionada a uma associação incomum com um outro gene (MIC) ou subtipos de HLA ainda não demonstrados[61].

Neste mesmo contexto, destacando valores intermediários de prevalência, Zouboulis *et al.*[36] (1997), avaliando inicialmente 218 pacientes catalogados no registro alemão da SB, observaram que a prevalência aumentou no oeste de Berlin de 0,65/100.000 em 1984 para 2,26/100.000 em 1994. Além disso, os autores evidenciaram uma discrepância importante na prevalência entre diferentes regiões de diversas colonizações da Alemanha, mostrando que a freqüência variou de 0,55/100.000 em regiões de origem alemã para 20,7/100.000 em regiões de origem turca. Essas diferenças também corroboram para uma influência étnica na expressão e severidade da doença como descrito no trabalho de Krause *et al.*[72] (2001).

Dentre os países de baixa prevalência, num estudo realizado no noroeste da Espanha, a prevalência encontrada foi de 0,66/100.000, referente a 16 pacientes (9 homens e 7 mulheres) que preencheram os critérios da ISGBD e que foram atendidos em hospital de referência de 1988 a 1997[64]. Graña *et al.*[65] (2001) publicaram em seguida um estudo reavaliando a prevalência de SB na Galícia, encontrando uma taxa de 10,8 por 100 mil habitantes. Nesse estudo os autores se embasaram em trabalhos anteriores realizados em La Coruña (cidade da Galícia), onde mostravam uma incidência anual de 0,32/100.000 e, em homens, de 0,53/100.000.

Até o momento, nenhum estudo de prevalência da SB foi realizado no Brasil, entretanto alguns trabalhos descritivos puderam mostrar dados referentes à freqüência da doença em ambulatórios de referência em oftalmologia[53,73,74,75]. Dentre eles, Barra *et al.*[53] (1991), em um trabalho bem conduzido e

amplamente citado na literatura internacional, encontraram 49 pacientes (2%) com a SB entre 2500 casos de uveítes atendidos durante um período de 16 anos no departamento de oftalmologia de uma escola de medicina. Gouveia *et al.*[76] (2004), avaliando as causas das uveítes em serviço terciário de São Paulo, descreveram que, num período entre fevereiro a agosto de 2002, das 262 fichas de pacientes do serviço de uveítes de outro hospital-escola, 26 (10%) pacientes apresentaram a SB, representando a 2ª causa de uveíte dentre as causas não infecciosas, atrás apenas da síndrome de Vogt-Koyanagi-Harada (13%). Mais uma vez, alertando para o conhecimento epidemiológico, etiopatogênico e clínico dessa enfermidade. Curiosamente, em outro estudo oriundo do mesmo centro, Gomi *et al.*[75] (1997) observaram, que dos 414 pacientes avaliados entre 17 e 40 anos, 63% manifestaram uveítes difusas, sendo a SB a etiologia mais freqüente (36%). Ressalta-se, entretanto, que a maioria dos autores desses estudos não demonstraram, em suas metodologias, os critérios validados para o diagnóstico da SB, expondo os dados pouco confiáveis dos seus resultados.

No que concerne à idade do aparecimento da SB, observa-se que a mesma predominantemente acomete adultos jovens, com idade média de início entre 20 e 40 anos, entretanto casos extremos já foram relatados iniciando na oitava década de vida, bem como em neonatos[61,77]. O país em que a doença tem a maior média de idade de início é o Japão (43,2 anos) seguido da Turquia (38,32 anos), China (36 anos), Singapura (33 anos) e Coréia do Sul(29 anos), sendo todos, países que compõem a "rota da seda"[38,78]. Na Europa, países como a Irlanda, Rússia, Inglaterra, Espanha, Portugal, Itália e Grécia possuem uma idade média de início da doença que varia de 20,8 a 29 anos, sendo a

Suécia e a Polônia os países europeus de maiores médias (33 e 37 anos)[36,37]. No Brasil, a média de idade de início da doença varia entre 17,5 a 33,5 anos[39,40,41,53,79,80]. A literatura ainda destaca uma característica bifásica de distribuição da doença, quando a maioria dos pacientes mostra sintomas entre 20 e 30 anos e entre 40 e 50 anos[81]. Dessa maneira, os sintomas podem aparecer em qualquer idade, mas a maioria dos casos tem início por volta da terceira década de vida e, usualmente, a doença desenvolve-se em torno dos primeiros 15 meses após a primeira manifestação[31]. Por outro lado, Scherrer e Oréfice observaram no Brasil, que o diagnóstico é realizado cerca de 5 anos (média) após o início da doença[79].

Quanto ao gênero, observa-se que o sexo masculino é o mais acometido pela SB, especialmente em países como a Turquia [masculino:feminino (M:F) - 2,2:1], Israel (M:F - 5:1), Alemanha (M:F – 3,7:1), Líbano (M:F – 2,9:1) e Índia (M:F – 1,76:1)[7,43,52,72,82]. Países como a Rússia, Suécia, Escócia e Inglaterra apresentaram uma razão de distribuição (M:F) que variou de 0,36 a 0,96:1.(52) No Brasil, há estudos mostrando uma razão de prevalência maior entre as mulheres variando de 1,5 a 3,4:1[39,40,41,80], enquanto outros observaram uma razão de distribuição M:F de 1,6 a 2,4:1[53,79]. Atualmente, a maioria dos estudos epidemiológicos e séries de casos apontam para proporções semelhantes entre os sexos, inclusive na grande parte dos países citados[52].

Como a SB não segue as leis de Mendel e a não detecção de uma alteração genética exclusiva, o número de casos familiares descritos na literatura é baixo (1-18%)[31]. Contudo, diversos estudos procuram mostrar esses dados epidemiológicos. A SB familiar é incomum nos caucasianos, mas uma história familiar positiva é observada em mais de 12% de pacientes não caucasianos;

além disso, em um estudo descritivo na Turquia, o risco relativo para a ocorrência entre gêmeos variou de 11,4 a 52,5, sugerindo um possível componente genético importante, como já observado em doenças genéticas complexas incluindo as doenças inflamatórias intestinais[5]. Intrigantemente, a ocorrência familiar nos coreanos (15,4%) é muito mais freqüente que nas famílias de origem chinesa ou japonesa (2,2-2,6%). Pacientes de origem arábica, judaica ou turca apresentam freqüências familiares mais altas (2-18,2%) do que em pacientes europeus (0-4,5%). Ressalta-se que pacientes juvenis apresentam uma ocorrência familiar mais alta do que se comparados com adultos: 16% *versus* 2% no Marrocos, 18% *versus* 2% na França e 25% *versus* 8% na Alemanha[52].

IIII OBJETIVOS

III. OBJETIVOS

III.1. Primário

O objetivo do presente estudo é descrever a prevalência de Síndrome de Behçet em indivíduos portadores de Úlcera Aftosa Recorrente em um ambulatório de referência.

III.2. Secundários

- Estimar a prevalência da SB no distrito Cabula-Beirú (Salvador-Bahia);
- Descrever a freqüência de outras variáveis referentes a UAR como: gênero e idade dos pacientes; número, localização, tamanho, tempo de evolução, número de episódios, tempo entre episódios, sintomatologia associada e tratamento submetido;
- Descrever a freqüência das manifestações clínicas na SB.

IV JUSTIFICATIVA

IV. JUSTIFICATIVA

A imigração e emigração, principalmente nos países de maior prevalência e incidência, suportaria a hipótese da provável mistura de material genético ou da transferência de um agente exógeno associado, o que estaria relacionado com a crescente expansão da SB no mundo atual. No Brasil não existem dados relativos à prevalência ou incidência da SB, porém a doença tem sido observada em poucas séries de diferentes regiões do país. A estomatite aftosa é a manifestação clínica mais comum da SB, por isso, dentro desse perfil, o grupo de estudo internacional da doença de Behçet (ISGBD) elaborou um conjunto mais conciso de critérios diagnósticos para a SB, no qual a UAR seria um critério obrigatório. Dessa maneira, tendo em vista a alta prevalência de 90-100% de estomatite aftosa em pacientes portadores da SB, este trabalho, pioneiramente, avalia a prevalência da SB em portadores de UAR acompanhados em um ambulatório especializado de uma instituição universitária.

V MATERIAL E MÉTODOS

V. MATERIAL E MÉTODOS

V.1. Delineamento do estudo

Este estudo investigou transversalmente a prevalência da SB em pacientes portadores de UAR atendidos no serviço de Estomatologia da Escola Bahiana de Medicina e Saúde Pública (Salvador-Bahia) entre agosto de 2006 e agosto de 2007. Este é um serviço de referência em Estomatologia para atendimento aos moradores do distrito Cabula-Beirú, cuja população residente corresponde a 385.109 habitantes. O estudo foi realizado em dois estágios. O primeiro estágio identificou os indivíduos com UAR dentre todos os pacientes examinados no ambulatório; o segundo estágio examinou criteriosamente os pacientes com UAR e outro sintoma associado sob condições hospitalares com o intuito de definir os portadores da SB.

V.2 Definição amostral e primeiro estágio do estudo

O tamanho amostral estimado foi de 45 pacientes com UAR, avaliando-se uma prevalência esperada de 3% de portadores da SB, com um intervalo de confiança de 95% e um nível de precisão de 5%. Essa estimativa foi baseada em estudos turcos, nos quais foram observadas freqüências da SB em pacientes com UAR entre 0,8 e 14%[7,54]. Para esta análise, foi utilizado o programa PEPI versão 4.04. No primeiro estágio da pesquisa, para cada paciente da amostra foi preenchida uma ficha-padrão com 26 questões (**Apêndice 1**), em que constou os dados de identificação do paciente e condições sistêmicas relacionadas a SB. Em relação às lesões, foram anotados número, localização, tamanho, tempo de evolução, número de

episódios por ano, tempo entre os episódios em meses, sintomatologia associada e tratamento submetido. A coleta de dados foi feita por entrevista, complementada com dados colhidos no prontuário e anotadas na ficha catalográfica. Para inclusão no estudo, os pacientes apresentaram UAR do tipo menor, maior ou herpetiforme com até dois dias de evolução, além de dois ou mais episódios nos últimos doze meses. Após a confirmação da presença de UAR, os pacientes foram submetidos a um teste de patergia*, realizados e reavaliados pelo mesmo investigador[83]. Ressalte-se que esta pesquisa foi submetida e aprovada pelo Comitê de Ética e Pesquisa do Hospital Santa Izabel (Salvador-Bahia) (**Apêndice 2**), e para inclusão na amostra, os pacientes assinaram um termo de consentimento livre e esclarecido (segundo a Resolução CONEP n° 196 de 1996, **Anexo 3)**.

V.3. Segundo estágio do estudo

No segundo estágio, todos os indivíduos com UAR e outra manifestação relacionada à SB receberam uma avaliação médica criteriosa nos ambulatórios de Reumatologia do Hospital Santa Izabel (Salvador- Bahia). Indivíduos que completaram os critérios do *International Study Group for Behcet's Disease (ISGBD)* foram definidos como portadores da síndrome para a estimada prevalência (Tabela II)[84].

* Patergia é uma hiper-reatividade não-específica em resposta a um mínimo trauma. Sua pesquisa habitualmente é feita com uma punção da pele até a derme, no antebraço do paciente, com agulha estéril (20 G). O teste é considerado positivo caso se forme uma pápula ou pústula, freqüentemente com halo eritematoso, dentro de 48 horas.

Tabela II. Critérios do grupo de estudo internacional para o diagnóstico da síndrome de Behçet (ISGBD)[84].

Ulceração Oral Recorrente	Aftose menor, aftose maior ou ulceração herpetiforme observada pelo médico ou paciente com recorrência de ao menos 3 vezes no período de 12 meses.
Mais 2 dos seguintes critérios:	
Úlcera genital recorrente	Ulceração aftosa e/ou cicatrizante observada pelo médico ou paciente.
Lesões oculares	Uveíte anterior, Uveíte posterior ou células do humor vítreo ao exame com lâmpada de fenda ou vasculite de retina observada pelo oftalmologista.
Lesões cutâneas	Eritema nodoso observado pelo médico ou paciente, pseudofoliculite ou lesões pápulopustulosas, ou nódulos acneiformes observados pelo médico em pós-adolescentes que não receberam tratamento com corticosteróide.
Teste de patergia positivo	Observado pelo médico em 24-48 hs.

A presença de UOR é um critério obrigatório e a presença de pelo menos mais dois outros critérios determina o diagnóstico da SB.

V.4. Análise dos dados

As variáveis categóricas foram analisadas usando o teste do Qui-quadrado ou o Exato de Fisher quando apropriado. As variáveis contínuas foram analisadas usando o teste t de Student. Para avaliar a distribuição da amostra o teste de normalidade Kolmorogov-Smirnov foi utilizado. Estas análises, incluindo os dados descritivos, foram realizadas utilizando o programa SPSS versão 13.0 com um nível de significância de 5%. O cálculo para a prevalência geral foi realizada através da razão entre a freqüência encontrada de pacientes portatores da SB atendidos em um ambulatório de referência sobre o número de habitantes do distrito Cabula-Beirú. O intervalo de confiança do resultado encontrado para prevalência foi realizado através do programa PEPI versão 4.04.

VI RESULTADOS

VI. RESULTADOS

Durante o estudo, foram atendidos 306 pacientes no serviço de Estomatologia, dos quais apenas 50 (16,6%) (95% IC, 12,5%-20.8%) apresentaram UAR e responderam o questionário padrão no primeiro estágio do estudo. Desses 50 indivíduos, 29 (58%) foram do sexo masculino e 21 (42%) do sexo feminino. Suas idades variaram entre 11 e 55 anos (média de 26,2±9,8), com uma média entre os homens de 27,6±11,3 e nas mulheres de 24,2±7,1. A idade da primeira manifestação de UAR foi de 17,4±8,8, sendo que 17±9,5 para homens e 17,9±7,9 para mulheres. Durante a execução do protocolo, nenhum indivíduo apresentou o teste de patergia positivo. Apenas 3 (6%) pacientes foram encaminhados para o segundo estágio do estudo e receberam avaliação médica criteriosa numa unidade de Reumatologia de referência. Somente um (2%) (95% IC, 0,1%-9,4%) paciente do sexo masculino, 35 anos, completou os critérios da *International Study Group for Behcet´s Disease (ISGBD)*, apresentando UAR, úlceras genitais recorrentes, manifestações cutâneas, articulares, oculares, vasculares e febre. No que tange a estimativa da prevalência geral da SB no distrito Cabula-Beirú, foi encontrada a freqüência de 0,259/100.000 (1:385.109) (95% IC, 0,2-0,4/100.000).

Os aspectos clínicos referentes aos 50 pacientes com UAR estão descritos na Tabela 3. A localização mais freqüente das lesões aftosas foram a mucosa jugal (56%) seguida dos lábios (54%). A média do tempo entre os episódios em meses (2,9±1,4 meses), do número de episódios por ano (4,5±4,2/ano), do número de úlceras por episódios (1,7±1,4) e a média de duração de cada episódio em dias (7,3±2,8) não diferem entre os sexos (estatisticamente não

significante). Sintomatologia álgica associada às úlceras foi relatada em 86% dos pacientes, sendo que 72% dos indivíduos referiram realizar algum tipo de tratamento tópico com o objetivo de acelerar o tempo de cicatrização das feridas. A triancinolona (Omcilon® em orabase) (62%), seguida do $NaHCO_3$ + KCL (Albicon®) (4%) foram os medicamentos mais utilizados. Outros medicamentos citados foram: dexametasona (Decadron®), Chamomilla recutita 10% (Ad-muc®), policresuleno (Albocresil®) e hidrocortisona + sulfato de neomicina (Gingilone®).

Tabela 3. Distribuição das características clínicas dos 50 pacientes com UAR, e comparação entre homens e mulheres.

	Frequência(%)	Homens (n=29)	Mulheres (n=21)	*Valor de p*
Idade no diagnóstico (anos ± DP)	26,2±9,8			
Idade do diagnóstico, razão entre homens e mulheres (anos ± DP)		27,6±11,3	24,2±7,1	NS
Idade da primeira manifestação (anos ± DP)	17,4±8,8			
Idade da primeira manifestação, razão entre homens e mulheres (anos ± DP)		17±9,5	17,9±7,9	NS
Localização				
Mucosa jugal	56	57	43	NS
Lábios	54	59,2	40,8	NS
Gengiva	12	66,6	33,4	NS
Língua	26	69,2	30,8	NS
Assoalho de boca	12	66,6	33,5	NS
Vestíbulo	18	55,5	44,5	NS
Palato	8	50	50	NS
Orofaringe	4	0	100	NS
Tempo entre episódios em meses	2,9±1,4	2,9±1,4	2,8±1,4	NS
Número de episódios por ano	4,5±4,2	4,4±4,3	4,6±4,1	NS
Número de úlceras por episódio	1,7±1,4	1,9±1,7	1,5±0,9	NS
Duração do episódio	7,3±2,8	7,1±2,4	7,7±3,2	NS
Tamanho úlceras (média em mm)	3±2	4±3	3±2	NS
Dor	86	58,1	41,9	NS
Uso de medicação	72	63,8	36,2	NS
Medicamento local				NS
Triancinolona	62	-	-	NS
$NaHCO_3$ + KCL	4	-	-	NS
Dexametasona	2	-		NS
Chamomilla recutita 10%	2	-	-	NS
Policresuleno	2	-	-	NS
Hidrocortisona + Neomicina	2	-	-	NS

NS: Estatisticamente Não Significante

Um perfil sistêmico dos pacientes também pode ser observado na tabela 4, em que, 10% apresentaram manifestações cutâneas com a predominância de

lesões acneiformes (10%), todos em homens. Apenas 6% dos pacientes apresentaram qualquer manifestação articular e 18,4% referiram sintomas neurológicos, particularmente cefaléia (16,3%). Doença gastro-intestinal foi observada em 10% dos indivíduos, mais freqüente em homens (80%). Vertigem foi relatada em 4% dos pacientes. Um indivíduo foi diagnosticado com retocolite ulcerativa e um outro paciente referiu realizar reposição de hormônio tireoidiano para tratamento de hipotiroidismo.

Tabela 4. Perfil sistêmico dos 50 pacientes portadores de UAR.

	Frequência(%)	Homens (n=29)	Mulheres (n=21)	*Valor de p*
Úceras Orais	100			
Úlceras Genitais	2	100	-	NS
Manifestções oculares	6	66,6	33,4	NS
Ceratoconjuntivite	6	66,6	33,4	NS
Manifestações cutâneas	10	100	-	0.04
Lesões acneiformes	10	100	-	0.04
Eritema nodoso	2	100	-	NS
Patergia	0			
Sintomas articulares	6	66,6	33,4	NS
Tromboflebite superficial	2	100	-	NS
Sintomas neurológicos	18,4	55,5	44,5	NS
Cefaléia	16,3	62,5	37,5	NS
Convulsão	2	100	-	NS
Manifestações gastro-intestinais	10	80	20	NS
Gastroduodenite	2	100	-	NS
Úlcera péptica	2	-	100	NS
Sintomas vestíbulo-cocleares	4	50	50	NS
Febre	2	100	-	NS
Retocoliteulcerativa	2	100	-	NS
Hipotiroidismo	2	100	-	NS

NS: Estatisticamente Não Significante

VII DISCUSSÃO

VII. DISCUSSÃO

A ulceração aftosa recorrente (UAR) é a condição mais comum das lesões inflamatórias orais nas Américas[4,11]. Sua prevalência depende especialmente da população estudada, embora se tenha relatado uma freqüência entre 5% e 50%. Além disso, foi descrita uma alta prevalência de 41,8% a 60% entre estudantes de Odontologia, Enfermagem e Medicina[85,86]. O presente estudo encontrou uma freqüência de 16,6% corroborando com estudos prévios[58]. Usualmente a UAR tem início na infância ou na adolescência, com uma tendência a uma diminuição em freqüência e severidade com a idade[10]. Como descrito, a idade de diagnóstico variou entre 11 e 55 anos com uma média de 26,2±9,8, semelhante ao estudo de Motta *et al.*[20] (2003), que evidenciaram uma média igual a 33,2±14,6, sendo que a maior prevalência da enfermidade ocorreu na faixa etária compreendida entre 15 e 45 anos. Em se tratando do sexo, os homens foram mais afetados que as mulheres na razão de 1,4:1 (M:F), diferindo da maioria dos trabalhos descritos. A observação de que a exacerbação da UAR nas mulheres pode correlacionar-se com o ciclo menstrual, levou a uma base hormonal da doença. Entretanto, a tendência mundial de distribuição aproximadamente igual da estomatite aftosa nos homens contraria essa idéia[87].

