Editorial

The magic of syndromes

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Received on September 6, 2006; accepted in revised form on September 10, 2006.

Clin Exp Rheumatol 2006; 24 (Suppl. 42): S56-S57.

Key words: Behçet's disease, polychondritis, MAGIC syndrome.

In this issue of *Clinical and Experimental Rheumatology,* three patients fulfilling classification or diagnostic criteria of both Behçet's disease (BD) (1) and relapsing polychondritis (RP) (2) are described (3, 4).

Without the knowledge of possibly discriminating features such as autoantibodies against cartilage components such as collagen type II (which can probably be detected in most RP patients) and of HLA associations (such as HLA-B51 with BD and HLA-DR4 suballeles with RP), Firestein and coworkers (5), some years ago, described a new "syndrome", which they named "MAGIC"- an acronym for " Mouth and Genital Ulcers with Inflamed Cartilage". They concluded this from their observations in 5 patients with overlapping symptoms of BD and RP.

The patient presented by our group clearly shows symptoms and the HLA genotype of both diseases, as well [HLA-B51, which is associated with BD in 70% of all cases, and HLA-DRB1*04, which as an HLA-DR4 subtype allele, is associated with relapsing polychondritis in 60 % of all cases (6, 7)]. The two cases of the Japanese group were positive for HLA-DR15, not for DRB1*04 or other DR4 alleles known to be associated with RP, and one was positive for HLA-B51, the other for HLA-B52 (the latter not being associated with BD, although the antigen has a very similar structure, differing in 2 amino acids only and being a split antigen of HLA-B5, similar to HLA-B51). HLA-DR15 is known to be associated with multiple sclerosis (MS) and myelodysplastic syndrome (MDS), but not with RP which is associated with HLA-DR4 suballeles similarly to rheumatoid arthritis (RA) (8, 9). HLA-B52 is associated with Takayasu arteritis (10). As in the cases described by Nanke *et al*., in which HLA-DR15 was present, one would recommend them to survey for the possible presence or development of an underlying myelodysplastic syndrome, with which RP may be associated (also as BD, although less frequently) (11, 12).

To date, including the three cases described in the present issue of Clin Exp Rheumatol, 14 [after subtraction of the 5 cases from the past literature not fulfilling ISBD classification criteria for BD (3)] patients fulfilling both the classification criteria for BD and RP have been described. Most of them had developed symptoms of BD before those of RP [almost all described before the three of this issue, the one by our group and one (case 2) of the Japanese group].

The finding that almost all of the cases (including case 2 of Nanke *et al.* and our case) described until now who fulfilled the criteria both for BD and RP and hence were diagnosed as "MAGIC" had BD symptoms before RP criteria were fulfilled clearly hints at a secondary pathogenesis of RP in association with BD. Unfortunately, due to the relatively early description of the cases of the MAGIC cases prior to the present ones, HLA typing was not performed in most of the previous case reports, nor was detection of collagen antibodies. This of course would have been helpful to differentiate BD from RP. In RP, collagen antibodies should be present, whereas in BD, HLA-B51 is positive in the majority of patients, and collagen antibodies and HLA-DR4 suballeles are negative. Pathergy testing could be helpful, however, the pathergy phenomenon is positive in only 30% of all BD patients (differing with the origin of the patients) and if it is negative, this does not necessarily mean that the patient does not have BD. Nevertheless – all this does not discriminate primary RP from RP occurring secondary to other diseases.

RP can occur as a primary entity without any underlying disorder, but it in 30% of all cases it is associated with other inflammatory rheumatic and autoimmune conditions such as vas-

culitides (polyarteritis nodosa, Wegener granulomatosis, Churg Strauss syndrome, Behçet's disease, Takayasu arteritis, temporal arteritis, cryoglobulinemic vasculitis), connective tissue diseases (systemic lupus erythematosus, Sjögren's syndrome, mixed connective tissue disease, systemic sclerosis), arthritides (rheumatoid arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, reactive arthritis), myasthenia gravis, diabetes, thymoma, thyroid autoimmune diseases. Furthermore, RP occurs secondary to haematologic diseases such as myelodysplastic syndromes, multiple myeloma, pernicious anemia and acute leukaemia. Additionally, RP often is associated with familial Mediterranean fever and glomerulonephritis (13, 14).

What is a syndrome? According to "Wikipedia" (www.wikipedia.org) - the internet encyclopedia, a syndrome is the association of several clinically recognisable features, signs, symptoms, phenomena or characteristics which often occur together, so that the presence of one feature alerts the physician to the presence of others. The term "syndrome" derives from Greek and literally means "run together". The term is most often used when the pathophysiology of the features occurring together (or the "syndrome") is unknown. Behçet's disease itself - due to its unknown pathophysiology , aetiology and its diverse symptoms - is often declared as " Behçet's syndrome". This is appropriate, as its diagnostic criteria (1, 15) require a combination of major and minor findings, which is also included in the definition of "syndrome". As RP clearly is a disease with diagnostic criteria (2) and with a probable pathophysiology - collagen antibodies occurring in most of the patients, hinting at a primary damage of connective tissue or cartilage - RP should be classified as "disease". BD is also commonly is classified as "disease", as there are well-defined classification criteria, although its pathogenesis is still unclear.

What is magic? The word *magic* ultimately derives from Magus, one of the Zoroastrian astrologer priests of the Medes. The word entered the English language in the late 14th century from Old French *magique*. Magic is commonly divided into *white magic* (healing, divination and other magic used for benign purposes) and *black magic* (malicious or harmful magic). The term "magic" today defines the art of entertaining an audience by performing illusions that baffle and amaze, often by giving the impression that something impossible has been achieved, almost as if the performer had magic or supernatural powers. Yet, this illusion of magic is created entirely by natural means (www.wikipedia.org).

The acronym "MAGIC" in the present and past cases is misleading- what have the symptoms of the patients to do with "magic" in the pure sense of the word? Nothing, of course (in case of black magic: hopefully)!

Although the word "MAGIC" sounds very attractive to me (and everyone else, I suppose), according to the evidence provided by the extensive literature research and the HLA-typing results (where available), and regarding the common association of RP with other – especially autoimmune and inflammatory rheumatic conditions including systemic vasculitides and the fact that in almost all cases described in the literature RP occurred after the onset of BD – I would prefer and recommend calling it "BD / RP overlap" or "RP secondary to BD".

The most probable hypothesis is that BD as systemic vasculitis induces damage to vascular tissue and hence disposition of collagen to cells of the immune system which in turn produce autoantibodies against collagen and symptoms of RP.

As in Goethe's *Zauberlehrling,* the sorcerer's apprentice cried for help while trying to fill the bath with water without his master's help:

"And they're running! Wet and wetter get the stairs, the rooms, the hall! What a deluge! What a flood! Lord and master, hear my call! Ah, here comes the master! I have need of Thee! From the spirits that I called Sir, deliver me!" ("Und sie laufen! Nass und nässer wird's im Saal und auf den Stufen, welch entsetzliches Gewässer! Herr und Meister, hör' mich rufen! Ach, da kommt der Meister! Herr, die Not ist groß! Die ich rief, die Geister werd' ich nun nicht los.")

Let's stop calling the overlap of BD with RP "MAGIC" syndrome, and reduce the number of syndromes in the medical world!

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