Com relação aos aspectos clínicos da UAR, ressalta-se que os resultados não diferem das séries de outros países, que apresentam uma prevalência de 75% a 85% de UAR do tipo menor (<10mm), 10% a 15% do tipo maior e de 5% a 10% do tipo herpetiforme[10,85]. O presente estudo observou 88% de UAR do tipo menor, 8% do tipo maior e 4% do tipo herpetiforme. O tipo complexa (padrão contínuo) foi encontrado em 8% dos pacientes, enquanto que o tipo simples foi

encontrado em 92% com recorrências que variaram de 2-6 vezes por ano. Geralmente as lesões eram dolorosas (86%), o que nos esclarece o número alto de pacientes submetidos a tratamento tópico (72%). A localização mais prevalente foi à mucosa jugal (56%) e os lábios (54%), como descrito em estudos anteriores[3]. O medicamento mais utilizado foi acetonido de triancinolona a 0,05% (62%), cujos efeitos colaterais não foram descritos pelos pacientes entrevistados, que por outro lado relataram que o seu uso diminuía o período de cicatrização. Nenhum individuo referiu uso de medicação sistêmica.

No que concerne a idade do aparecimento da UAR, encontrou-se uma média de 17,4±8,8, contrastando com a literatura, que mostra uma freqüência média de início da doença bifásica entre 0 e 9 anos e entre 10 e 19 anos[88]. Este achado possivelmente reflete a teoria de que não apenas a condição genética é *sine qua non* para o aparecimento da doença, mas fatores ambientais como o estresse, fumo e a exposição a agentes infecciosos podem interferir no processo etiopatogênico da doença[89]. Em cerca de 80% dos pacientes, a UAR desenvolve-se inicialmente antes dos 30 anos de idade, sugerindo que a manifestação tardia da doença pode estar relacionada a um fator predisponente específico ou com condições sistêmicas mais complexas como a própria Síndrome de Behçet[10].

Nenhum paciente apresentou o teste de patergia positivo. O teste é um fenômeno dinâmico que pode aparecer e desaparecer durante o curso da SB, por isso como apenas um paciente foi diagnosticado com a SB completa, este resultado é condizente com o cenário estudado[90]. O paciente diagnosticado com a SB apresentou UAR do tipo menor e complexa, úlceras genitais recorrentes, manifestações cutâneas (lesões acneiformes e eritema nodoso),

articulares (artrite), oculares (uveíte e ceratoconjutivite), tromboflebites, hipoacusia e febre. Tal como o paciente, na SB as UAR são geralmente do tipo menor, complexas e em maior número[31]. Poucas manifestações sistêmicas foram encontradas nos 50 pacientes com UAR. Dentre elas destacam-se as manifestações cutâneas (10%) com predominância de lesões acneiformes; 18,4% de sintomas neurológicos, em especial a cefaléia (16,3%); além de manifestação gastro-intestinais (10%). Úlcera péptica, gastroduodenite e retocolite ulcerativa foram encontradas em três pacientes respectivamente, sendo que a retocolite é um diagnóstico diferencial importante para a UAR[10].

O presente estudo evidenciou uma prevalência de 2% de SB em indivíduos portadores de UAR com um IC (95%) que variou entre 0,1% e 9,4%. O IC alargado, dentro desse perfil, evidencia que nossa amostra foi pequena para a referida prevalência encontrada e que um novo estudo com uma amostra mais ampla seria necessário para uma melhor precisão dos dados.

Sabendo que a UAR é condição *sine qua non* para o diagnóstico da SB, a baixa freqüência encontrada dentro desse universo amostral, atenua uma grande preocupação dos Reumatologistas e Estomatologista no que concerne o diagnóstico dessa síndrome que mantém uma taxa de mortalidade importante no nosso meio, além de graves seqüelas como as oftalmológicas (cegueira), neurológicas (alterações cognitivas) e vasculares (paresias e plegias). Todavia, um único caso encontrado não discarta, mas enfatiza a necessidade do clínico médico e dentista estar preparado para seu diagnóstico, uma vez que a SB mesmo incomum, é uma realidade clínica.

Estudos com modelo semelhante são raros e com resultados discrepantes. Assim, num estudo realizado em Istambul, Turquia, que é o país de maior

prevalência da SB, foram encontrados 101 casos da SB em 700 pacientes portadores de UAR[7]. Por outro lado, num outro estudo realizado em 7 vilas da zona rural do oeste da Turquia, Cakir *et al.*[54] (2004) observaram que dos 5203 indivíduos participantes (4861 maiores de 10 anos de idade), 124 (2,3%) apresentavam ulceração oral recorrente (UAR), 4/124 obtiveram o teste de patergia positivo e apenas 1 (1:124 - 0,8%) indivíduo completou os critérios de diagnóstico para a SB *(ISGBD)*. Com isso, a prevalência relatada foi de 20:100.000 indivíduos, a mais baixa dentre todos os estudos previamente conduzidos naquele país. Jaber *et al.*[58] (2002), em uma vila árabe de Israel em que 44% dos casamentos são consangüíneos, após avaliarem 4876 indivíduos observaram que 849 (17,4%) apresentavam UAR e apenas 6 (6:849 - 0,7%) adultos preencheram os critérios da *ISGBD* (5 mulheres e 1 homem).

No Brasil não existem dados epidemiológicos sobre a SB, porém, se considerarmos o total da população do distrito estudado (385.109), observamos uma prevalência estimada de 0,259/100.000, o que se assemelha aos dados observados em países como EUA, Inglaterra, Alemanha e Espanha (0,27-20,75/10^5 e 0-0,33/10^5)[36,52]. Vale ressaltar que esse não foi o objetivo primário do estudo e que essa prevalência pode estar subestimada uma vez que nem todos pacientes com UAR procuram atendimento especializado. Adicionalmente, eventuais casos de SB com aftas orais menos sintomáticas, sem preencher os critérios para UAR também não estariam incluídos nesse cálculo. Notadamente, a prevalência da SB pode variar drasticamente tendo em vista um número maior ou menor de descendentes e imigrantes de países de maior prevalência como a própria Turquia. Isso suportaria a hipótese da provável mistura de material genético (freqüência do gene polimórfico HLA-

B51) ou da transferência de um agente exógeno associado. A baixa prevalência encontrada em Salvador-Bahia-Brasil sugere que, mesmo que este seja um pólo turístico importante, desconhecem-se regiões ou bairros onde há isolamento de comunidades oriundas de outros países, principalmente os que compõe a "rota da sêda". Dessa maneira, cidades mais cosmopolitas como São Paulo, onde existem bairros de colonização judaica, japonesa, turca e de outras etnias, podem apresentar uma maior prevalência da SB.

Em conclusão, a observada prevalência de SB em portadores de UAR demonstra a necessidade de outros estudos de base populacional sejam desenvolvidos no nosso meio para que a real prevalência dessa condição seja definitivamente estabelecida, particularmente pela gravidade com que a doença pode se apresentar, mas que o diagnóstico precoce pode mudar o prognóstico de maneira significante.

VIII LIMITAÇÕES E PERSPECTIVAS

VIII. LIMITAÇÕES E PERSPECTIVAS

VIII.1 Limitações

- Este não é um estudo de base-populacional, por isso não podemos inferir a prevalência geral encontrada para toda a população de Salvador-Bahia.
- A prevalência da UAR encontrada em um ambulatório de referência pode ainda estar subdiagnosticada, uma vez que nem todos os pacientes que são portadores de úlceras orais procuram este tipo de atendimento.
- Alguns casos da SB dentre os pacientes portadores de UAR poderiam ter sido também subdiagnosticados, uma vez que a SB apresenta diagnóstico clínico e que alguns pacientes podem apresentar uveítes do tipo crônica e assintomática.

VIII.2 Perspectivas

- Tendo em vista que a prevalência encontrada para a SB teve um IC bastante alargado, um novo estudo com uma amostra mais ampla seria necessário para podemos estabelecer uma frequência mais precisa da SB dentre os portadores de UAR.
- Esta tese de mestrado é o marco inicial de uma linha de pesquisa do departamento de Reumatologia do HSI, cujo propósito é estudar os aspectos clínicos, epidemiológicos, etiopatogênicos e tratamento da SB. O próximo passo é executar o projeto intitulado "Avaliação imunogenética dos pacientes portadores da SB em Salvador-Bahia".

IX CONCLUSÃO

IX. CONCLUSÃO

1. Foi observada uma prevalência baixa para a SB dentre os portadores de UAR atendidos em um ambulatório de referência.

X SUMMARY

X. SUMMARY

Prevalence of Behcet's Syndrome in patients with Recurrent Aphthous Ulcerations in Brazil

Introduction/Objectives. Behcet's Syndrome (BS) is a clinical entity characterized by the appearance of recurrent oral and genital ulcers, in addition to a broad spectrum of clinical manifestations. It has been seen more frequently in countries such as Turkey and Japan, but also in Brazil, although there are no consistent epidemiologic data in our country. The aim of the present study is to evaluate the prevalence of BS in patients with recurrent aphthous ulcerations (RAU), to test the hypothesis that BS could be under diagnosed in our medium. **Material and Methods.** This is a cross-sectional investigation of the prevalence of BS in patients with RAU attended by the Stomatology service of the Bahian School of Medicine and Public Health ("Escola Bahiana de Medicina e Saúde Pública") (Salvador-Bahia-Brazil) between August 2006 and August 2007. The first stage identified the individuals with RAU among all the patients examined at the ambulatory clinic; the second stage carefully examined the patients with to identify the patients with BS. **Results.** Three hundred and six patients were attended at the ambulatory clinic in the study period, but the standard questionnaire was applied to 50 (16.6%) patients, 29 men and 21 women, identified as having RAU. Only one patient met the international criteria for diagnosis of SB [*International Study Group for Behcet´s Disease (ISGBD)*], presenting RAU of the smaller and complex type, recurrent genital ulcers, cutaneous, articular, ocular, and vascular manifestations, hypoacusia and fever, and a prevalence of 2% of BS was defined in this subgroup of patients. **Conclusion.** In Brazil there are no data relative to the prevalence or incidence

of BS, however, the disease has been observed in different regions of the country. In the present study, the frequency of 2% of BS in patients with RAU demonstrates the need for further population-based studies to be developed in our medium, in order to definitively establish the real prevalence of this condition.

Key words: The Behcet's syndrome, recurrent aphthous ulceration, prevalence.

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XII APÊNDICES E ANEXOS

XII.1. APÊNDICE 1 - MODELO DE QUESTIONÁRIO

PROTOCOLO DE INVESTIGAÇÃO CLÍNICA PARA UAR

Protocolo N°.....
Instituição de origem: .....
Nome:.....
Idade..... Sexo..... Cor.....
Data de Nasc..... Profissão.....
Endereço: .....
Tel: .....
Data da entrevista...../...../.....

A) Primeira manifestação:
__Úlceras aftosas orais __Úlceras genitais __ Uveíte ___Vasculite retinal ___Manifestações articulares __ Outras lesões_____

B) Presença de lesões em mucosa oral: Presente(P) e/ou Passado(p)
Região afetada:
__Mucosa jugal __lábios __gengiva __língua __assoalho de língua __orofaringe __palato __vestíbulo
Outros_____

Características das lesões
Tempo do inicio do aparecimento das lesões em meses__
Numero de úlceras/semana __
Tempo médio de duração em dias__
Tamanho em mm na maioria das lesões:__
Dor a palpação: Sim ( ) Não( )
Submetida(s) a tratamento(s) anterior(es)__ Quando _____
Medicamento(s) _____ Duração _____
Efeitos positivos _____
Efeitos negativos _____

C) Presença de lesões em genitália: Presente(P) e/ou Passado(p)
Região afetada:
__Mucosa vaginal __grandes lábios __pequenos lábios __ escroto __ pênis __Virilha __região perianal ____região perineal __Outros (descrever)_____
(locais)_____

Características das lesões
Tempo do inicio do aparecimento das lesões em meses__
Numero de úlceras/semana__
Tempo médio de duração em dias__
Tamanho em mm na maioria das lesões:__
Dor a palpação: Sim ( ) Não( )

D) Manifestações articulares: Presente(P) e/ou Passado(p)
__Artrite __artralgia __simétrica __aditiva __migratória __Monoartrite __Poliartrite
Principais articulações acometidas_____

E) Manifestações cutâneas Presente(P) e/ou Passado(p)
__Eritema nodoso __lesões acneiformes __Patergia __Pioderma gangrenoso __Úlceras

F) Manifestações vasculares: Presente (P) e/ou Passado (p)
__Flebite superficial: Descrever locais_____
__TVP: Descrever número, locais e ano_____
__Aneurismas: Descrever locais e ano_____
__Pulso débil: Descrever local e características_____

G) Manifestações oculares: Presente(P) e/ou Passado(p)
__Uveíte anterior __unilateral __bilateral __Pan uveíte __Vasculite retinal __Catarata
__Conjuntivite números de episódios __
Outros_____

H) Manifestações vestíbulo cocleares: Presente(P) e/ou Passado(p)
__Hipoacusia __Tontura rotatória

I) Manifestações Neurológicas Presente(P) e/ou Passado(p)
__Cefaléia __convulsões __AVC __SNC __SNP
Descrever número e ano_____

J) Manifestações Gastrointestinais: Presente (P) e/ou Passado (p)
__Gastroduodenite __Úlcera péptica __Diarréia __Proctorragia __Dor abdominal __Náusea

K) Outras Manifestações:
a) Manifestações Cardíacas b) Manifestações pulmonares c)Manifestações Renais d)Epididimite e)Hepatoesplenomegalia f)Edema em membros

XII.2. APÊNDICE 2 – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Termo de informação e de consentimento

É importante que você leia com atenção as informações abaixo. Esta folha contém informações sobre o tratamento que você poderá vir a fazer. O responsável pelo estudo discutirá com você e responderá a qualquer dúvida que você possa ter.
Sua participação no estudo é voluntária e você está livre para retirar-se do mesmo a qualquer momento.

Termo de Informação para Participação em Pesquisa

Título da Pesquisa: **Estudo descritivo, transversal da prevalência de síndrome de Behçet em pacientes portadores de UAR.**

Instituição: Hospital Santa Izabel
Endereço: Praça Almeida Couto nº 500, Nazaré. Salvador/Ba.

Investigador Responsável: Dr. Roberto Santos Tunes
Tel: (71) 3245-2717; 9157-7717

Orientador: Mittermayer Barreto Santiago
Tel: (71) 8835-5001; 2203-5276

1. Dados de Identificação do Sujeito da Pesquisa ou Responsável Legal:

Nome:_____

Nº do Documento de Identidade:_____Sexo: M ( ) F ( )

Data de Nascimento: ____/____/____

Endereço:_____

Bairro:_____Cidade: _____Estado:_____

CEP:_____Telefone( )_____

2. Informações sobre a pesquisa científica:

Este documento contém informações sobre esta pesquisa, da qual o Sr(a) poderá participar. Por favor, leia atentamente e, em caso de dúvidas, estaremos à sua disposição para esclarecimentos.

Objetivos da pesquisa:

Esta pesquisa pretende mostrar a proporção de indivíduos portadores de UAR que possuem a síndrome de Behçet.

Benefícios ao paciente:

Melhorar as condições de diagnóstico, principalmente nos ambulatórios de Estomatologia, da síndrome de Behçet.

O que será realizado no paciente:

Será realizada anamnese e um exame clínico completo. O exame também inclui um teste de patergia que consiste na realização de uma punção da pele, no antebraço, com agulha estéril. É um exame rápido que não provoca sofrimento, dano físico ou moral ao Sr(a).

Compensação:

Não há previsão de indenizações ou pagamentos aos pacientes, pois não existirão gastos ou riscos graves relacionados à pesquisa. Os procedimentos realizados farão parte da rotina de investigação e tratamento das doenças pesquisadas. Não há riscos, pois a pesquisa tem um caráter investigatório através apenas da anamnese e exame clínico.

Quando a pesquisa terminar, o Sr(a) continuará sendo atendido neste serviço para o tratamento da doença.

Garantias ao paciente:

Como participante desta pesquisa, o Sr(a) terá acesso aos resultados obtidos e permitirá o acesso dos mesmos aos pesquisadores envolvidos e aos membros da Comissão de Ética. Os resultados deste trabalho poderão ser apresentados em congressos ou publicados em revistas científicas, sendo a identidade do Sr(a) sempre preservada.

O Sr(a) terá acesso, a qualquer tempo, às informações sobre os procedimentos e benefícios da pesquisa. Além disso, o Sr(a) terá direito à privacidade e todas as informações obtidas dos prontuários clínicos e ambulatoriais permanecerão confidenciais, nos âmbitos da lei, assegurando a proteção de sua imagem e identidade.

Está assegurada ao Sr(a) a liberdade de retirar seu consentimento a qualquer momento, e de deixar de participar da pesquisa, sem que isto lhe traga qualquer prejuízo.

Caso seja necessário, o contato com os pesquisadores responsáveis poderá ser feito pelos telefones: Dr. Roberto Santos Tunes (71 – 91577717; 3245-5183); Thiago...

CONSENTIMENTO LIVRE ESCLARECIDO

Declaro que, tendo lido e compreendido o termo de informação e consentimento para a pesquisa, concordo em participar deste estudo. Sei que minha participação é voluntária e que posso interrompê-la a qualquer momento, sem penalidades. Autorizo a utilização dos dados obtidos pelos pesquisadores para a publicação em revistas científicas e apresentação em Congressos.

Recebi uma cópia do termo de informação para participar da pesquisa.

Salvador, _____ de _____ de _____.

_____

Assinatura do Paciente

_____

Assinatura do Pesquisador

XII.3. ANEXO 1 – OFÍCIO DO COMITÊ DE ÉTICA EM PESQUISA (CEP) DO HSI, APROVANDO A INVESTIGAÇÃO.

HOSPITAL SANTA IZABEL
SANTA CASA DE MISERICÓRDIA DA BAHIA

COMITÊ DE ÉTICA EM PESQUISA HOSPITAL SANTA IZABEL

Salvador, 24 de abril de 2006

1. IDENTIFICAÇÃO DO PROJETO

TÍTULO DA PESQUISA: Avaliação da Prevalência da Síndrome de Behçet em Pacientes Portadores de Úlcera Aftosa Recorrente
PESQUISADORA RESPONSÁVEL: Dr. Mittermayer Santiago
CARGO: Médico
INSTITUIÇÃO: Hospital Santa Izabel

2. OBJETIVO PRINCIPAL DO ESTUDO

Avaliar a prevalência de Síndrome de Behçet em portadores de Úlcera Aftosa Recorrente acompanhados num ambulatório de referência

3. PARECER DO(A) RELATOR(A) AD-HOC (Dr. Celso Figueirôa)

Tratando-se de trabalho observacional de corte transversal e de acordo com as normas da Resolução 196/96, este Comitê aprova a realização do referido projeto no Serviço de Reumatologia do Hospital Santa Izabel.

4. PARECER DO CEP

O Comitê de Ética em Pesquisa do Hospital Santa Izabel, acatando o parecer do relator designado para o referido projeto, em uso de suas atribuições, aprova o Projeto de Pesquisa, estando o mesmo de acordo com as Resoluções 196/96 e 251/97.

Cordialmente,

Prof. Dr. Celso Luiz Santiago Figueirôa
Presidente do Comitê de Ética em Pesquisa
Hospital Santa Izabel

Pça Almeida Couto,500 CEP 40050-410 Salvador-BA Tel: (71)326-8444 Fax: (71)326-8494
CGC.15.153.745/0002-49

XIII PRODUTOS DA DISSERTAÇÃO

XIII. PRODUTOS DA DISSERTAÇÃO

1. **Artigo (1)** aceito para publicação pela revista Rheumatology International (Qualis A Internacional CAPES) – **"Prevalence of Behcet's Syndrome in patients with Recurrent Aphthous Ulcerations in Brazil".**

2. **Artigo (2)** aceito para publicação pela revista Reumatology Reviews (Qualis A Internacional CAPES) – **"Behcet's syndrome: Literature Review"**

3. **Artigo (3)** submetido para a revista Rheumatology International (Qualis A Internacional CAPES) – **"Clinical aspects of Behcet´s syndrome in Brazil: a review of 16 cases".**

4. **Artigo (4)** – submetido para a revista Clinical Oral Investigations (Qualis A Internacional CAPES) – **"Clinical and Epidemiological Aspects of Recurrent Aphthous Ulcerations in Brazil: A Cross Sectional Study".**

5. **Artigo (5)** publicado (revista local não indexada) – **"Tunes, R.S.; Santiago, M.B. Síndrome de Behçet: Revisão de Literatura. Juntas/Joints. 1(2); p.40-72, 2007".**

6. Trabalho (pôster) – **"Aspectos Clínicos da Síndrome de Behçet no Brasil: uma série de 12 casos"**, apresentado na XIX Jornada Brasileira de Reumatologia.

7. Apresentação tema livre do projeto **"Avaliação da prevalência da SB em pacientes portadores de UAR: resultados preliminares"** na IV jornada PIBIC/EBMSP.

8. Apresentação tema livre **"Avaliação da prevalência da SB em pacientes portadores de UAR: resultados preliminares"** na V jornada PIBIC/EBMSP.

ARTIGO 1

----- Original Message -----

> Ref.: Ms. No. RHEI-D-08-00103R1
> Prevalence of Behcet's Syndrome in patients with Recurrent Aphthous
> Ulcerations in Brazil
> Rheumatology International (Clinical and Experimental Investigations)
>
> Dear Prof. Santiago,
>
> I am pleased to tell you that your work has now been accepted for
> publication in Rheumatology International (Clinical and Experimental
> Investigations).
>
> It was accepted on 05-08-2008.
>
> Thank you for submitting your work to this journal.
>
> With kind regards
>
> Monika Suschka
> Managing Editor (Editorial Office)
> Rheumatology International (Clinical and Experimental Investigations)

Prevalence of Behcet's Syndrome in patients with Recurrent Aphthous Ulcerations in Brazil

Roberto S. Tunes (1)

Tiago C. Anjos(2)

Gabriela B. Martins (3)

Enio R. M. Barreto (4)

Mittermayer B. Santiago (5)

1. Master's Course Student at the Fundação Bahiana para o Desenvolvimento das Ciências (FBDC), Salvador, Brazil.
2. Undergraduate Student at the Dentistry Course of the FBDC, Salvador, Brazil.
3. Adjunct Professor of the Dentistry Course of the FBDC, Salvador, Brazil.
4. Head of the Dermatology Service of Hospital Santa Izabel; Adjunct Professor at the Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, Brazil.
5. Head of the Rheumatology Service of Hospital Santa Izabel; Adjunct Professor at the EBMSP, Salvador, Brazil.

Correspondence: Mittermayer B Santiago. Praça Conselheiro Almeida Couto, 500, Nazaré, Salvador, CEP: 40000-000, Bahia, Brazil, Telephone (fax): +55 71 3326-5276, mitter@svn.com.br.

Summary

Introduction/Objective: Behcet's Syndrome (BS) is a clinical entity characterized by the appearance of recurrent oral and genital ulcers, in addition to a broad spectrum of clinical manifestations. The aim of the present study is to evaluate the prevalence of BS in patients with recurrent aphthous ulcerations (RAU) and to test the hypothesis that BS could be under diagnosed in Brazil. *Materials and Methods*: This is a cross-sectional investigation of the prevalence of BS based on the International Study Group for Behcet´s Disease (ISGBD) criteria in patients with RAU attended in a stomatology service. *Results:* Three hundred and six patients were attended at the ambulatory clinic in the study period, but the standard questionnaire was applied to 50 (16.6%) patients, 29 men and 21 women, identified as having RAU. Only one patient met the ISGBD criteria presenting RAU of the minor and complex type, recurrent genital ulcers, cutaneous, articular, ocular, and vascular manifestations, hypoacusia and fever. Thus, a prevalence of 2% of BS was defined in this subgroup of patients. *Conclusion.* In the present study, the frequency of 2% of BS in patients with RAU demonstrates the need for further population-based studies to be developed in order to definitively establish the real prevalence of this condition.

Key words: Behcet Syndrome; recurrent aphthous ulceration; prevalence.

Introduction

Recurrent aphthous ulceration (RAU), also called aphthous stomatitis, is an inflammatory disease of the oral mucosa, whose prevalence in the world population is around 5-25%, attaining up to 60% in specific groups (Ship, 1972; Scully *et al.*, 2002). The disorder is characterized by the appearance of painful and recurrent single or multiple ulcerations that preferentially affect the non-keratinized oral mucosa (Rogers, 1997a). Important considerations must be pointed out with regard to the differential diagnosis, which includes the complex aphthous stomatitis and variants related to systemic manifestations, such as those associated with hematologic, hormonal, nutritional and gastro-intestinal alterations (Rogers, 1997b). In view of these factors, the clinician needs to be prepared, by means of an anamnesis and a well elaborated clinical exam, to diagnose the clinical conditions that involve RAU and other systems, such as the Behcet syndrome (BS) (Rogers, 1997a).

BS is an inflammatory, complex and multisystemic condition, classically characterized by recurrent oral ulcerations, genital ulcerations and ophthalmologic alterations, but which can affect any system, including the muscle-skeletal, vascular, neurological, respiratory and gastrointestinal system (Marshall, 2004). Its pathogenesis remains uncertain, but epidemiological data suggest an interaction among genetic, immunologic and infectious factors (Gul, 2001). It has a universal geographic distribution, although it is more frequent in the Mediterranean area, Japan and the Middle East, attaining up to 420 cases per 100 thousand inhabitants (Azizlerli *et al.*, 2003). In view of the high prevalence of 90-100% of aphthous stomatitis in patients with BS and the nonexistence of substantial data in the literature, with regard to the real

prevalence and incidence of this syndrome in Brazil, this pioneering study evaluates the prevalence of BS in patients with RAU, followed up in a specialized ambulatory clinic of a university institution.

Materials and Methods

This study is a cross-sectional investigation on the prevalence of BS in patients with RAU attended in the Stomatology service of the Escola Bahiana de Medicina e Saúde Pública, Salvador-Bahia-Brazil between August 2006 and August 2007. This is a reference Stomatology service in a district with 385.109 inhabitants. The study was conducted in two stages: The first stage identified the individuals with RAU among all the patients examined at the ambulatory clinic; the second stage carefully examined the patients with RAU with the purpose of defining patients with BS.

The estimated sample size was 45 patients with RAU, and an expected prevalence of 3% of patients with BS was evaluated, with a confidence interval of 95% and a level of precision of 5%. This estimate was based on studies conducted in Turkey, in which frequencies of BS in patients with RAU between 0.8 and 14% were observed (Azizlerli *et al.*, 2003; Cakir *et al.*, 2004). In the first stage of the research, for each patient in the sample, a standard chart containing 26 questions was filled out, stating the patient's identification data and the systemic conditions related to BS. With regard to clinical features, the number, location and size of the oral ulceration as well as the age at disease onset, time of development, number of episodes per year, time between episodes in months, associated symptomatology and treatment were noted.

Data collection was done by interview and complemented with data collected on the case history chart.

Included in the study were patients that presented the minor type of RAU, major or herpetiform type, with up to two days of development, with two or more episodes over the last twelve months. After the presence of RAU was confirmed, the patients were submitted to the pathergy test performed by the same investigator (MacCormack and Phillips, 2007). Afterwards, all the individuals with RAU were evaluated with regard to the criteria of the International Study Group for Behcet´s Disease (ISGBD) (ISGBD, 1992).

The study was submitted to and approved by the research ethics committee of Santa Izabel Hospital (Salvador-Bahia), and all the patients signed the term of free and informed consent.

Results

During the study period, 306 patients were attended in the Stomatology service, of whom only 50 (16.6%) presented with RAU, and replied to the standard questionnaire in the first stage of the study. Of these 50 individuals, 29 (58%) of were men and 21 (42%) were women. Their ages ranged between 11 and 55 years (mean 26.2 ± 9.8 years). The mean age at the time of the first manifestation of RAU was 17.4 ± 8.8 years. While the protocol was being performed, no individual presented a positive pathergy test. Only one patient met the criteria for the diagnosis of BS. The patient was a 35-year old man, presenting RAU, recurrent genital ulcers, cutaneous, ocular, and vascular manifestations and fever. Thus a prevalence of 2% (95% CI, 0.1%-9.4%) of BS in patients with RAU was established, and considering the total population of

the studied district (385 109), the estimated prevalence of BS was 0.259/100 000 (95% CI, 0.2-0.4/100 000).

Although without fulfilling the criteria for classification of BS, some patients with RAU presented systemic manifestations, such as those seen in BS. Therefore, 18.4% complained of neurological symptoms, particularly headaches, 10% presented cutaneous manifestations with a predominance of acneiform lesions, 6% presented some articular manifestation and vertigo was observed in 4% of the patients.

Discussion

The present study evidenced a prevalence of 2% (95% CI, 0.1%-9.4%) of BS in individuals with RAU. Studies with a similar model are rare, and have discrepant results. Therefore, in a study conducted in Istanbul, Turkey, the country with the highest prevalence of BS, 101 cases of BS were found in 700 patients with RAU (Azizlerli *et al.*, 2003). On the other hand, in another study conducted in 7 villages in the rural zone in the west of Turkey, Cakir *et al.* (2004) observed that of the 5203 participant individuals (4861 over the age of 10 years), 124 (2.3%) presented with recurrent oral ulceration (ROU), 4/124 obtained a positive pathergy test and only 1 (1:124 – 0.8%) individual completed the diagnostic criteria for BS (ISGBD). Thus, the reported prevalence was 20:100 000 individuals, the lowest among all the studies previously conducted in that country. Jaber *et al.* (2002), in an Arab village in Israel, in which 44% of marriages are consanguineous, after evaluating 4876 individuals, they observed that 849 (17.4%) presented RAU and only 6 (6:849 – 0.7%) adults me the ISGBD criteria (5 women and 1 man).

In Brazil there are no epidemiological data about BS, but if we consider the total population of the studied district (385 109), we observe an estimated prevalence of 0.259/100 000, which is similar to the data observed in countries such as the USA, England, Germany and Spain (0.27-20.75/100 000 and 0-0.33/100 000) (Zouboulis *et al.*, 1997; Zouboulis, 1999). It is worth pointing out that this was not the primary objective of the study and that this prevalence could be underestimated, since not all the patients with RAU sought specialized attendance. Furthermore, eventual cases of BS with less symptomatic oral aphthae, without meeting the criteria for RAU are also not included in this calculation.

In conclusion, the observed prevalence of BS in patients with RAU demonstrates the need for further population-based studies to be developed in Brazil in order to definitively establish the real prevalence of this condition, particularly because of the severity with which the disease can present, but that early diagnosis could significantly change the prognosis.

Ethical aspects

The study was submitted to and approved by the research ethics committee of Santa Izabel Hospital (Salvador-Bahia), and all the patients signed the term of free and informed consent.

Conflicts of interest

Roberto Santos Tunes: none.

Thiago C. Anjos: none.

Gabriela B. Martins: none.

Enio Ribeiro Maynard Barreto: none.

Mittermayer B. Santiago: none.

Authors' contributions

Roberto S. Tunes designed the study, collected the data and wrote the manuscript.

Thiago C. Anjos participated in data collection.

Gabriela B. Martins participated in data collection.

Enio R. M. Barreto participated in the study designed.

Mittermayer B. Santiago coordinated the study and revised and submitted the final version of the manuscript.

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ARTIGO 2

----- Original Message -----
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Manuscript Title: Behcets syndrome Literature Review

Dear Dr. Santiago

Thank you very much for submission of your manuscript. I send it to reviewers. I will contact you soon,
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Dr. Mittermayer Santiago, please view comments for **158505 Behcets syndrome Literature Review**.

Comment Date	12-NOV-07
Originality	Good
Technical quality	Good
Importance in its field	Fair
Over all the paper is	Fair
Recommendations	Accept as it is with minor changes
Comments	1 It is a nice review article for Behcets syndrome but seems too long to digest. For instance, the Epidemiology part seems talking too much. It can be concised.2 Readers may be more interesting whats the differences in many aspects of Behcets syndrome between Western patients and Eastern patients What are important factors to influence the different results in different ethnic groups.3 Regarding the etiology and pathogenesis, it is better to add one or two Fogurss to list the contributing factors.4 In order to understand easily about the frequency of oral, genital, skin and eye involvement in different races people. It is better to give a few Tables.

Behcet's syndrome: Literature Review

Roberto Tunes (1)

Mittermayer Santiago (2)

Master's Course Student in Medicine and Human Health of the Fundação Bahiana para o Desenvolvimento das Ciências

Head of the Rheumatology Service of Hospital Santa Izabel; Adjunct Professor at the Escola Bahiana de Medicina e Saúde Pública-Salvador– Bahia – Brazil.

Correspondence: Mittermayer B Santiago. Praça Conselheiro Almeida Couto, 500, Nazaré, Salvador, CEP: 40000-000, Bahia, Brasil, telefone (fax): (71) 3326-5276, mitter@svn.com.br.

Abstract

Behcet's syndrome (BS) is a multisystemic inflammatory disorder characterized by recurrent oral and genital ulcers and ophthalmic alterations, but also involving other systems, including joints, blood vessels, nervous, respiratory and gastrointestinal tracts. Its etiopathogenesis remains unknown, but epidemiologic data suggest an interaction among genetic, immunologic and infectious factors. BS has a worldwide distribution being most frequently seen in the Mediterranean area, Japan and Middle East. In Brazil there are no substantial data regarding its prevalence or incidence. The aim of the present study was to review the main epidemiologic data, clinical features, diagnostic criteria and current treatment of BS.

Key words: Behcet's syndrome;.epidemiology; pathogenesis; treatment

Introduction

Behcet's Syndrome (BS) is a multisystemic, chronic disorder, characterized by oral and genital aphthous ulcers, arthritis, cutaneous lesions, ocular, gastrointestinal and neurological manifestations. Also classified as a systemic vasculitis, BS can involve the arteries and veins of any organ.(1) It was described for the first time by the Greek ophthalmologist Benedict Adamantiades in 1931, but it was in 1937 that the Turkish dermatologist Hulusi Behcet made a complete description of the disease, recognizing the systemic nature of the disease and establishing the classical triade composed of recurrent aphthous oral ulcers, genital ulcers and hypopyon uveitis.(2, 3) Nevertheless, since his initial description, the concept of BS has been expanded and at present, it is known that the disease can affect any system.(4)

The etiology of this syndrome remains obscure, but the hypothesis most commonly accepted in the literature for its pathogenesis is established when a profound inflammatory response is deflagrated by an infectious agent in a genetically susceptible host.(5, 6)

BS has a distinct geographic distribution, with high incidences in Mediterranean countries and Japan, with Turkey presenting the highest prevalences, attaining up to 420 cases per 100 thousand inhabitants.(7, 8) It is rarer in northern Europe, North of Asia, the African continent not bathed by the Mediterranean sea, and the Americas.(2, 9, 10) BS more frequently affects young patients (15 – 45 years of age) occurring equally in men and women, although it seems that the prognosis is worse in men.(10, 11) In Brazil, Aguiar *et al.*(12) in a retrospective study with 22 patients with BS, found a man/woman ratio of 1:3.4, whereas Coimbra *et al.*(13) and Vitral *et al.*(14) demonstrated a greater prevalence in men with BS, with ratios of 2:1 and 1.5:1, respectively.

The disease most commonly presents in the form of recurrent attacks of acute inflammation.(5) The main morbidity of the syndrome is blindness that develops after

repeated attacks of ocular inflammation. Involvement of the central nervous system (CNS) and large vessels can be serious, leading to the patient's death.(15-18) Moreover, an increased risk for cancer has been observed, associated with collagen diseases and new cases of malignant neoplasias related to BS have been related.(19) The development of diagnostic tests and the recognition of prognostic factors have allowed the international medical community to arouse greater interest in the syndrome, particularly with the introduction of therapeutic measures that would diminish the rate of co-morbidities and lethality of the disease.(20, 21) Therefore, the latest studies are focused on elucidating the etiopathogenesis of the disease and establishing a more efficient therapeutic strategy.

Epidemiology

As mentioned above, BS has a higher prevalence and incidence between the Mediterranean area and East of Asia, in a historic trading region called the "silk route".(22) This term, widely used by medical literature, according to Ohno *et al.*(23), possibly reflects a genetic predisposition to the disease, which spread among the tribes and traders that traveled between the Arab world and the East. Verity *et al.*(24) corroborated these findings when they compared the world distribution of HLA-B51 and the migration of *Homo sapiens* between 300,000 and 10,000 years ago. However, these authors showed that the high prevalence of the gene HLA-B51 in certain regions of the globe, as in America itself (prevalence of 11.1% of HLA-B51 in Amazonia), may not be exclusively related to a high incidence of BS. This evidences the multifactorial characteristic of BS and a possible influence of environmental factors on the epidemiologic reality of the disease.

When a geographic correlation is established with the prevalence of BS in the countries in which data are available, it is found that there is a relation between the latitude and

prevalence of the disease (Table 1).(24) Therefore, in patients with the same ethnical origin, the prevalence of the syndrome also appears to be strongly related to latitude and longitude. Prevalence in the Turkish population diminishes with the increase in the distance of the East of Turkey in the Western direction. On the other hand, in Japan, the prevalence has a tendency to diminish when one moves from north to south, attaining zero in Japanese living in the United States of America (USA) and Hawaii.(25) In Brazil, few patients of Japanese origin have been reported to have BS.(26)

According to Azizlerli *et al.*(8), Turkey is the country that has the highest world prevalence of BS, with a ratio that extends to 20-420/100,000 inhabitants. In a study conducted in Istanbul (the largest and most cosmopolitan city in Turkey) 101 cases of BS were found for 23,986 individuals, evidencing a prevalence of 42/10,000 inhabitants. This discrepancy of prevalence among the different regions of Turkey could be explained by the ethnic and racial diversity of the region, in addition to more or less access to medical care among these communities. Immigration and emigration, particularly in countries with higher prevalence and incidence, would support the hypothesis of the probable mixture of genetic material or transfer of an associated exogenous agent, which would be related to the growing expansion of BS in the present day world.(9)

In 1981, Dimirhindi *et al.*(27), conducting the first study of BS prevalence in Turkey, by means of a sample of 4940 inhabitants in 9 villages, found a prevalence of 80/100,000. Next, Yurdakul *et al.*(7) assessed 5131 inhabitants, over the age of 10 years, from a village in the North of Turkey, and evidenced a prevalence of 38/10,000, similar to the most recent study of Azizlerli *et al.(9)* The authors also described a higher prevalence of HLA-B5 in hospitalized patients with BS.

Idil *et al.*(28), in a population based prevalence study in Ankara in Turkey, showed a prevalence of 0.11%, that is, 16 patients out of the 17256 participants had BS, 11 being women and 5 men (woman/man = 2.2:1). Nine patients out of the 16 had previously been diagnosed and 5 were diagnosed during the research. The authors mentioned that although a lower prevalence was observed in the region in comparison with previous studies, it is possible that there are many subdiagnosed cases of the disease, which indicates a much higher number of BS cases in Turkey.

In another study conducted in 7 villages in the rural zone in the east of Turkey, Cakir *et al.*(29) observed that the 5203 participant individuals (4861 over the age of 10 years), 124 (2.3%) presented with recurrent oral ulceration (ROU), 4/124 showed a positive pathergy test and only 1 (0.02%) individual fulfilled the criteria of the *International Study Group for Behcet's Disease (ISGBD)*. Thus, the reported prevalence was 20/100,000 individuals, the lowest among all the studies previously conducted in that country.

The country with the second highest prevalence of BS is Japan, with a prevalence that ranges from 0.99 to 30.5/100,000 inhabitants. The highest prevalence in that country was found in the Hokkaido region, where there were 30.5 cases per 100 thousand persons, while the lowest prevalence was found in the Kyushu region with 0.99/100,000.(30) More recent data suggest an estimate that there are 16.750 individuals with the disease in Japan, evidencing a prevalence of 13.5/100.000.(31)

In addition to Turkey and Japan, South Korea is also a "silk route" country with an extremely high prevalence, as demonstrated by Bang *et al.*(32) in a retrospective multicentric study. The authors analyzed epidemiologic data in 20 hospitals between 1997 and 1999, finding 382 cases of BS in a sample of 3497 patients. Thus, the authors demonstrated an exceptional prevalence of 10.9%. However, Davatchi *et al.*(33), in their

2005 review, related that the Korean data are hardly consistent, and do not represent the exactness of the epidemiologic scenario in that country.

Countries such as Switzerland, Great Britain, Germany, Portugal, Spain, Poland, Italy and the USA (Hawaii) have a prevalence between 0-2.5/100,000, while in the North of China, Iran and Saudi Arabia, that are other countries that compose the "silk route", it ranges between 13.5 to 20 cases per 100 thousand inhabitants, an intermediate frequency, when compared with Turkey and Japan (Table 1).(9, 10, 32, 34) It is worth pointing out that in some regions of countries where the disease is rare, the prevalence may be high, due to the larger number of descendants and immigrants from countries of higher prevalence, such as Turkey itself.(9, 10, 35)

In a prevalence study in an Arab village in Israel, in which 44% of the marriages are consanguineous, the authors observed a prevalence of 12/10,000 after assessing 4876 individuals. This study followed an almost strict methodology for describing the prevalence of BS, based on seeking patients with ROU. Of all the participants assessed, 849 presented ROU and only 6 adults met the *ISGBD* criteria (5 women and 1 man).(36) Krause *et al.*(37) observed a considerably lower prevalence in the North of Israel of 15.2/100,000. Notably, in this study the authors related an even higher prevalence of 26.2/100,000 in the Arabian community and of 146.4/100,000 for an Islamic community in Israel (the Druzes).(37) Thus, it is observed that BS is markedly prevalent in Israel, but that the prevalence rate may vary sharply among the different regions of the country.

As previously described, the opposite can also occur when, for example, in China – a country that is part of the "silk route" – there is a contradiction in the prevalence rates between the northern and southern regions. In Hong Kong, a southern city, in a 22-year study that assessed the prevalence of BS in the four largest hospitals in the city, it was observed that of a population base of 1.41 million inhabitants, only 37 patients

completed the *ISGBD* criteria, estimating a prevalence of 2.62/100,000. According to the authors, this low prevalence could be related to an uncommon association with another gene (MIC) or subtypes of HLA not yet demonstrated.(38)

In this same context, emphasizing intermediate prevalence values, Zouboulis *et al.*(9), initially assessing 218 patients catalogued in the German BS register, observed that the prevalence increased in West Berlin from 0.65/100,000 in 1984 to 2.26/100,000 in 1994. Furthermore, the authors evidenced an important discrepancy in prevalence among the different regions of various colonizations in Germany, showing that the frequency ranged from 0.55/100,000 in regions of German origin to 20.7/100,000 in regions of Turkish origin. These differences also corroborate the ethnic influence on the expression of severity of the disease, as described in the work of Krause *et al.*(39).

Among the low prevalence countries, a study conducted in the north east of Spain, found a prevalence of 0.66/100,000, with reference to 16 patients (9 men and 7 women) that met the *ISGBD* criteria, and who were attended at a reference hospital from 1988 to 1997.(34) Graña *et al.*(40) then published a study reassessing the prevalence of BS in Galicia, finding a rate of 10.8 per 100 thousand inhabitants. In this study, the authors based themselves on previous studies conducted in La Coruna (city of Galicia), where they showed an annual incidence of 0.32/100,000 in women, and 0.53/100.000 in men.

Up to now, no BS prevalence study has been conducted in Brazil, however, some descriptive studies were able to show data with reference to the frequency of the disease in reference ambulatory care centers.(26, 41-43) Among them, Barra *et al.*(26), in a well conducted study, widely mentioned in international literature, found 49 patients (2%) with BS among 2500 uveitis cases attended during a period of 16 years in the ophthalmology department of a medical school. Gouveia *et al.*(44), assessing the causes of uveitis in a tertiary service in Sao Paulo, mentioned that in the period between

February and August 2002, of the 262 patient record cards of the uveitis service from another teaching hospital, 26 (10%) patients presented with BS, representing the 2nd ranked cause of uveitis among the non-infectious causes, falling behind only the Vogt-Koyanagi-Harada Syndrome (13%). Curiously enough, in another study from the same center, Gomi *et al.*(43) observed that of the 414 patients between the ages of 17 and 40 year assessed, 63% manifested diffuse uveitis, BS being the most frequent etiology (36%). It is however, pointed out that these studies, did not utilize the validated diagnosis criteria for BS in their methodologies, thus exposing hardly reliable data in their results.

As regards the age of BS onset, it is observed that it predominantly affects young adults, with a mean onset age of between 20 and 40 years, however, extreme cases have been related with onset in the eighth decade of life, as well as in newborns.(38, 45) The country where the disease has the highest mean onset age is Japan (43.2 years) followed by Turkey (38.32 years), China (36 years), Singapore (33 years) and South Korea (29 years), all being countries part of the "silk route".(11, 46) In Europe, countries such as Ireland, Russia, England, Spain, Portugal, Italy and Greece have a mean age of disease onset ranging from 20.8 to 29 years. Sweden and Poland being the European countries with the highest means (33 and 37 years).(9, 10) In Brazil, the mean age of disease onset ranges between 17.5 and 33.5 years.(12-14, 26, 47, 48) Furthermore, the literature emphasizes the biphasic nature of the disease distribution, when the majority of patients present symptoms between 20 and 30 years and between 40 and 50 years.(49) Thus, the symptoms may appear at any age, but in the majority of cases onset occurs in around the third decade of life, and usually, the disease develops in around the first 15 months after the first manifestation.(2) On the other hand, Scherrer and Orefice observed that in Brazil, diagnosis is made around 5 years (mean) after disease onset.(47)

With regard to gender, it is observed that men are more affected by BS, especially in countries like Turkey [man:woman (M:W) – 2.2:1], Israel (M:W - 5:1), Germany (M:W – 3.7:1), Lebanon (M:W – 2.9:1) and India (M:W – 1.76:1).(8, 16, 25, 39, 50) Countries such as Russia, Sweden, Scotland and England present a distribution ratio of (M:W) ranging from 0.36 to 0.96:1.(25) In Brazil, there are studies that show a higher prevalence ratio among women, ranging from 1.5 to 3.4:1 (12-14, 48), while others observed a M:W distribution ratio of 1.6 to 2.4:1(26, 47). At present the majority of epidemiologic studies and case series point towards similar proportions between the sexes, including in part of the above-mentioned countries.(25)

As BS does not follow the laws of Mendel, and the non detection of an exclusive genetic alteration, the number of familial cases described in literature is low (1-18%).(2) Familial BS is uncommon in Caucasians, but a positive family history is observed in over 12% of non-Caucasian patients; moreover, in a descriptive study in Turkey, the relative risk for the occurrence between twins ranged from 11.4 to 52.5, suggesting a possible important genetic component, as has been observed in complex genetic diseases, including inflammatory intestinal diseases.(1) It is intriguing that familial occurrence in Koreans (15.4%) is much more frequent than in families of Chinese or Japanese origin (2.2-2.6%). Patients of Arabian, Jewish or Turkish origin present higher familial frequencies (2-18.2%) than European patients do (0-4.5%). It is pointed out that young patients present a higher familial occurrence when compared with adults: 16% *versus* 2% in Morocco, 18% *versus* 2% in France and 25% *versus* 8% in Germany.(25)

Etiology and Pathogenesis

The etiology of BS remains uncertain, however it is admitted that its pathogenesis is mediated by a combination of factors involving immune deregulation, inflammatory mediators and infectious agents, such as the herpes virus and *Streptococcus spp.*(5)

Infectious Agents

The geographic distribution and the different manifestations of the syndrome favor an infectious cause of BS. However, no microorganism was reproductively isolated from lesions in patients with BS, rather corroborating that these pathogens function as a trigger factor instead of an etiologic agent of the syndrome itself.(5, 51, 52)

A viral etiology was suggested for BS in its first publications, particular attention being given to the herpes simplex virus type 1 (HSV-1). The HSV-1 genome has been identified in lymphocytes and monocytes, by hybridization in the peripheral blood of patients with BS. Seric antibodies against HSV-1 were found in high proportion in patients with BS and not in healthy controls.(53) A DNA fragment of the herpes simplex type 1 virus (HSV-1), was found in peripheral blood lymphocytes and in genital and oral ulcer biopsies, using the polymerase chain reaction (PCR) technique. The DNA protein 289bp and 211bp was also detected in these lesions, but not in controls.(53, 54) Furthermore, the same findings were also observed in intestinal ulcers and in the saliva of BS patients, who also obtained beneficial results with the use of aciclovir.(51) Thirty per cent of mice inoculated with HSV were reported as having manifestations similar to those of BS, with genital ulcers, cutaneous and ocular lesions.(55)

Nevertheless, immunity with the presence of anti-HSV is common in healthy persons, and the benefit of antiviral treatments in BS is still controversial.(56)

BS "starts" through the oral mucosas (ROU is the first manifestation of BS in over 90% of patients), however it would not be uncommon to presuppose that the oral microbiota could be implicated in the pathogenesis of BS.(1, 56)

Clinical observations such as, increase in oral manifestations in BS soon after dental treatment, high incidence of dental caries and tonsillitis, caused by *Streptococcus spp*,

hypersensitivity after cutaneous tests with *Streptococcus spp*, dominance of atypical Streptococcus in the oral microbiota, in addition to the benefit of antibacterial treatment, suggest an important etiologic role of these bacteria in BS. *Streptococcus sanguis* and *S. oralis* can be found in the oral microbiota of BS patients in high concentrations, and could contribute to ROU, constituting a possible trigger factor for the disease.(57) Moreover, Mumcu *et al.*(58) suggested that oral health was linked to the severity of BS.

Other infectious agents could be related to BS, such as the hepatitis virus, parvovirus B19; some bacteria, including mycobacteria, *Borrelia burgdorferi*, *Escherichia coli*, *Helicobacter pylori;* and more recently even the *Saccharomyces cerevisiae* fungus, being found in a sample of 48.1% of BS patients.(1, 59)

The pathogenesis of the infectious cause occurs when an immunological reaction is deflagrated by an infectious agent, particularly by molecular mimetism. The HSP proteins (*heat shock proteins*), especially HSP 60/65 kD (HSP 65), are possible candidates for antigens in BS. Various immunologic mechanisms are related in the literature describing the relationship of HSPs in infection (tuberculosis and *chlamydia*), in autoimmune diseases (rheumatoid arthritis and multiple sclerosis) as well as in malignant and vascular disorders (atherosclerosis).(52, 60)

The systemic immunologic reactivity to HSPs among mammals and some bacteria is similar. Over 90% homology is observed for HSP65s between mycobacteria and *Streptococcus spp*; and around 50% homology between HSP65 of mycobacteria and human HSP60 in BS. Four peptides of mycobacteria HSP65-kD (111-125, 154-172, 219-233, 311-325) and their peptides of homologous human HSP60-kD (136-150, 179-197, 224-258, 336-351) were identified in epitopes by T cell mapping in British BS patients. An increase in the response of T cells against these peptides was later verified in

Japanese and Turkish BS patients. It is postulated that this homology could indicate autoimmune reactions, which would attempt to explain the complexity of the etiopathogenesis of BS.(5, 56)

Increased T and B cell activity against HSP 60/65-kD is observed in different populations with BS, involving T cells type αβ and γδ. It is pointed out that Tγδ lymphocytes, in specific situations such as in mucocutaneous disease and neurological involvement, constitute 60% of the circulating peripheral lymphocytes. Although this specific response is still not clear, some animal models inoculated with HSP peptides, either orally or subcutaneously, developed uveitis, suggesting an important role of the HSPs in the immunopathogenesis of BS. Recent studies on innate system in BS described the role of the TLR receptors (Toll Like Receptors) and HSP60 as ligand to TRL-2 and TLR-4, suggesting that HSP60 would be a dangerous endogenous signal to the immune system, favoring the rapid release of inflammatory cytokines, intensifying an adaptive response of the Th-1 type. Activation of both the innate and adaptive responses by HSPs fits perfectly in a clinical spectrum of BS with both early and limited responses (ROU, pathergy, etc) and chronic responses (posterior uveitis, thrombosis, neuro-Behcet, etc).(60)

Thus, the idea of only one etiologic agent for BS seems to be unjustified as all these studies point to a state of hyper-reactivity to common antigens in the environment.(61)

Genetic Factors

The onset of BS is probably triggered by some environmental factors affecting genetically predisposed individuals, as a multifactorial disease.(51) It is well evidenced in the literature that BS is associated with the allele HLA-B*51 (chromosome 6p21), which is relatively frequent (45%-70%) in many ethnic groups, including countries adjacent to the ancient "silk route", such as Turkey, Iraq, Israel, Greece, Italy, Spain, China, Japan and Korea.(62-67) As has been described, the frequency of HLA-B51 varies

a great deal among these countries. Thus, the relative risk varies greatly among studies. A relative risk was found for BS in HLA-B51 carriers, of 11.5 in Italy, 6.7 in Japan, 6.2 in Turkey, 3.51 in Iran and 1.3 in the USA.(64-66, 68) The literature also shows that the allele HLA-B*5101 (one among the 34 allelic variables of the gene HLA-B*51) was always found in the majority of patients, showing predisposition, particularly in men, to more serious disease, such as uveitis and erythema nodosum.(7, 62, 66) Thus, the positivity of the allele HLA-B51 would be related to a more complete and serious expression of the syndrome.(69) According to Verity *et al.*(24), in Brazil the prevalence of the allele HLA-B51 is of 11.1% in the North of the country, which could be justified by the ancient trade routes that ran along the same latitudes, facilitating the distribution of the haplotype through these regions. Curiously, Vitral *et al.*(14) found a higher frequency of HLA-B51 in the southeast of Brazil, in BS than in the control (56.4% against 2.6%) with specificity of 97%. Also in the southeast, Barra *et al.*(26) and Scherrer and Óréfice(47) found a frequency of 45.5% and 66.6%, respectively, for the gene HLA-B51.

The importance of the specific peptides of HLA-B51 and their restricted link to T CD-8 cells in the pathogenesis of BS is still unknown; however, it would appear that this association could be important in the activation of neutrophils. Possibly, HLA-B51 presents an endogenous antigen to cytotoxic lymphocytes, activating a cascade of cytokines, causing the release of superoxide from neutrophils not primarily lesioned.(56)

Other genes such as MICA (alleles A6 and A9), PERB, ORC, NOB and TNF-1031C (all located close to HLA-B) are also shown as probable predisposers for BS. The MICA gene is located at around 46Kb centromers from the gene HLA-B and marks high susceptibility to BS.(70) Mizuki and Ohno were the first to associate this haplotype of

the genes MICA (HLA class I), TNF-α and the region of HLA-B, in chromosome 6, with BS.(71) Other studies disagreed with this association because of observing a low heterogeneity of the gene MICA, in addition to linkage disequilibrium between the two genes: MICA and HLA-B51. On the other hand, there is growing evidence that the gene MIC is responsible for stimulating Tγδ lymphocytes and NK cells, ranking it as the second most relevant gene for BS.(5, 56)

Therefore, it is important to emphasize that the two genes HLA-B51 and MICA, both in conjunction and in isolation, may in some way contribute to the pathogenesis of the syndrome.

Polymorphism in other genes located outside of the haplotype HLA may be candidates for other susceptible loci in the chromosome 6p, including the coagulation factor V, intercellular adhesion molecule -1 (ICAM-1469E), HLA-DRw8, HLA-DRB1 and the endothelial nitric oxide synthase factor (E-NOS). These genes could help both to elucidate the pathogenesis of BS and have important therapeutic implications.(1, 2, 65, 72)

Immunologic factors

There are various immunologic alterations described in the literature, which could corroborate the etiopathogenic process of BS. Among them are: the presence of circulating immune complexes (IC); serum elevation of complement molecules and acute phase proteins; presence of autoantibodies of the oral mucosa; cytotoxic effect of lymphocytes in the oral mucosa; cutaneous hypersensitivity of the retarded type; exacerbated production of certain cytokines; diminished chemotaxis; transformation of peripheral lymphocytes; increase in number of T CD-4, T CD-8 and Tγδ cells; increase in activation of circulating memory T lymphocytes; increase in the seric concentrations of soluble CD-8 and CD-25; deficient activation of peripheral NK cells; and even

polyclonal activation of B lymphocytes.(73) However, basically 4 mechanisms are proposed as etiopathogenic model for the disease. In a first model, Gül(5) explains the importance of the nonspecific inflammatory response in BS, particularly when an increase in the responsiveness to small traumas or stimuli is observed (the pathergy test would be a classical example). This response is verified predominantly in the active stage of the disease, both by an increase in proinflammatory cytokines secretion (IL-6, TNF-α and IL-8), and neutrophilic activation, with an increase in their chemotaxis and generation of superoxides, stimulation of IL-12 and IL-18, in addition to an increase in the expression of adhesion molecules.

The other model proposed, and the one most studied, is that an endogenous antigen (HSP-60) or an exogenous antigen (HSP-65), derived from some virus or bacteria, would be recognized by macrophages in the context of HLA-B51 (Class I). This would stimulate the Th1 cells that would produce cytokines (IL-2, IL-12, IL-18, and TNF-α), which could be directly damaging as well as being able to stimulate chemotaxis and activation of neutrophils. These activated neutrophils would be capable of producing high concentrations of proinflammatory cytokines and superoxides responsible for the endothelial lesion (TNF- α, IL-1β), in addition to stimulating themselves via autocrine (TNF- α, IL-6 and IL-8), reinitiating the inflammatory cycle in BS.(73)

A third, more up-to-date model is proposed by Emmi *et al.*(74) (1997), suggesting that the inflammatory response is deflagrated when internalization of external antigens by macrophages occurs. In this model, the exogenous factor (virus or bacteria) would be recognized by T CD4 cells in the context of MHC Class II antigens. Activated T Helper-1 cells will produce cytokines (IL-2, IFN- γ, TNF-β) and will induce the proliferation of B cells. IFN-γ will activate macrophages to release TNF-α, IL-1 and IL-8, which will induce the expression of adhesion molecules in endothelial cells. IL-8 will

also induce chemotaxis and activate neutrophils, leading to the passage of activated polymorphonuclear and T lymphocytes through the endothelium to the inflamed area, suggesting a predominantly Th-1 type response. These authors proposed that other genes could be involved in the pathogenesis of BS.

The autoimmune disease model cannot be completely discarded as a result of the large number of studies reinforcing this theory. Polyclonal B cell activation with various autoantibodies against antigens derived from organs affected by BS has been related in the literature. The seric levels of Ig-A are increased irrespective of the activity of the syndrome, while the IgG and IgD may be elevated only in the active phases. The elevation of the circulating IC with a reduction in complement titers is generally observed in an initial active stage of the disease. The increase in IC may be pathogenic because histologic studies have demonstrated important IC depositions, especially in patients negative for HLA-B51, of which the neutrophils do not reveal an excessive chemotaxic activity, different from those that were positive for HLA-B51 typing. Antiphospholipid autoantibodies (anticardiolipin antibodies and lupus anticoagulant) have also been suggested as being important in the development of vascular lesions in some patients. Anti-neutrophil cytoplasmic antibodies (ANCA) are rare in patients suffering from BS. Curiously enough, autoantibodies against the S protein of coagulation may be related to the thrombotic events in BS.(73)

The literature is concise in showing the role of endothelial cells in the pathogenesis of BS when they are lesioned, mainly by means of a consistent balance of the coagulation system and fibrinolytic activity. Endothelial injury due to the inflammatory process deflagrated, and the resultant endothelial loss and/or dysfunction, appear to be primordial for the prethrombotic state of these patients.(75, 76) In this context, Demirer *et al.*(75) found high levels of the Von Willebrand factor and plasminogen activators in vascular BS, emphasizing that the clinical thrombosis observed in patients

with BS could reflect the expression of some of these markers. Nevertheless, bearing in mind the excessive fibrinolysis also evidenced, the real function of these endogenous substances in the etiopathogenesis of the disease is not clear, and the real risk factors of vascular disease in BS is even less clear.(75, 76)

Nitric oxide (NO) is an inorganic free radical that is produced by the vascular endothelium by an isoenzyme denominated nitric oxide synthetase. Nitric oxide is basically express through two isoforms: iNOS, which is induced by macrophages and hepatocytes and cNOS, which is dependent on calcium and calmodulin. These two forms are responsible for various important phenomena in the physiopathology of cardiovascular and nervous system diseases, as well as cancer. Thus, some authors have evidenced increases in seric levels of NO, nitrite and nitrates; and urinary NO in active BS, which can promote critical biologic alterations relevant to vascular events in periods of BS activity.(77-79)

In conclusion, in the absence of consensus about its etiopathogenesis, BS must be considered a multifactorial pathologic entity, unable to be classified as an isolatedly genetic, immunologic or infectious disease.

Clinical Manifestations

A broad clinical spectrum and unpredictable outcome are the most representative characteristics of BS. Therefore, clinically, BS presents a great variety of cutaneous and mucosal lesions, ocular manifestations, and various abnormalities in the central nervous system, joint, gastrointestinal tract, that is, any organ or system can be involved in BS.(2)

Mucocutaneous Manifestations

Recurrent Oral Ulcers (ROU)

ROUs are present in 90-100% of cases, and at present, constitutes a *sine qua non* condition for the diagnosis of BS, however, this manifestation is not specific to BS and

can be observed, as differential diagnosis, in the acquired immunodeficiency syndrome (AIDS), cyclic neutropenia, Celiac disease, in Crohn's disease and in systemic erythmatous lupus.(25) In BS, this manifestation is observed in 90% of the patients in Australia, 92% in Egypt, 96.8% in Iran, 98.8% in Korea, 98.2% in Japan, 99% in Germany, 100% in China, 100% in Turkey, 100% in Morocco, 100% in England and 97.5-100% in Brazil.(9, 14, 25, 32, 46, 80)

Oral ulcers in BS can be classified according to severity into simple and complex, and according to morphology as small (<1 cm), large (>1 cm) and herpetiform, such as in ROU, or can have a striatic pattern resembling *lichen planus*. The ulcers are predominantly complex, in larger number, and according to location in order of frequency, appear in lips, cheeks (jugal mucosa), tongue, gingiva, palate, tonsils and oropharynx. They usually start as a slightly raised, erythematous lesion, that develops to ulceration within 48 hours.(2, 81)

Oral ulcers have frequently been described in the literature as the first manifestation of BS, and in the majority of patients, the episodes of repeated oral ulceration persist for 1 to 8 years before other signs and symptoms of the disease appear.(2) The interval between recurrence of episodes varies between the first attack and the subsequent ones, from a few days up to several months or an indefinite time.(2, 21)

The majority of patients develop oral ulcers of the smaller type, also described as punctiform, which regress spontaneously and without treatment in 10 to 14 days. These lesions tend to be round or oval, painful, flat to deep, always having an erythmatous border covered by a yellowish or whitish necrotic fibrinous base. When they are superficial and numerous (more than 50) they are denominated the miliary type, being found mostly on the lips and cheeks.(81, 82) Ten per cent of patients, however, develop the larger, more persistent type of ulcer, which may heal; being the cause of dysphagia and even of stenosis of the larynx.(82) Krause *et al.*(83) observed that the frequency of

larger ROU in BS patients can be significantly higher (37%), of longer duration, multiple (more than 6 ulcers), in addition to being more severe when compared with a group with idiopathic ROU (9%).

There seem to be no important differences between adults and children in the clinical expression of BS, and corroborating this, Borlu *et al.*(84), investigating 17 children (4-16 years of age) with BS, observed the presence of ROU in 100% of the patients, with the majority presenting the smaller type of ulceration and only two patients presenting ulceration of the larger type (> 1cm).

It must be emphasized that a more efficient and strict diagnostic differential obviously changes the epidemiological scenario of a region.(85) Therefore, among patients being followed up due to the presence of ROU, 3.8% were diagnosed as having BS in Turkey, while in Korea, this prevalence attained 52%.

Trauma has been related as an inductive factor of this condition, whereas tobacco has been observed as a protective factor, hypothetically being based on an epithelial hyperkeratosis induction.(86, 87) Furthermore, cases report suggest that nicotine adhesive could be beneficial in BS.(88) To the contrary, Korkmaz *et al.*(89) suggested that smoking is a direct and indirect risk factor (it raises the blood homocysteine levels) for vascular disease in BS. Some substances produced by T lymphocytes, such as the fibroblast growth factor (FGF), which stimulate and accelerate the growth of fibroblasts, and TNF-α, could play an important role in the pathogenesis of ROU.(2)

Genital ulcers

Genital ulcers generally start as papulas or pustules that rapidly develop with rounded or oval erosion, either painful or not, habitually covered by fibrin and with a hardened, edematous halo, capable of causing difficulty with walking, dysuria and dyspareunia.(52, 90)

In BS, genital ulcers are the most frequent lesion after oral ulcers, affecting between 57-94% of patients.(1, 90) They may appear in any location in the genital region, including the groin, perianal and perineal region, either accompanied by secondary infection or not.(82) Morphologically, they present as similar to oral ulcers, however, they are usually larger, heal slowly, and are less recurrent.(33) In men they are usually located in the scrotum and penis, leaving scars. In women they are frequently larger than 10 mm and deeper than in ROU, and can occur on the major and minor labia, being less frequent in the vagina and cervix. Complications of these lesions are cystic or urethral fistulas. Eventually, genital ulcers can be gigantic and develop with an aspect similar to gangrenous pyoderma.(81) When not infected, genital ulcers usually cure in three weeks.(84)

According to Borlu *et al.* (84), genital ulcers occur 94% of the cases in children, and the scrotum and pubis would be the regions most affected in men, while the major labia would be the most affected region in women.

Acute vulvar ulcer is a condition that generally also includes episodes of ROU and can be associated with an infectious pathogenesis, related to gastroenteritis, such as those that occur in typhoid fever and in tuberculous enteritis.(91) This condition is described in the literature as a form of "incomplete BS".(2, 25, 33, 82)

Cutaneous Manifestations

Cutaneous lesions include papulo-pustular lesions (acneiform) or pseudofolliculitis, erythema nodosum, superficial thrombophlebitis, cutaneous ulcers and nodules, cellulitis type lesions, Sweet's syndrome, gangrenous pyoderma, other rarer lesions, in addition to the pathergy test itself.(48) They are observed in around 38-99% of patients with BS.(25, 90)

The papulo-pustular eruptions (acneiform) appear to be the commonest cutaneous manifestation in SB (60-80%), however, in children and patients that have received

treatment with corticosteroids, the lesions are difficult to diagnose and truly correlate with the disease.(2, 25, 33, 82) It is emphasized that various studies have shown approximately equivalent frequencies between erythema nodosum and aceiniform lesions.(68)

Acneiform lesions may occur in both sexes, however it would appear that these lesions mainly occur in men, being located on the face, neck and dorsum, and can be associated with traumatism, such as shaving, due to cutaneous hyperactivity that is the basis of the pathergy test described below.(68) They consist of papulo-erythmatous lesions, 10-20 mm in diameter, crowned by pustules on a non follicular base, and can be multiple and profuse.(81) They are similar to juvenile acne, however they are more diffusely distributed.(52, 81)

The prevalence of erythema nodosum is 40-50%.(2) They are more frequent in women, in the inferior members, painful, generally they do not ulcerate, and when they heal, they leave a hyperpigmented surface.(52) They appear as multiple, subcutaneous nodules, more erythematous and edematous than the classical pattern.(81, 84)

Cutaneous ulcers are uncommon, however they are the most characteristic cutaneous lesion of BS.(33) They are ulcerations from 20 to 30 mm in diameter, with a yellowish necrotic base that leave round atrophic scars.(81) They occur mainly on the internal part of the thighs, but can affect other locations, such as genital, axilla, and infra mammary areas, interdigital space, perianal and thorax regions.(33, 81)

Thrombophlebites are lesions that appear mainly as painful erythematous nodules that are predominantly located in the inferior extremities and can present in a characteristic migratory pattern. They must be clinically differentiated from erythema nodosum.(52)

Cellulitis in BS has erroneously been confused with Sweet's syndrome, however, histologically, these cellulitis show a vasculitis and not a neutrophilic dermatitis, as in

Sweet's syndrome. They are large, painful, erythmatous, edematous lesions that are located mostly in lower limbs, but also in arms and face.(33)

Gangrenous pyoderma shows similarity to the pathergy test; as it starts as a pustule and it may also be precipitated by trauma.(81, 82)

Other cutaneous and subcutaneous findings described in the literature are pseudo-urticarial, livedo racemosa, recurrent erythema multiform, rash with necrotic papulas, psoriasiform-lichenoid-like dermatosis, erythema induratum of Bazin and Weber-Christian's panniculitis, when associated with a feverish condition.(33, 81)

The pathergy test is a nonspecific hyperreactivity in response to a minimum trauma. It is usually tested by puncturing the patient's forearm skin with a sterile needle (20-22 Gauge). The test is considered positive if a papula or pustule is formed, usually with an erythmatous halo, within 48 hours. When positive, the test becomes extremely important for diagnosing BS (specificity of up to 100% in some studies), however, some studies debate its sensitivity, which ranges between 10 and 68%.(1, 92) Positive testing has been related in healthy persons, rarely in spondyloarthropathies, and positive in over a quarter of the patients with chronic myeloid leukemia treated with interferon-α.(52) Yurdakul *et al.*(7) suggested that a pathergy test in conjunction with typing for HLA-B51 positive could be related to the severity of the syndrome. Borlu *et al.*(84) demonstrated a pathergy test positivity of 76% in children, evidencing a higher frequency than in adults.

The test is a dynamic phenomenon and can appear and disappear during the course of the disease.(52) Therefore, when an attempt was made to compare the effectiveness of the test in patients that had either been submitted to treatment or not, it was observed that the percentage of positive tests in untreated patients was higher (14-81%) than in the treated patients (5-47%).(93) Scherrer *et al.* (94), related that the positivity of the

test diminishes when the disease persists for longer than 5 years and, as previously shown, its frequency could be influenced by the disease activity or therapy.

Other Mucocutaneous Manifestations

There are other forms of mucocutaneous manifestations. Among them there are anal aphthous that have the same characteristics as genital ones, and are generally external and close to the sphincter. Recurrent conjunctival ulcerations are small and ephemeral, therefore rarely diagnosed.(33)

Purpuras or hemorrhagic lesions are very rare, but can be isolated and seen with other mucocutaneous lesions. They are generally small and round, but may manifest in a disseminated manner, as a superficial hemorrhage, (pettechia and/or hematomas).(33, 81)

Ophthalmologic Manifestations

Inflammatory involvement of the eye, is considered a serious manifestation of BS. It is the main cause of blindness in Japan.(95) Generally speaking, it affects around 20-85% of the patients, being much more frequent (70%) in young men.(2) It usually appears in the 2-3 initial years of the disease, manifesting in recurrent episodes that last between 2-4 weeks, followed by periods of quiescence.(26, 82) In children, ocular involvement occurs with a frequency of 14-27% in patients with BS, however, some studies show similar prevalences of ophthalmologic manifestations between juvenile BS and adult BS, mainly to the differences between the diagnostic criteria used.(84, 96)

Ocular manifestations are varied, from a moderate conjunctivitis to vasculitis, atrophy or progressive retinal destruction.(2) In 10-20% of the BS patients, it may be the only apparent clinical manifestation at a certain time.(1, 82) It is bilateral in around 90% of cases, and affects the posterior chamber of the eye more severely than the anterior chamber, leading to blindness. Ocular complaints are pain in the eye, blurred vision, and complete or partial loss of sight.(1, 2, 82)

Uveitis are common manifestations of BS.(14, 52) They are characterized by an inflammation generally resulting from severe vasculitis, and considering the anatomical aspect, are defined as anterior uveitis (≅ 19-40% of ocular lesions) that predominantly affect the anterior segment of the eye (iritis, iridociclitis); intermediate uveitis (≅ 9.5-12.5% of ocular lesions) that primarily affect the vitreous and peripheral retina; posterior uveitis (≅ 13-40% of ocular lesion) that affect the retina and choroid; diffused uveítis (panuveitis) (≅40-69% of ocular lesions), those that affect all the segments of the eye.(20, 50, 68, 97) Anterior uveitis represents an important finding for the diagnosis of BS. This is mobile, found in up to one third of patients, and can disappear in a few days without sequelae, but can represent a worse ocular prognosis if it is not in the isolated form.(14) In the beginning it is almost exclusively constituted of polymorphonuclear leukocytes, with lymphocytes appearing at a later stage.(43) Diffuse uveitis, particularly affecting the posterior chamber, are considered of great value for the diagnosis of BS, in addition to becoming increasingly frequent and generally causing lesions.(81) These alterations, in the form of nongranulomatous vasculitis or panuveitis, generally run a chronic and asymptomatic course and are responsible for the most typical ophthalmologic lesions of BS.(68) Their prevalence is approximately 38-50%, and they represent a true vasculitis, with occlusion of arteries and veins, retinal hemorrhage, papilledema and neovascularization.(14, 26, 52)

As regards the appearance of other ocular lesions, ophthalmologic exam can show choroid or retinal exudates, conjunctivitis, scleritis, keratitis, corneal ulcerations, cytoid bodies, macular disease, neuritis and anterior and posterior synechiae. Terminal disease is characterized by venoarterial thrombosis, optic and retinal atrophy associated with complications, such as secondary glaucoma, macular degeneration and cataract, which may be potentiated by the use of corticosteroids.(26, 52)

Joint Manifestations

The joint manifestations in BS are described in 16 to 93% of patients. It is worth pointing out that these epidemiologic data also vary in accordance with the center responsible for research, which modifies the prevalence of joint manifestations, for example, in Turkey from 16% to 47.4%, the later figure when conducted in an ambulatory rheumatology care center.(33, 52, 80)

Sinovitis, arthritis and/or arthralgia may occasionally occur before other symptoms of the disease. These episodes may imitate various joint conditions, from an acute and migratory form of arthritis, as in rheumatic fever, or more rarely, a chronic form of arthritis resembling rheumatoid arthritis.(1, 33) Arthropathy, of the inflammatory type, is observed in 57% of patients in Japan, 15.2% in Iran, 9.8% in Israel, 62.4% in Morocco, 45% in Lebanon, 11-47% in Turkey and 44-69% in Brazil.(14, 25, 30, 33, 47) The joints most commonly affected are the ankles, wrists and knees, and the episodes can last for several days or even weeks.(1, 2) In children, the prevalence of joint manifestations appears to be lower than in adults.(84, 96) Lesions of the destructive type rarely occur, and sacroiliitis and involvement of the spine are not among the common manifestations of BS, and can even serve as differential diagnosis for Reiter's syndrome.(82)

Neurological Manifestations

Acute or chronic neurological disease (Neuro-Behcet or NB) develops in approximately 2 to 30% of the cases, and is considered one of the most serious manifestations of BS, because it is associated with a higher morbi-mortality in these patients.(25) Different series have shown extremely high prevalence, such as in England, Saudi Arabia, and especially in Brazil, affecting 31%, 44% and 54% of the patients with BS, respectively.(12, 25, 33) The high frequencies of NB observed in some series are also owing to a high presence of headaches in these patients. Therefore, it is suggested that

headaches should only be considered as a criterion of NB, if accompanied by another neurological sign or symptom.(52)

The classical manifestation of NB is meningoencephalitis, however, all the forms of neurological manifestations have been reported, ranging from behavioral problems through serious conditions of organic brain syndrome (memory deficit, dementia, apathy, psychomotor agitation, mania, insomnia and delirium) and strokes.(2, 12) Other findings in NB are seizures, sphincter dysfunction, hearing loss, cerebellar, pyramidal and extrapyramidal disfunction, pseudotumor *cerebri* (bilateral papilledema); peripheral and cranial neuropathy, myelopathies and mononeuritis multiplex.(1, 33, 82, 94) The mean time for the first neurological symptom varies greatly, from a few months to years from onset of the disease, and the estimated mortality rate is between 5 and 10%.(33, 98, 99)

Involvement of the cerebral parenchyma (cortex, brain stem, cerebellum and spinal cord) is generally attributed to small vessel vasculitis, predominantly venous.(98, 99) Sinovenous thrombosis is another classical form of neurological manifestation in BS (headache, nerve palsy and mental confusion). Vasculitis in the *vasa vasorum*, is a causal factor for the formation of small cerebral aneurisms.(68)

Spinal fluid exam may range from a normal pattern to an increase in the number of neutrophils, with or without lymphocytes (pleocytosis), increase in the concentration of proteins and increase in pressure.(1, 2)

Nuclear Magnetic Resonance (NMR), as expected, is more sensitive than computerized tomography (CT) for evaluating the involvement of the central nervous system in BS, generally showing diffuse, hyperdense, and small lesions in different locations of the brain.(52, 99) In a study assessing 200 patients with NB, 70% had alterations noticeable in the NMR, whereas only 31% presented alterations at TC level. In the CT

hypodense areas are observed instead of the characteristic hyperdense pattern of NMR.(99)

Vascular Manifestations

Vascular involvement is common and represents the primary lesion (vasculitis) of BS, affecting arteries and veins of all size, being observed in 2 to 37% of the cases.(52)

Arterial manifestations include arteritis with thrombosis, eventually forming aneurisms, which may occur in large size vessels, such as pulmonary and carotid arteries. Pulmonary artery aneurism is a serious and potentially lethal complication. This finding has a prevalence of around 1% of the total vascular manifestations, almost always occurring in adult male, and typically presenting symptoms of massive hemoptyses.(100)

Deep venous thrombosis (DVT) is the most frequent venous manifestation, followed by superficial phlebitis. Phlebitis are characterized by the presence of subcutaneous nodules erythema nodosum-like, predominantly located in the lower limbs. Thrombosis may also occur in other sites as superior and inferior cava veins, mesenteric, hepatic, supra-hepatic vein (with Budd-Chiari's syndrome), etc. Curiously enough, pulmonary embolism is a rare condition in BS.(33, 52)

Other rare vascular manifestations in BS include intracardiac thrombus, coronary artery vasculitis, valvular lesions, aortic aneurisms, pericarditis, endomyocardial fibrosis, portal hypertension.(82)

Reduction in prostacyclin synthesis by endothelial cells, defective fibrinolytic activity, increase in endothelin-1 levels, and mutation of the coagulation factor V have been described in patients with BS, however, no cause and effect relation with clinical thrombosis has yet been proved.(52) Thrombophilic factors such as anticardiolipin antibodies related with the induction of intravascular clots has not commonly been described in association with the thromboembolic complications of BS.(1)

Gastrointestinal Manifestations

Gastrointestinal manifestations (GI) are not rare in BS, and classically, are characterized by aphtous ulcers (similar to the oral ulcers) located in any position in the GI tract, most frequently affecting the ileocecal junction (terminal ileum). This form of ulceration may lead to the appearance of a large spectrum of symptoms such as dyspepsia, anorexia, vomiting and diarrhea.(25, 48, 101)

In a series of BS, it was observed that 45% of the patients presented GI manifestations, with predominance of diffuse abdominal pain (22.7%), chronic colitis, gastric ulcer and pancreatitis in 9% of the patients. Enteritis always occurred in the ileocecal region, presenting perforation in 9% of the cases, which increases the morbidity of patients with BS.(12)

BS shares many signs and symptoms of inflammatory intestinal disease, such as Crohn's disease and necrotizing ulcerative rectocolitis. However, the ulcers in BS are generally round to oval and have a focal distribution, while in Crohn's disease they have a segmentary or diffuse pattern.(1, 101)

Other Manifestations

Pulmonary Manifestations: These manifestations have different etiologies such as vasculitis, embolism, fibrosis, pleuritis and infection. Even though they are rare, according to some authors, pulmonary manifestations are one of the main causes of death of patients with BS, especially where vasculitis is concerned.(100)

Cardiac Manifestations: They are as rare as pulmonary manifestations and include angina pectoris or acute myocardial infarction and pericarditis.(33)

Renal Manifestations: Some patients may present renal alterations and biopsy can reveal focal and segmentary thickening of the glomerular loops with necrosis of the glomerular tophus, characterizing focal glomerulonephritis.(52)

Miscellaneous

Moreover, other findings may be encountered in BS: vesicovaginal fistula, orchitis and epididymitis, rhinosinusitis, otalgia, recurrent otitis, hypoacusia, Raynaud's phenomenon, sacroiliitis, among others. As previously reported, BS can affect any organ and system, therefore, the most uncommon manifestations can be found.(102-104)

Histopathology

The common histopathologic pattern of the majority of clinical manifestations in BS is vasculitis. The lesions are characterized by perivascular cellular infiltrate of lymphocytes and monocytes, with or without fibrin deposition on the vessel wall. A significant infiltrate of neutrophils is also found, particularly in recent lesions including those of the pathergy test.(1)

A monocytic and lymphocytic infiltrate in the dermus or mucosa, particularly around small vessels, characterize histologically genital and oral ulcers.(52, 81)

Histologically, acneiform cutaneous lesions appear as a vasculitis of small vessels, characterized by a neutrophilic infiltrate and necrosis. Similarly, in erythema nodosum, a vasculitis of the small vessels is observed.(1, 81, 84)

In the nervous system, the histopathologic exam shows that demyelinization of the cerebrospinal tract is the predominant finding, followed by encephalomalacia, perivascular cellular infiltrate, multifocal necrosis and cerebral atrophy.(105)

Laboratory Profile in BS

There are no specific laboratory findings for BS, however, some alterations may be found, such as a moderate anemia of chronic disease, and a neutrophilic leukocytosis which may be observed in up to 15% of the patients. The auto-antibodies, such as the rheumatoid factor, antinuclear antibody and ANCA are negative. Nonspecific inflammation tests, such as C-reactive protein, and the erythrocyte sedimentation rate (ESR) may be normal, even with orogenital, ocular or neurological disease activity.(1)

However, Cheng *et al.*(106) evidenced an elevated ESR in 79.4% of the patients tested, with a mean of 32mm/1st hour (ranging between 3 and 135). Some studies have suggested that β-2 microglobulin and ferritin could be useful for measure disease activity, but these data are still not conclusive in the literature. The pathergy test has also been mentioned as a disease activity marker, but few studies have been published in this connection.(1) Evereklioglu *et al.*(79) proposed that urinary NO levels measured in series, could be used as a new activity marker of BS.

Differential Diagnosis

As with any other disease, when it concerns a syndrome without diagnostic tests, it is undoubtedly essential for the clinician to obtain a meticulous clinical history with the purpose of establishing an appropriate differential diagnosis. Depending on the type of clinical manifestation, the differential diagnosis must be established and may include herpes simplex infection, Neumann's bipolar aphthosis, Reiter's syndrome, systemic erythematous lupus, Sweet's syndrome, AIDS, immunoinflammatory skin diseases (pemphigus, pemphigoid, lichen planus, erythema multiform), sarcoidosis, multiple sclerosis, Steven-Johnson's syndrome, PFAPA syndrome (periodic fever with aphtous pharyngitis and adenitis), MAGIC syndrome (mouth and genital ulcers with inflamed cartilage), Vogt-Koyanagi-Harada's syndrome, Crohn's disease and celiac disease.(2) Ghate and Jorizzo(107) proposed that an assessment subsequent to the presence of ROU must include a complete history, with a detailed review of the systems in search of rheumatologic, neurological, gastrointestinal or ocular signs and symptoms; a complete skin examination with biopsy of suspect lesions; culture or PCR for HSV; determination of the levels of vitamin B-12, folate and iron, urine analysis to check renal function; determination of glucose-6-P-dehydrogenase levels (candidates to the use of dapsone) and HLA-B27 and B-51 genotype assessment.

Diagnostic Criteria

There is a debate in the literature as regards the correct use of the term Behcet's syndrome (BS) or Behcet's disease (BD). Those that prefer to use the term BD believe that the disease is characterized by a singular process with different clinical manifestations. As the etiopathogenesis of the disease is uncertain, others prefer to use the term syndrome, designating a set of signs and symptoms of a pathologic entity with unknown cause and pathogenesis. Therefore, considering that there may be differences in the pathogenesis and patterns of how patients are affected in BS, in addition to the nonexistence of a specific etiologic agent, it is common to use the terms neuro-Behcet, vasculo-Behcet or entero-Behcet, to characterize patients by their most prevalent manner of being affected. This, together with the geographic differences among the forms of presentation, emphasizes the preference of calling it "Behcet's" syndrome, instead of "Behcet's disease".(68, 108)

Different criteria have previously been proposed for diagnosing BS, but in 1990, the *International Study Group for Behcet's Disease (ISGBD)*, made an attempt to uniformize these sets of criteria. Therefore it was proposed a set of diagnostic criteria for BS, in which recurrent oral ulceration would be a mandatory criterion, followed by the presence of at least another two other criteria, among which are recurrent genital ulceration, ocular lesions, cutaneous lesions and positive pathergy testing. These are the most used criteria in International literature (Table 2).(108)

It is important to consider that these criteria are useful for classifying a group of patients, but in the event of diagnosing an isolated case, the predictive value will depend on the prevalence of the disease in the referred population. Tunç *et al.* (109) found a good performance of the international criterion in the classification of 302 patients with BS and 438 patients with other inflammatory conditions, especially Crohn's disease, ulcerative rectocolitis and Familiar Mediterranean Fever. Therefore,

these criteria assure the uniformity of patients included in scientific research, particularly, allowing comparison among groups.

Some studies observed that the sensitivity of 86.2% and accuracy of 91% of the ISGBD criteria were low, and therefore, in view of these results, some modifications in the criteria were proposed, which are as follows: omit the mandatory presence of oral aphthous and give two points to ocular alterations. Thus, the criteria would be as follows: Oral aphthous; one point; genital aphthous: one point; cutaneous manifestations: one point; positive pathergy: one point; ocular alterations, such as uveitis or retinal vasculitis: two points. The diagnosis will be fixed by the presence of three points. Such changes would involve a gain in sensitivity, specificity and accuracy for the diagnosis of BS of 96.7%, 94.5% and 95.8%, respectively.(81) Table 3 shows the performance of the criteria described, as well as of others eventually used:

When dealing with the diagnosis of isolated cases in the rheumatology clinic, other criteria of the past are still extremely useful. Thus, the criteria of Curth (1946)(110), Mason and Barnes (1969)(111) and of the Japanese Behcet's Disease Research Committee of 1972 (reviewed in 1987)(112), assessed the signs of the syndrome, considering them as major or minor, not as a function of their clinical importance, but of their frequency.

For the Japanese Committee, a complete type of BS occurs when all the major signs are present, whether simultaneously or not. The incomplete type can occur when three of these signs are present, or when two major signs are observed with two minor signs; only two major signs (one of them must be the typical ocular symptom); or even, in the presence of only two minor signs. Furthermore, the Committee established the types "suspect" (when two major signs are manifested) and "possible" (when only one sign is found).(112)

For Mason and Barnes(111) the following are considered major manifestations: ROU; genital ulceration; cutaneous lesions and inflammatory ocular disease (decreasing order of prevalence). The minor manifestations comprise: arthralgias or arthritis; neurological lesions; vascular lesions; gastrointestinal lesions; epididimitis; cardiac and pleuropulmonary lesions and family history.

Another set of criteria still used in rheumatology for diagnosing BS is the Iranian Diagnostic Tree diagram. (Figure 1) This, in turn, allows BS to be suspected early, possibly when only two criteria are present, contributing to these patients being followed up and submitted to a more careful assessment. Many of these patients may not fill the ISGBD criteria, being excluded from the research protocols. The disadvantage of these criteria is the fact that all the symptoms have the same diagnostic value, although with different degrees of sensitivity, specificity and accuracy.(33)

In 1994 a protocol called *Behcet´s disease Current Activity Form (BDCAF)*, was drawn up by an international committee, with the purpose of instituting a standardized and reproducible instrument for assessing the activity of the syndrome. The BDCAF content was based on a previous study that compared two already available in the literature for measuring the activity of the disease: the Iranian - *The Iranian Behcet´s Disease Dynamic Measure (IBDDAM)*; and the English.(113) Afterward, Lawton *et al.*(114), from the BDCAF, created a one-dimensional numerical index for measuring the activity of BS, which they called *Behcet´s Disease Activity Index (BDAI)* (Table 4). The severity of the disease can be estimated by means of the classification proposed by Krause *et al.*(39), into light, moderate and severe, as observed in Table 5.

Another classification is also utilized when age is used as an important parameter of the disease expression. In Iran, the patients have been classified into 3 groups: Juvenile Group (juvenile disease, the symptoms are completed before 16 years of age), Juvenile

Onset Group (disease at an adult age, first manifestation occurs before the age of 16 years, but other appear in the adult phase) and Adult Group (disease at an adult age, disease onset occurs after the age of 16 years).(81)

Treatment

The diversity of clinical manifestations of BS is accompanied by various therapeutic interventions, demanding an interdisciplinary approach among the specialists. There is no standard treatment for all patients with BS, and therefore, therapy must be individualized, in accordance with the most involved clinical compromise and the degree of severity of each case.(115)

Topical Treatment

ROUs of the moderate type can be controlled with the use of corticosteroid solutions, such as prednisolone (0.5%), triamcinolone (0.05-0.5%), fluocinolone (0.05-1%), betametasone (0.1%), in the form of mouthwashes (5 times a day, avoiding mouthwash ingestion); and corticosteroids (triamcinolone) in Orabase, through inhalatory devices or in intralesional injections, for use in large and deep ulcers.(1, 91, 116) Gonzalez-Moles *et al.*(117), in a clinical trial with 30 patients, showed that mouthwashing with 0.05% clobetasol is a safe and efficient option for the treatment of chronic and severe erosive oral lesions. According to Alpsoy *et al.*, in a randomized, placebo-controlled clinical trial with 40 patients with SB, the topical use of sucralphate (an aluminum hydroxide and sucrose-based composite) was shown to be effective for healing recurrent oral and genital ulcers by buffering the lesions, protecting them and maintaining them under the action of the tissue cicatrisation factors.(118)

The literature suggests coadjuvant treatments that include lidocaine (2-5%), mouthwashes with chlorexidine solutions (0,.12%) or tetracyclin (250mg in 5ml of glycerin).(107) Potent corticosteroids (clobetasol propionate) in the form of creams can

be beneficial for genital ulcers; however, their chronic use can lead to dermal atrophy. Intraarticular injections of corticosteroids may be effective in cases of severe joint involvement. Midriatics/steroids are useful during acute ocular episodes, particularly helping to prevent sinequiae.(52)

Systemic Treatment

The systemic treatment of BS may be a complex issue, since it is very common to use a combination of medications with the purpose of controlling the different clinical manifestations. There are few clinical trials and little evidence published with regard to the efficacy of the most indicated drugs.(1, 52, 68, 82)

In a recent systematic review about drug therapy in BS, 32 references of potential relevance were analyzed for the study, with only 10 studies being included for analyses, making up a total of 670 patients. The study sought evidences with regard to some of the classical treatments in BS, among which were the use of colchicine, cyclophosphamide and corticosteroids for ocular involvement; azathioprine e colchicine for arthritis; and aciclovir, colchicine and interferon, used topically for the ROUs. The results confirmed the protective effect of cyclosporine and azathioprine in ocular involvement, in addition to penicillin benzathine for new arthritic attacks in BS, but the authors emphasized that further randomized, double-blind, placebo-controlled trials are necessary with the purpose of making it possible for the results to be generalized.(119)

Antibiotic Therapy

Taking into account the microbiological role in the etiopathogenesis of BS, the routine use of antibiotic therapy in BS is still controversial, considering the few evidences about the effectiveness of these medications in the treatment of BS. Calguneri *et al.* in a randomized, blind and controlled study with 120 patients, observed that the treatment

with colchicine (1,5mg/day) associated with intramuscular penicillin benzathine administration (1.2 milliion UI/every 3 weeks) prevented the recurrences of arthritis, which was not evidenced in the group treated with colchicine alone. The results were not statistically significant with regard to duration, severity and the pattern of the arthritis episodes among the groups.(120) In another prospective trial with 154 patients, published by Calguneri *et al.*, the authors concluded that the prophylactic use of penicillin benzathine associated with colchicine is more effective than the treatment with colchicine alone for the control of mucocutaneous manifestations in BS.(121) Al-Waiz *et al.*,in another clinical trial, also evidenced the beneficial action of penicillin benzathine associated with colchicine in BS. It is pointed out that in this study the authors did not analyze only one clinical variable, but a clinical manifestation index.(122) The use of minocycline was also assessed in the literature in the study by Kaneko *et al.* In this study, the authors concluded that the continuous use of 100 mg of minocycline for at least 3 months was effective for the reduction of clinical manifestations and the production of inflammatory cytokines of peripheral blood mononuclear cells in 13 patients with BS.(123)

Colchicine

Colchicine (1.0 to 2.0 mg/day), one of the drugs of choice for the treatment of gout, inhibits the migration of neutrophils and has been very popular for the treatment of various manifestations of BS. It is more effective for erythema nodosum, arthritis, ROU and genital ulcers in women, but only for arthritis in men. It can be used in combination with cyclosporine, which diminishes the recurrence of ocular attacks, and has an important action in SB of moderate degree.(1, 52)

Dapsone

Dapsone (50-100mg/day) is a sulphone with antineutrophilic activity, which demonstrated a good response in the treatment of mucocutaneous lesions, improving parameters such as the number, size, frequency and duration of ROUs, genital ulcers and cutaneous lesions. Its most serous side effects are: hemolysis, methahemoglobinemia and agranulocytosis.(124)

Thalidomide

Thalidomide, 100-300 mg/day, is very effective for oral and genital ulcers, and for cutaneous lesions (particularly in papulopustular lesions), in addition to possibly preventing ocular and gastrointestinal disease in BS. Its action seems to be associated with the regulation of TNF production in various cells. Paradoxically, studies have shown that there could be exacerbation of erythema nodosum associated with the use of this medication. Furthermore, thalidomide is teratogenic and neurotoxic, and should therefore be used with extreme caution.(52) The incidence of polyneuropathy seems be between 6 and 50%, and if it is not detected early, it could be irreversible. Sedation is a less serious side effect.(82)

Pentoxifilin

Pentoxifilin is another anti-TNF agent that has been used to control orogenital ulcerations in BS. It also seems to have a suppressor effect on T CD8 lymphocytes, probably because of inhibiting the perphorins, in addition to suppressing free radical production and reducing neutrophil-induced lesions. Clinical trials are required to indicate its use as an effective BS treatment option.(1)

Systemic corticosteroids

The systemic use of these medications is extremely valuable in the treatment of uveitis (acute stage) and during severe acute episodes of arterial and neurological manifestations, particularly when combined with other immunosuppressant/cytotoxic

drugs. When treatment of mucocutaneous manifestations with colchicine and thalidomide is not responsive, the use of prednisone can be indicated at doses of around 20 mg/day. Subcapsular injection of corticosteroids administered by ophthalmologist can be useful in the treatment of posterior uveitis.(52)

Pulse therapy with high doses of corticosteroids is used in the progressive intra-axial lesions of the CNS, followed by immunosuppressant drugs (cyclophosphamide, chlorambucil, methotrexate or azathioprine). Acute episodes of NB may be treated with oral prednisolone (1 mg/Kg) for 4 weeks or until the condition is resolved, or high intravenous doses of methylprednisolone (1g/day) for 3-7 days. To prevent recurrences, both regimes need to be continued with oral corticosteroid for a minimum of 2-3 months.(125) According to the review of Savi *et al.*(125), the extra-axial forms, such as cerebral venous sinus thrombosis (CVST), normally respond to corticosteroids either with or without anticoagulants, not requiring immunosuppressants for the prevention of recurrences. Nevertheless, the literature points out that this measure is controversial, in view of the large number of case series that show the combined use of corticosteroids, immunosuppressants and anticoagulants in these situations.(126-128) Martin-Araguz *et al.*(129) have related that the decision to use anticoagulant therapy with heparine in CVST is controversial and depends on the possible risks and/or benefits in each individual case. Therefore, according to these authors, the clinical findings, etiology, topography and severity of the venous thrombosis must be carefully assessed, in order to be able to decide precisely whether or not the therapy should be instituted. Savi *et al.* also related that for the combined use of the therapy with anticoagulants for CVST in BS, the presence of aneurisms (pulmonary or others) must be reassessed, which will make it impossible to take this option. Callejas *et al.*(130) stated that prolonged therapy with anticoagulants in CVST would seem to be the most

suitable choice, giving this complication a satisfactory prognosis. Nevertheless, even with a suitable anticoagulant, the authors affirmed that recurrences are not discarded. That is why the association with corticosteroids is necessary to reduce the inflammatory component of the vascular wall.

Azathioprine

Azathioprine, 1 to 2.5 mg/Kg/day, reduces the development of the disease and of acute ocular episodes. It has a favorable effect on arthritis, oral and genital ulcers, and thromboembolism, improving the long term prognosis. It can also be used in association with prednisone to treat neurological manifestations.(131)

Methotrexate (MTX)

The literature shows that this medication (7;5-20 mg per week) diminishes neuropsychiatric disease progression, has a beneficial action in cutaneous vasculitis and in cases of refractory arthritis. Some studies have shown that low weekly doses of MTX, associated with other immunosuppressants, could be effective for controlling neurological and ocular manifestations.(1, 52) Nevertheless, patients using these medications must be monitored with regard to possible hepatotoxicity.(82)

Cyclosporin A

Cyclosporin A (2 to 5 mg/day) is a fast and effective drug for the relief of acute uveitis episodes (preserving the visual acuity of these patients), but also diminishing the frequency of recurrences of ocular disease and extraocular manifestations. Moreover, it appears to have a positive effect on hearing loss and reduction in the frequency of oral aphthous and cutaneous lesions of BS. Bartynski *et al.*(132) described a neurotoxic reaction in 22 selected patients with cerebral image alteration while they received treatment with cyclosporin A. Such findings, particularly in BS, have been corroborated

by others.(133) Therefore, the treatment of BS with cyclosporin appears to cause neurotoxicity, or even accelerates the development of CNS symptoms.

Tacrolimus

Tacrolimus (FK506) is an immunosuppressant agent with activity similar to cyclosporin A; it is better tolerated, helps in the treatment of recurrent uveitis, particularly when cyclosporin is not responsive. Cyclosporin and tacrolimus are the drugs of choice for ocular involvement in BS, however, they may cause renal failure and/or arterial hypertension, and their use must therefore be regularly monitored.(52) Nevertheless, it is known that tacrolimus is less associated with hyperlipidemia, *diabetes mellitus*, hypertrichosis and/or gingival hyperplasia.(1)

Cyclophosphamide

Monthly intravenous pulse therapy with cyclophosphamide (0.75 mg/m^2 of body surface) has been shown to be as effective as cyclosporin in the long term treatment of uveitis, but also has shown excellent results in the treatment of neurological and arterial manifestations in BS.(52). It can be used in association with systemic corticosteroid, but has a variety of side effects, such as, induction of infertility, hematological dyscrasias and cancer, which limit its use.(1, 82)

Chlorambucil

For a long time, it was used as the drug of choice in ocular BS, at the dose of 0.1 to 0.2 mg/kg/day, however, in recent times this medication is not used often, in view of its important cancerigenous and myelotoxic effects.(134)

Biological Therapy

In spite of the advance in therapy with the classical immunosuppressants, studies have shown that there are still persistent risks of morbidity, mainly for ocular and neurologically compromised patients, in addition to the frequent presence of adverse

reactions.(135) Therefore, new therapeutic modalities, such as those with biological agents have been introduced on the market, and are another BS treatment option.

The interferons (IFN) are cytokines with antiviral, antitumoral and immunoregulatory activity, which appear to be effective in the treatment of BS, basically because of their action of inhibiting T lymphocytes and stimulating NK cells. The onset of their action is fast (1 to 4 weeks), being an effective treatment particularly for severe, refractory cases and those associated with malignancy or infectious disease. In a meta-analysis published in 1998, Interferon-α demonstrated a partial or complete response in 74% of the patients with mucocutaneous manifestations (diminished pain and frequency of ROU and cutaneous lesions), 95% of the patients with uveitis and 93% of the patients with artropathy. The regimes with 2a-interferon-α were more effective than the regimes with α-2b for mucocutaneous manifestations (46% versus 7% for complete responsiveness) and ocular (67% versus 8% for complete responsiveness). Among the commonest adverse effects found, are transitory symptoms influenza-like such as, nausea, vomiting, anorexia, diarrhea, weight loss, transitory increase in hepatic transaminases, reversible leukopenia and alopecia.(136) It is emphasized that the quality of this systematic review was poor, mainly because of lack of inclusion and exclusion criteria, and by the absence of randomized and controlled clinical trials. Although the results described are limited, new randomized, placebo-controlled trials have been published, showing the effective results of this therapy. Alpsoy *et al.*(137), showed that 2a-interferon-α is an effective alternative, particular for management of mucocutaneous lesions in BS. In this study with 50 patients, the treated group obtained significant improvement in the duration and pain of oral ulcers; and of the frequency of genital ulcers and papulopustular lesions. The treatment also improved the joint and ophthalmologic manifestations, although without reaching statistical significance.

Kotter *et al.*(138), in another systematic review including 32 original articles and assessing 338 patients, concluded that the treatment with 2a-interferon-α is beneficial even for resistant posterior uveitis, with long periods of remission and maintenance of visual acuity. Moreover, as already described, its action was also effective in the remission of mucocutaneous manifestations. In another randomized and controlled study, Demiroglu *et al.*(139) observed that the therapy with 2b-interferon-α associated with colchicine and penicillin benzathine seemed to be an effective regime for the prevention of acute episodes of ocular manifestations and extraocular complications.

Some case reports have shown good results with the use of anti-TNF therapy in patients with BS with ocular, gastrointestinal or neurological manifestations. Infliximab has been used at the dose of 3-5 mg/kg weight initially, at intervals of 2 to 6 weeks and afterwards, every 8 weeks. Thus, infliximab could be a therapeutic alternative for severe cases of BS that are not responsive to conventional treatment.(140) In a case report, Souza *et al.*(115) obtained complete remission of BS manifestations with persistent mucocutaneous, joint and neurological involvement, by intravenous administration of 3mg/kg of infliximab, and Merino *et al.*(141), assessing the effectiveness and safety of the use of infliximab in 5 patients, found that ocular and extraocular inflammation was completely suppressed in all of the patients during the period of observation, without presenting any serious adverse reaction. At present, however, the use of infliximab in BS is limited, particularly in developing countries, because of its high cost and the lack of substantial data in the literature. Therefore, some controlled clinical trials are being conducted in order to demonstrate whether or not this medication really is superior to conventional therapy.

Other Treatments

Correction of hematological iron, vitamin B_{12} or folate deficiencies is an important nonspecific intervention, as these complications can aggravate ROUs.(142)

Sulphasalasine at the dose of 2-3 g/day constitutes a treatment option for gastrointestinal lesions and persistent cases of joint manifestations, together with azathioprine and methotrexate.(1, 52, 143)

The NSAIDS (nonsteroidal antiinflammatory drugs) can be used to relief the symptoms with reference to joint pain, but when the use of colchincine is not effective, the best option is to use prednisone for a short period of time.(52)

Surgical intervention may be required in cases of pulmonary artery aneurisms and in cases of severe intestinal involvement, unfortunately with a high rate of recurrence and mortality.(52)

Other drugs, such as mycophenolate mophetyl (specific inhibitor of B and T lymphocytes) and monoclonal antibodies anti-CD52 (CAMPATH-1H), used in transplants, are options that have been related in the literature for the treatment of BS, but deserve clinical trials that assess their effectiveness and safety.(144, 145) Lockwood *et al.*(145) in a clinical trial with 18 patients with BS, observed that in 6 months, 72% (13/18) of the patients obtained remission with the use of anti-CD52, in addition to a diminution of the mean daily dose of prednisolone from 17.7 to 6.7 mg/day. At re evaluation between 6 and 60 months, 7 patients had recurrences after a mean period of 25 months; 5 required the introduction of immunosuppressants and 2 were retreated with CAMPATH-1H. No opportunist infections were evidenced. However, further controlled studies are required to prove the effectiveness of this treatment.

Competing Interests

Mittermayer Santiago: None

Roberto Tunes: None

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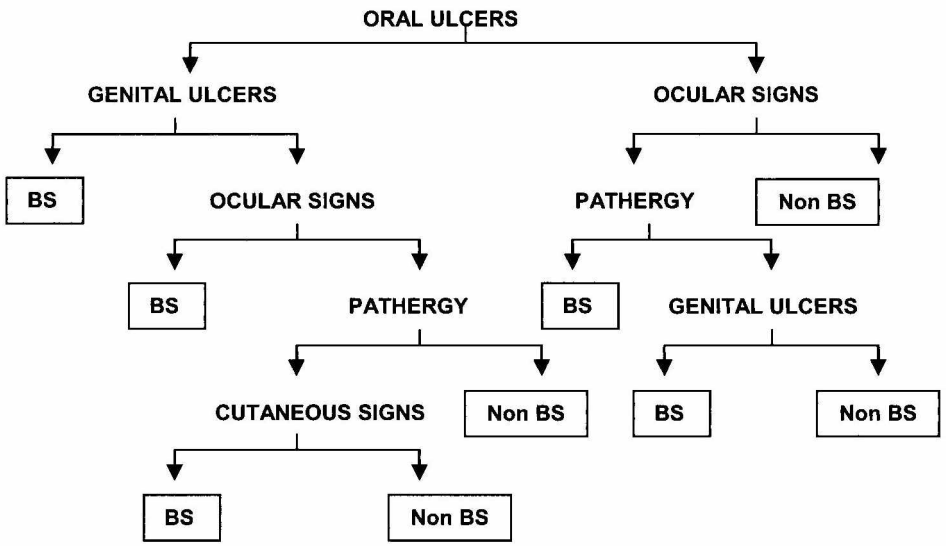
Figure 1. Iranian criteria for the diagnosis of Behçet´s syndrome (33)



LEGENDS: BS= Behçet's syndrome; Non BS= Absence of Behçet's syndrome

Table 1. World distribution of Behçet's syndrome

Country	Year	Latitude (°N)	HLA-B51	Prevalence of BS per 100,000 inhabitants
ASIA				
Turkey[7, 8, 28, 29, 80]	1981-2004	39	26.3	20-420
Japan[30]	1991	36	22.3	0.99-30.50
Israel[36, 37]	2002-2007	31	81	8.6-146.4
Iran[33]	2005	32	34	16.7
China [25, 38]	1998-2002	32	56	2.62-14
Korea[32]	2001	35	13	109.2*
Saudi Arabia [25, 146]	1997	26	72	20
AFRICA				
Egypt (Alexandria)[25]	1997	30	---	7.5
EUROPE				
Spain[34, 40]	1998	41	6.1-24.5	0.32-10.8
Italy[09]	1988	42	17.4	2.5
Portugal[147]	1991	17	53	1.53
Sweden[148]	1990	60	3	1.18
Switzerland[149]	1991	52	66	0.65
England[09]	1977-1992	52	25	0.27-0.64
Germany[09]	1994	52	36	0.55-20.75
AMERICA				
USA[25]	1975-1985	46	13	0-0.33

*The first multicentric study in Korea, observing a prevalence of 109.2/100,000 inhabitants

Table 2. International study group criteria for the diagnosis of Behçet's syndrome (BS)(150).

Recurrent Oral Ulcers	Minor aphthous, major aphthous or herpetiform ulceration observed by the doctor or patient with recurrence of at least 3 times in the period of 12 months
Two of the following criteria: Recurrent genital ulcer	Aphthous ulceration and/or cicatrization observed by the doctor or patient
Ocular lesions	Anterior uveitis, Posterior uveitis or vitreous humor cells when examined with slit-lamp, or retinal vasculitis observed by the ophthalmologist
Cutaneous lesions	Nodular erythema observed by the doctor or patient, pseudofolliculitis or papulopustular lesions, or acneiform nodules that did not receive treatment with corticosteroid, observed by the doctor in post-adolescents .
Positive pathergy test	Observed by the doctor in 24-48 hs.

The presence of recurrent oral ulcers is a mandatory criterion and the presence of at least another 2 other criteria determine the diagnosis of BS

Table 3. Performance of the different criteria for the diagnosis of Behçet's syndrome according to Davatchi *et al.*(33).

Criteria	Sensitivity	Specificity	Accuracy
international	86.2%	97.5%	91%
Modified international	96.7%	94.5%	95.8%
Classification Tree	97.1%	95.1%	96.2%
Japan revised	93.2%	96.4%	94.7%
Dilsen	91.7%	89.3%	90.7%
O´Duffy	80.3%	97.6%	87.6%
Mason and Burnes	74.2%	99.4%	84.9%

Table 4. Clinical criteria for assessing the activity of Behçet's syndrome, as suggested by Lawton *et al.* (114)

1. Headache
2. Oral ulcers
3. Genital ulcers
4. Nodular Erythema
5. Pustules
6. Arthralgia
7. Arthritis
8. Nausea and vomiting
9. Diarrhea
10. Signs or symptoms of ocular activity
11. Signs or symptoms of activity in the central nervous system
12. Signs or symptoms of activity in large vessels
13. Patient's self-assessment (on a semi-quantitative scale)
14. Clinician's general impression (on a semi-quantitative scale)

The presence of the above criteria in the four previous weeks is used to quantify the activity of Behçet's Syndrome and an index is produced by the simple sum of the positive criteria.

Table 5. Classification of the severity of Behçet's syndrome according to Krause *et al.* (39)

Mild	Oral aphthosis
	Genital ulcers
	Typical skin lesions (erythema nodosum, papulopustular lesions, folliculitis, leucocytoclastic vasculitis)
	Arthralgia
	Recurrent headaches
	Epididymitis
	Mild gastrointestinal symptoms (chronic diarrhoea, chronic recurrent colicky abdominal pain)
	Pleuritic pains
	Superficial veins thrombosis
Moderate	Arthritis
	Deep vein thrombosis of the legs
	Anterior Uveitis
	Gastrointestinal bleeding
Severe	Posterior uveitis/pan uveitis, retinal vasculitis
	Arterial thrombosis or aneurisms
	Major veins (cava, hepatic vein) thrombosis
	Neuro-Behçet
	Bowel perforation

The presence of one of the criteria is sufficient for classification in its respective group.

ARTIGO 3

ARTIGO SUBMETIDO POR VIA POSTAL

Mittermayer B. Santiago
Serviço de Reumatologia
Hospital Santa Izabel
Praca Almeida Couto, 500, Nazare,
Salvador, Bahia, CEP- 40000-000
BRAZIL

December 12th, 2007

Professor Ernst Lemmel

Editor-in-chief of
Rheumatology International

Dear Professor,

We would like to submit our manuscript entitled "**Clinical Aspects of Behcet's syndrome in Brazil: A Review of 16 Cases**" to the Editorial Board of **Rheumatology International**. We believe it will be very interesting for the readers of this journal.

Additional information:

It has been read and approved by all authors.

It has not been published before

Sincerely,

Mittermayer Santiago MD, PhD

Clinical Aspects of Behcet's syndrome in Brazil: A Review of 16 Cases

Roberto Santos Tunes (1)

Renata Amorim Marques (2)

Mittermayer Barreto Santiago (3)

6. Post-Graduation student of the Post-Graduation Course in Medicine and Human Health of the "Fundação Bahiana para o Desenvolvimento das Ciências", Salvador, Brazil
7. Medical student at "Escola Bahiana de Medicina e Saúde Pública"
8. Adjunct Professor at "Escola Bahiana de Medicina e Saúde Pública", Coordinator of the Serviço de Reumatologia do Hospital Santa Izabel; Salvador, Brazil.

Correspondence: Mittermayer B Santiago. Praça Conselheiro Almeida Couto, 500, Nazaré, Salvador, CEP: 40000-000, Bahia, Brasil. Telephone (fax): (71) 3326-5276, mitter@svn.com.br.

Summary

OBJECTIVES Behcet's Syndrome (BS) is a clinical entity characterized by the appearance of recurrent oral and genital ulcers, in addition to a broad spectrum of clinical manifestations. It has been seen more frequently in countries such as Turkey and Japan, but also in Brazil, although there are no consistent epidemiologic data in our country. The aim of this study is to describe the clinical characteristics of a series of BS cases seen at a reference service in collagen vascular diseases in Bahia, Brazil.

METHODS All of the patients diagnosed as having BS by the criteria of the International Study Group for Behcet's Disease (ISGBD) followed up by the Rheumatology Service of the "Hospital Santa Izabel" in the year 2007 were included in the study, and were submitted to a clinical and laboratory evaluation.

RESULTS Sixteen patients were identified as having BS, with an equal distribution between the sexes. Their ages ranged between 19 and 58 years (mean 35.6 ± 12.9 years). The mean age at the time of disease onset was 27.8 ± 12.4 years. The clinical manifestations observed include oral ulcers in all cases, genital ulcers in 75% of the patients and cutaneous lesions in 81.3%. As regards the cutaneous lesions, there were predominantly acneiform lesions (75%) and erythema nodosum (37.5%). There were 68.8% of ophthalmologic manifestations and articular involvement was present in 81.3%; vestibulocochlear symptoms were found in 50% with predominance of vertigo and hypoacusia; neurological symptoms were seen in 75% of the patients. Superficial thrombophlebitis and deep venous thrombosis (12.5%) were the most frequent vascular manifestations. All the patients were treated with corticosteroids and immunosuppressant agents.

CONCLUSION In Brazil, there are no data relative to the prevalence or incidence of BS, however, the disease has been observed in different regions of the country. In the present series, it was observed that the spectrum of clinical manifestations of the disease did not differ from series arising in other countries.

Keywords Behcet's Syndrome, case series.

Introduction

Behcet's syndrome (BS) was first described by the Turkish dermatologist Hulusi Behcet as a three-symptom complex comprising oral aphthae, genital ulcerations and uveitis (Zouboulis and Kaklamanis 2003). Today we know that the disease is a multisystemic, recurrent, inflammatory disorder affecting any site including oral, genital, cutaneous, ocular, articular, neurological, vascular, gastrointestinal and pulmonary systems (MacCormack and Phillips 2007). Occurring most frequently in Middle East, BS is endemic in the historic *"silk route"*, which extended from eastern Asia to the Mediterranean area, most frequently between the northern latitudes of 30° and 45° in Asian and European populations (James 1986). Turkey is the country with the highest prevalence of the disease, estimated to be between 20 and 420 per 100,000, whereas in Japan it is 0.99-30.5 per 100,000, and the prevalence in the UK and USA is estimated at 0-2.5 per 100,000 (Azizlerli *et al.* 2003; Nakae *et al.* 1993; Zouboulis *et al.* 1997). The disease has a very wide spectrum of clinical features and it is characterized by unpredictable periods of exacerbations and remissions (Gul 2001). Its main morbidity is related to blindness due to repeated attacks of ocular inflammation, whereas involvement of the central nervous system or major vessels may be serious enough to lead to death (Marshall 2004).

In Brazil there are no substantial data regarding the prevalence, incidence or clinical features of BS, except for rare series of patients seen at ophthalmologic clinic (Barra *et al.* 1991). The aim of the present study was to describe the clinical features of 16 cases of BS seen at a Rheumatologic center in the city of Salvador, in the North East of Brazil.

Materials and methods

The study sample included all patients with BS seen at the Reumatology Unit of Hospital Santa Izabel, Salvador, Brazil, between February 2007 and August 2007. The diagnosis of BS was based on the criteria of the International Study Group for Behcet's Disease (ISGBD). According to these criteria, the patient is diagnosed with BS if he/she presents with recurrent oral ulceration (recurrent at least three times in a 12-month period) plus two of the following manifestations: recurrent genital ulceration, eye lesions, skin lesions or positive pathergy test. Suspected or possible types of SB (as seen in other criteria) were not included in this study. Patients with aphthous stomatitis, herpes simplex virus infection, AIDS, Reiter's syndrome, sarcoidosis, Stevens-Johnson syndrome, Cohn's disease and ulcerative colitis, systemic lupus erythematosus, celiac disease, mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome were all excluded from this series.

A standard questionnaire containing data on clinical and laboratory features was filled out. Medical records with data from regular follow up visits, as well as previous hospital admission were also reviewed. The study had the approval of the ethics review board of our institution.

Statistical analysis, including the descriptive data, was performed using SPSS version 13 software. For the male and female comparison, the categorical variables were analyzed using chi-square test or Fisher's exact test, as appropriate. The continuous variables were analyzed using the Student t-test. Significance was set at the 5% level.

Results

Sixteen patients who fulfilled the ISGBD criteria were identified in our institution, being 8 men and 8 women. The patients' mean age at the time of diagnosis was

35.6±12.9 years with no difference between men and women. The onset of the disease occurred more often during the twenties at a mean age of 27.8±12.4. The racial distribution was as follows: 8 (50%) patients were Caucasian, 4 (25%) *mulatto* and 4 (25%) black. No family history of BS was recorded (Table 1).

The clinical features of the patients and the sex distribution are presented in table 2. There was no difference between men and women with regard to the frequency of most of the disease manifestations, apart from genital ulcers, overall skin lesions, joint and vestibular-cochlear symptoms (p=0.009, p=0.02, p=0.02 and p=0.04).

Recurrent oral ulceration (ROU) was the first manifestation, alone or associated with genital ulcers or skin lesions in 11 cases (68.8%). ROU were recorded in all 16 patients and genital ulcers occurred in 75% of the patients. The oral ulcers were predominantly complex, in larger number, painful and appearing in places such as lips, cheeks, tongue, gingiva, oropharynx and palate, measuring from 4 to 15mm. Genital lesions were frequently single, painful and most commonly seen on the man's penis, and the vulva and large labia in women. Skin lesions were observed in 13 (81.3%) of patients; they consisted of a variety of lesions, including acne, erythema nodosum, skin ulcers and vasculitis. Thirteen patients (81.3%) had joint symptoms, consisting of arthralgia or recurrent arthritis mainly in large joints such as knee, ankle, shoulder, elbow and wrist. Twelve patients presented neurologic involvement (75%) characterized by headache, stroke and aseptic meningitis. The main ocular manifestation was uveitis (seen in 37.5% of the patients), followed by retinal vasculitis (12.5%). As vascular involvement, superficial thrombophlebitis and deep venous thrombosis were identified in 12.5% each. Raynaud's phenomenon was seen in only 1 patient. One additional patient developed a pulmonary artery aneurysm. An unusual case of BS was associated with inflammatory

pseudotumor of the myocardium. This patient died soon after the heart surgery. The frequency and sex distribution of these clinical features are presented in Table 2.

Discussion

Behcet's syndrome has been described as having a genetic influence, partially explaining the regional variability of expression of the disease, already well described in the literature (Krause *et al.* 2001). According to Ohno *et al.* (1982), the difference in incidence and prevalence observed in different parts of the world may be due to the spread of related genes among the tribes and traders that traveled between the Arab world and the East. In Brazil there is no study on the incidence or prevalence of this syndrome, although a few case series from cosmopolitan cities, such as São Paulo have been described, emphasizing the ophthalmologic features of the disease (Barra *et al.* 1991; Aguiar *et al.* 1997; Gouveia *et al.* 2004; Gomi *et al.* 1997).

We previously investigated the frequency of BS using the ISGBD criteria in 50 patents with recurrent oral ulceration attended at a university center (Tunes *et al.* 2007). We identified only one case (2%) of BS, demonstrating a far lower prevalence than that observed in a country like Turkey. However, it showed us that further studies in should be undertaken to clarify the frequency of clinical and laboratory features of this disorder in Brazil, as well as the epidemiologic figures.

In our study, we found a similar proportion of cases between men and women, similar to that observed in other series (Lacerda 1992; Azizlerli *et al.* 2003; Scherrer and Oréfice 1988), moreover, the age of the disease onset seemed to be similar to that mentioned in previous studies (Azizlerli *et al.* 2003; Scherrer and Oréfice 1988; Barra *et al.* 1991; Hamdan *et al.* 2006; Krause *et al.* 2007).

In the present series the frequency of genital ulcers, overall skin lesions, joint and vestibular-cochlear symptoms were statistically higher in women than in men (Table 2). Although we do not have a convincing explanation for these findings, we cannot exclude the possibility of influence of the genetic background of the studied population, since conflicting results on these frequencies have been reported in the literature. Thus, Yazici *et al.* (1984) and Tursen *et al.* (2003) also reported higher prevalence of genital ulcers and over all skin lesions among women patients, however, showing that there is a significantly higher frequency of acneiform lesions in men. As regards joint involvement, reports have demonstrated similar distribution in both sexes (Tursen *et al.* 2003).

Although genetic background and environmental influence may play a role in the discrepancy in prevalence of the clinical manifestation of BS among several studies, one additional factor seems to be the origin of the data. Thus, Barra *et al.* (1991) and Lacerda (1992) describing series of BS from university ophthalmologic centers, reported a higher frequency of ocular involvement (83.3-100%) when compared with skin lesions (51-71%),

As serious manifestations of BS, one of our patients had a potentially fatal pulmonary artery aneurism and another, who died after the heart procedure, had BS as a manifestation of myocardium inflammatory pseudotumor. The latter condition has rarely been described in the literature. Additionally, two other patients presented stroke, one of them due to an aneurysm rupture leading to hemiparesis. These cases should not be interpreted as BS having a worse prognosis in Brazil, but it may be a selection bias, as our service is a tertiary referral center for connective tissue diseases.

From the present study we could conclude that BS occurs in Brazil and the spectrum of clinical manifestation does not seem to differ from that of other studies, except for the

frequency of neurological features, which were more common in our series. This may be explained by the inclusion of headache as a neurological feature, whereas other authors have analyzed headache separately and considered only "neuro-Behcet", that is, stroke, meningitis, etc, as neurological complication (Table 3).

Competing interests

Roberto Santos Tunes: None

Renata Amorim Marques: None

Mittermayer Santiago: None

Authors' contributions

Roberto Santos Tunes designed the study, collected the data and wrote the manuscript.

Renata Amorim Marques participated in data collection

Mittermayer Santiago coordinated the study and revised and submitted the final version of the manuscript.

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Table 1. Demographic data of 16 patients with Behcet's syndrome

	Frequency (%)	Male (n=8)	Female (n=8)	*P* value
Age at diagnosis (years ± SD)	35.6±12.9	35±12.9	36.2±13.7	NS
Age of the disease onset (years ± SD)	27.8±12.45	26.1±9.9	29.6±15	NS
Ethnic distribution				
Caucasian	50	50	50	NS
Mulatto	25	50	50	NS
Black	25	50	50	NS

Abbreviations: NS=not significant

Table 2. Frequency and sex distribution of clinical features of 16 patients with Behcet's syndrome.

	Frequency (%)	Male (n=8)	Female (n=8)	*P* value
Oral ulcers	100			
Overall skin lesions	81.3	62.5	100	0.02
Erythema nodosum	37.5	25	50	NS
Skin ulcers	31.3	12.5	50	NS
Acneiform lesions	75	62.5	87.5	0.05
Genital ulcers	75.0	50	100	0.009
Overall ocular disease	68.8	87.5	50	NS
Anterior uveitis	12.5	12.5	12.5	NS
Posterior uveitis	12.5	25	0	NS
Pan-uveitis	12.5	12.5	12.5	NS
Retinal vasculitis	12.5	12.5	12.5	NS
Cataract	6.3	12.5	0	NS
Conjunctivitis	25	12.5	37.5	NS
Blindness	6.3	12.5	0	NS
Cutaneous vasculitis	12.5	0	25	NS
Joint symptoms	81.3	62.5	100	0.02
Neurological features	75	58.3	41.7	NS
Overall gastrointestinal disease	62.5	50	75	NS
Gastroduodenitis	18.8	12.5	25	NS
Vestibular-cochlear symptoms	50	37.5	62.5	0.04
Fever	43.8	50	37.5	NS
Superficial thrombophlebitis	12.5	12.5	12.5	NS
Deep venous thrombosis	12.5	12.5	12.5	NS
Pulmonary aneurism	6,3	12.5	0	NS
Raynaud's phenomenon	6,3	0	12.5	NS
Cardiac disease (inflammatory pseudotumor)	6.3	12.5	0	NS
Fibromyalgia	6.3	0	12.5	NS

Abbreviations: NS=not significant

Table 3. Prevalence of various clinical manifestations in patients with Behcet's syndrome from different ethnic groups

	Current study	Krause *et al.* (2007)	Azizlerli *et al.* (2003)	Mok *et al.* (2002)	Gonzalez-Gay *et al.* (2000)	Zouboulis *et al.* (1997)	Sakane *et al.* (1999)
	N=16	N=112	N=101	N=37	N=16	N=196	N= 3316
Year of study	2007	2007	2003	2002	2000	1997	1991
Country	Brazil	Israel	Turkey	China	Spain	Germany	Japan
Clinical features							
Oral ulcers	**100**	100	100	100	100	99	98
Genital ulcers	**75**	67.9	70.2	81	88	74.5	73
Overall ocular disease	**68.8**	52.7	27.7	35	44	75.5	69
Overall skin lesions	**81.3**	41.1	80.1	73	88	58.9	87
Joint symptoms	**81.3**	69.6	32	54	63	59	57
Vascular lesions	**37.5**	15.9	10.8	11	44	25.1	9
Neurological features	**75**	11.6	NA	5	31	12.8	11
GI involvement	**62.5**	NA	NA	14	19	15.8	16
Heart signs	**6.3**	NA	NA	NA	NA	2.3	NA

Abbreviations: GI: gastrointestinal; NA: not available

ARTIGO 4

09-Aug-2008

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Clinical and Epidemiological Aspects of Recurrent Aphthous Ulcerations in Brazil: A Cross Sectional Study

Roberto S. Tunes (1)

Tiago C Anjos(2)

Gabriela B. Martins (3)

Mittermayer B. Santiago (4)

9. Master's Course Student at the Fundação Bahiana para o Desenvolvimento das Ciências (FBDC), Salvador, Brazil.
10. Undergraduate Student at the Dentistry Course of the FBDC, Salvador, Brazil.
11. Adjunct Professor of the Dentistry Course of the FBDC, Salvador, Brazil.
12. Head of the Rheumatology Service of Hospital Santa Izabel; Adjunct Professor at the Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, Brazil.

Correspondence: Roberto S. Tunes. Rua Conde Filho, 238/1201, Graça, Salvador, CEP: 40150-150, Bahia, Brazil, telephone (fax):+55 71 3245-5183, robertotunes@terra.com.br.

Abstract

Recurrent Aphthous Ulcerations (RAU) has been related as the most prevalent oral inflammatory disease in the world scenario, although consistent and up-to-date epidemiological data are scarce in our country. The aim of the present study is to describe the prevalence and clinical aspects of RAU in Brazil. This is a cross sectional investigation of the prevalence of RAU in individuals attended by a Stomatology service between August, 2006 and August, 2007. The first stage identified patients with RAU among all of the patients examined in the ambulatory clinic; the second stage carefully examined the patients with RAU and another associated symptom, under hospital conditions, in order to diagnose other related diseases. Three hundred and six patients were attended, but the standard questionnaire was applied to 50 (16.6%) patients, 29 men and 21 women, identified as having RAU. RAU of the minor type was observed in 88%; the major type in 8% and the herpetiform type in 4%. The complex type of RAU was found in 8% of patients, while the simple type was found in 92%, with recurrences that ranged from 2-6 times per annum. Among the systemic manifestations related to RAU, one patient was diagnosed as having the Behcet syndrome, another with ulcerative colitis and another with hypothyroidism. The general prevalence found corroborates the existent data in the world scenario.

Keywords Recurrent aphthous ulcerations - epidemiology - clinical features - differential diagnosis - treatment

Introduction

Recurrent aphthous ulcerations (RAU), also referred to as aphthous stomatitis, is an inflammatory disease of the oral mucosa, whose prevalence in the world population is around 5-25%, reaching up to 60% in specific groups [1, 2]. The affliction is characterized by the appearance of painful and recurrent, single or multiple ulcers, that preferentially affect the nonkeratinized oral mucosa [3]. The etiopathogenesis of RAU points towards an immunological alteration, however, the mechanisms that set off the lesions is unknown. Diagnosis is based exclusively on the patient's history and clinical aspect of the lesions [4]. The literature with respect to it is vast from the clinical and therapeutic point of view, even so, the clinical development of the patient requires a correct diagnosis and classification of the disease based on morphology and severity [5]. Important considerations must be pointed out with regard to the differential diagnosis, which includes complex aphthous stomatitis and variants related to systemic manifestations, such as those associated with hematologic, hormonal, nutritional and gastro-intestinal alterations [6]. In view of these factors, the clinician needs to be prepared, by means of an anamnesis and a well elaborated clinical exam, to diagnose the clinical conditions that involve RAU and other systems [3]. In Brazil, no significant population-based survey has ever been conducted; however, a few studies have endeavored to show the national reality, particularly in children and the elderly. Therefore, the aim of the present study is to describe the prevalence and clinical aspects of RAU in a specialized ambulatory clinic of a university institution.

Methods

This study conducted a cross-sectional investigation into the prevalence of RAU in patients attended by the Stomatology service of the Escola Bahiana de Medicina e Saúde Pública, Salvador-Bahia-Brazil between August 2006 and August 2007. This is a reference Stomatology service in a district with 385,109 inhabitants. The study was conducted in two stages: the first stage identified the individuals with RAU among all the patients examined at the ambulatory clinic; the second stage carefully examined the patients with RAU with the purpose of defining patients with other related diseases.

The estimated sample size was 151 patients to be attended by the service, and an expected prevalence of 11% of patients with RAU was evaluated, with a confidence interval of 95% and a level of precision of 5% [7]. In the first stage of the research, for each patient in the sample, a standard chart containing 26 questions was filled out, in which the patient's identification data and related systemic conditions were stated. With regard to lesions, the number, location, size, age at the disease onset, number of episodes per year, time between episodes in months, duration of episode in days, associated symptomatology and treatment submitted to were noted. Data collection was done by interview and complemented with data collected on the case history chart and noted on the catalographic chart.

Included in the study were patients that presented the minor type of RAU, major or herpetiform type, with up to two days of development, and with two or more episodes over the last twelve months. After confirmation of the presence of RAU, the patientes were submitted to a pathergy test performed by the same investigator [8]. Afterwards, the individuals that presented other signs and symptoms of associated diseases such as acute vulvar ulcer, hematinic deficiencies, gluten-sensitive enteropathy (celiac disease), inflammatory intestinal disease, cyclic neutropenia, AIDS (acquired immunodeficiency syndrome), Systemic Lupus Erythematosus (SLE), MAGIC syndrome (mouth and genital ulcers with inflamed cartilage), PFAPA syndrome (periodic fever, aphthosis, pharyngitis and adenitis), Sweet's syndrome, Reiter's syndrome and Behcet's syndrome (BS), were referred for careful medical evaluation in the hospital environment.

The study was submitted to and approved by the research ethics committee of Santa Izabel Hospital (Salvador-Bahia), and all the patients signed the term of free and informed consent.

Statistical analysis, including descriptive data, was performed using the SPSS version 13.0 software. For the male and female comparison, the categorical variables were analyzed using chi-square

test or Fisher's exact test, as appropriate. The continuous variables were analyzed using the Student's-*t* test. Significance was set at the level of 5%.

Results

During the study period, 306 patients were attended by the Stomatology service, of whom only 50 (16.6%) (95% IC, 12.5%-20.8%) presented with RAU, and replied to the standard questionnaire in the first stage of the study. Of these 50 individuals, 29 (58%) of were men and 21 (42%) were women. They ranged between 11 and 55 years of age (mean 26.2±9.8), with a mean among men of 27.6±11.3 and women 24.2±7.1. The age of disease onset was 17.4±8.8, being 17±9.5 for men and 17.9±7.9 for women. While the protocol was being performed, no individual presented a positive pathergy test. Only 3 (6%) patients were referred to the second stage of the study, and received careful medical evaluation in a reference unit. One patient (2%), a 35-year old man, fulfilled the criteria of the *International Study Group for Behcet's Disease (ISGBD)*, presenting RAU, recurrent genital ulcers, cutaneous, ocular, and vascular manifestations and fever. One individual was diagnosed as having ulcerative colitis, and another patient reported undergoing thyroid hormone replacement for the treatment of hypothyroidism.

The clinical aspects with reference to the 50 patients with RAU are described in Table 1. The most frequent location of the aphthous lesions was in the buccal mucosa (56%), followed by the lips (54%). The mean time between episodes, in months (2.9±1.4 months), the number of episodes per annum (4.5±4.2/year), number of ulcers per episode (1.7±1.4) and the mean duration of each episode (7.3±2.8) did not differ between the sexes. Algic symptomatology associated with the ulcers was reported in 86% of the patients, and 72% of the individuals reported performing some type of topical treatment with the object of accelerating the healing time of the wounds. Triamcinolone (Omcilon® in oral base) (62%), followed by $NaHCO_3$ + KCL (Albicon®) (4%) were the most used medications. Other medications mentioned were: dexamethasone (Decadron®), Chamomilla recutita 10% (Ad-muc®), polycresulen (Albocresil®) and hydrocortisone + neomycin sulfate (Gingilone®).

The patients' systemic profile can be observed in Table 2, in which 10% present cutaneous manifestations, with the predominance of acneiform lesions (10%), all in men. Only 6% of patients presented joint manifestations and 18.4% reported neurological symptoms, particularly headaches (16.3%). Gastrointestinal disease was observed in 10% of the individuals, more frequently in men (80%). Vertigo was reported in 4% of the patients.

Discussion

The present study evidenced a prevalence of 16.6% (95% IC, 12.5%-20.8%) of RAU in an ambulatory Stomatology clinic which, although similar to that observed in previous studies [9], it should be emphasized that such number, because of being obtained in a specialized center, could be overestimated and not reflect the reality of the local population. Embil et al. [10], in a classical study in 1975, observed the following distribution of RAU among six continents: 30.5% in Africa; 45.3% in Asia; 33.1% in Oceania; 36.3% in Europe; 57.9% in North America and 26.2% in South America. Shulman et al.[11], in the third National Health and Nutrition Survey in 1988-1994 (NHANES III) related that RAU was the thirteenth most common oral lesion and the inflammatory lesion most prevalent in the USA. In Brazil, no population-based survey as significant as NHANES III has ever been conducted, however, a few studies have endeavored to show the national reality, particularly in children and the elderly. Within this pattern, Mesas et al.[7], in a sample of 267 elderly persons, with a mean of 66.5 years of age, observed that oral ulcers were the most prevalent inflammatory lesions among them (11.3%). Dos Santos et al.[12] in a cross sectional cut with 587 individuals of an indigenous community in Central Amazonia, which did not have the habit of consuming alcoholic beverages, smoking or using pacifiers, found a low prevalence of RAU (1.2%) for children under the age of twelve, in addition to a general frequency of 0.9%. Therefore, population based studies are necessary in order to determine the real prevalence of this disease in Brazil.

Usually, the onset of RAU is in childhood or adolescence, with a trend towards diminishing in frequency and severity with age [4]. As described, the diagnostic age ranged between 11 and 55 years, with a mean of 26.2±9.8, similar to the study of Motta et al.[13], who evidenced a mean equal to 33.2±14.6, with the greater prevalence of the infirmity occurring in the age range comprised between 15 and 45 years. Where sex is concerned, men were more affected than women in the ratio of 1.4:1 (M:W), differing from the majority of studies described. The observation that the exacerbation of RAU in women could be correlated with the menstrual cycle, led to a hormonal basis of the disease. However, the world trend towards approximately equal distribution of aphthous stomatitis in men contradicts this idea [14, 15].

With regard to the clinical aspects of RAU, it is emphasized that the results did not differ from the series of other countries, which present a prevalence of 75% to 85% of the minor type of RAU

(<10mm), 10% to 15% of the major type and 5% to 10% of the herpetiform type [4, 16]. The present study observed 88% of RAU of the minor type, 8% of the major type and 4% of the herpetiform type. The complex type (continuous pattern) was found in 8% of patients, while the simple type was found in 92%, with recurrences that ranged from 2-6 times per annum. Generally, the lesions were painful (86%), which explains the high number of patients submitted to topical treatment (72%). The most prevalent location was in the buccal mucosa (56%) and lips (54%), as described in previous studies. The most used medication was Triamcinolone acetonide 0.05% (62%), whose side effects were not described by the patients interviewed, who on the other hand related its use would diminish the healing period. No individual reported the use of systemic medication.

Where the age of RAU onset is concerned, a mean of 17.4±8.8 was found, in contrast with the literature, which shows a mean two-phased frequency of disease onset between 0 and 9 years and between 10 and 19 years [17]. This finding possibly reflects the theory that not only the genetic condition is *sine qua non* for the appearance of the disease, but environmental factors, such as stress, smoking and exposure to infectious agents can interfere in the etiopathogenic process of the disease [18]. In around 80% of the patients, RAU initially develops before 30 years of age, suggesting that the late manifestation of the disease could be related to a specific predisposing factor or to more complex systemic conditions such as the Behcet Syndrome itself [4].

The patient diagnosed as having BS presented with RAU of the minor and complex type, recurrent genital ulcers, cutaneous (acneiform lesions and erythema nodosum), articular (arthritis), ocular (uveitis and keratoconjunctivitis) manifestations, thrombophlebitis, hypoacusia and fever. As with the patient, in BS the RAUs are generally of the minor type, complex and in larger number [19]. Few systemic manifestations were found in the 50 patients with RAU. Among them, the outstanding were cutaneous manifestations (10%) with predominance of acneiform lesions; 18.4% of neurological symptoms, especially headaches (16.3%); in addition to gastrointestinal manifestations (10%) (Table 2). Peptic ulcer, gastroduodenitis and ulcerative colitis were found in three patients respectively, rectocolitis being an important differential diagnosis for RAU [4].

The presence of RAU lesions is critical for the diagnosis of a series of systemic diseases, such as BS, MAGIC syndrome, PFAPA syndrome, which becomes a much rarer condition without the presence of the ulcers. As was observed, the Behcet Syndrome, in addition to being a complex infirmity, constitutes a reality, and in the face of this, by means of anamnesis and a well prepared clinical exam, the

clinician needs to be prepared to diagnose it. Therefore, it is emphasized that further studies about the diagnosis, etiopathogenesis, epidemiology and treatment are necessary to enable us to understand the reality of RAU in Brazil.

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Table 1 Distribution of the clinical characteristics of the 50 patients with RAU, and comparison between men and women.

	Frequency(%)	Men (n=29)	Women (n=21)	*P* value
Age at time of disease diagnosis (years ± SD)	26.2±9.8			
Age at time of the disease diagnosis, men to women ratio (years ± SD)		27.6±11.3	24.2±7.1	NS
Age of disease onset (years ± SD)	17.4±8.8			
Age of the disease onset, men to women ratio (years ± SD)		17±9.5	17.9±7.9	NS
Location				
Buccal mucosa	56	57	43	NS
Lips	54	59.2	40.8	NS
Gingiva	12	66.6	33.4	NS
Tongue	26	69.2	30.8	NS
Floor of the Mouth	12	66.6	33.4	NS
Vestibule	18	55.5	44.5	NS
Palate	8	50	50	NS
Oropharynx	4	0	100	NS
Time between episodes in months	2.9±1.4	2.9±1.4	2.8±1.4	NS
Number of episodes per year	4.5±4.2	4.4±4.3	4.6±4.1	NS
Number of ulcers per episode	1.7±1.4	1.9±1.7	1.5±0.9	NS
Duration of episode in days	7.3±2.8	7.1±2.4	7.7±3.2	NS
Size of ulcers (mean in mm)	3±2	4±3	3±2	NS
Pain	86	58.1	41.9	NS
Use of medication	72	63.8	36.2	NS
Local medication				NS
Triamcinolone	62	-	-	NS
$NaHCO_3$ + KCL	4	-	-	NS
Dexamethasone	2	-		NS
Chamomilla recutita 10%	2	-	-	NS
Polycresulen	2	-	-	NS
Hydrocortisone + Neomycin	2	-	-	NS

NS: Not Statistically significant

Table 2 Systemic Profile of the 50 patients with RAU.

	Frequency(%)	Men(n=29)	Women (n=21)	*P* value
Oral ulcers	100			
Genital ulcers	2	100		NS
Overall ocular disease	6	66.6	33.4	NS
Keratoconjunctivitis	6	66.6	33.4	NS
Overall skin lesions	10	100		0.04
Acneiform lesions	10	100		0.04
Erythema nodosum	2	100		NS
Pathergy	0			
Joints symptoms	6	66.6	33.4	NS
Superficial thrombophlebitis	2	100		NS
Neurological symptoms	18,4	55.5	44.5	NS
Headache	16,3	62.5	37.5	NS
Convulsions	2	100		NS
Overall gastrointestinal disease	10	80	20	NS
Gastroduodenitis	2	100		NS
Peptic Ulcer	2		100	NS
Vestibular-cochlear symptoms	4	50	50	NS
Fever	2	100		NS
Ulcerative colitis	2	100		NS
Hypothyroidism	2	100		NS

NS: Not Statistically significant

ARTIGO 5

JUNTAS / JOINTS
BOLETIM DO SERVIÇO DE REUMATOLOGIA DO HOSPITAL SANTA IZABEL

ARTIGO DE REVISÃO

Síndrome de Behçet: Revisão de literatura

Roberto Tunes[1], Mittermayer Santiago[2].

RESUMO

A síndrome de Behçet é uma síndrome inflamatória, complexa e multissistêmica caracterizada classicamente por ulcerações orais recorrentes, ulcerações genitais e alterações oftalmológicas, mas que pode afetar qualquer sistema, incluindo o sistema músculo-esquelético, vascular, neurológico, respiratório e gastrointestinal. Sua patogenia permanece incerta, mas dados epidemiológicos sugerem uma interação entre fatores genéticos, imunológicos e infecciosos. A síndrome de Behçet tem distribuição geográfica universal, embora seja mais freqüente na bacia do Mediterrâneo, Japão e Oriente médio. No Brasil, não existem dados substanciais na literatura quanto à real prevalência e incidência dessa síndrome. Logo, este trabalho visa apresentar uma revisão de literatura enfocando os principais aspectos epidemiológicos, etiológicos, clínicos, os critérios diagnósticos e o tratamento da síndrome de Behçet.

Palavras-chave: Síndrome de Behçet; epidemiologia, patogenia, tratamento.

ABSTRACT

Behçet's syndrome (BS) is a multisystemic inflammatory disorder characterized by recurrent oral and genital ulcers and ophthalmic alterations, but also involving other systems, including joints, blood vessels, nervous, respiratory and gastrointestinal tracts. Its etiopathogenesis remains unknown, but epidemiologic data suggest an interaction among genetic, immunologic and infectious factors. BS has a worldwide distribution being most frequently seen in the Mediterranean area, Japan and Middle East. In Brazil there are no substantial data regarding its prevalence or incidence. The aim of the present study was to review the main epidemiologic data, clinical features, diagnostic criteria and current treatment of BS.

Key words: Behçet's syndrome; epidemiology; pathogenesis; treatment

[1] Aluno do curso de mestrado em Medicina e Saúde Humana da Fundação Bahiana para o Desenvolvimento das Ciências.
[2] Chefe do Serviço de Reumatologia do Hospital Santa Izabel; Professor-Adjunto da Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia.
Correspondência: Mittermayer B. Santiago. Praça Conselheiro Almeida Couto, 500, Nazaré, Salvador, CEP: 40000-000, Bahia, Brasil, telefone (fax): (71) 3326-5276, mitter@svn.com.br.