



#### INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited. The length of a letter should not exceed 800 words, with a maximum of 10 references and no more than 2 figures or tables; and no subdivision for an abstract, methods, or results. Letters should have no more than 4 authors. Financial associations or other possible conflicts of interest should be disclosed.

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#### Inverse Association Between Obesity and Antinuclear Antibodies in Women

To the Editor:

More than 70% of all autoimmune illnesses occur in women, a figure that has been attributed to stimulation of the Th2 response by estrogens. However, a little-explored relationship is that which may exist between obesity and autoimmune disorders in women. Since the discovery of lep-

tin<sup>1</sup> it has been known that the cytokine-producing capacity of adipose tissue is high. Serum concentration of leptin is 3- to 4-fold higher in women than in men. However, little is known about the reasons for this difference. To date no studies have investigated the relationship between leptin and autoimmune disease in the general population. Our aim was to determine whether there was any association, in the general population, between obesity and the presence of antinuclear antibodies (ANA).

We studied the first 702 individuals enrolled in the "CDC de Canarias" cohort study, whose participants were drawn randomly from the adult general population. Some of the findings for this cohort study have been reported earlier<sup>2</sup>. Obesity was identified as body mass index (BMI)  $\geq 30$ . Abdominal obesity was considered to exist when waist circumference was  $\geq 88$  cm in women or  $\geq 102$  cm in men<sup>3</sup>, and also when waist circumference was  $\geq 80$  cm in women and  $\geq 94$  in<sup>4</sup>. Obesity was also identified as a waist/height ratio of  $\geq 0.55$ .

ANA titer was measured with an indirect immunofluorescence technique that used HEp-2 cells as the substrate (Nova Lite™, Inova Diagnostics, San Diego, CA, USA). Samples were considered ANA-positive when fluorescence was seen at a serum dilution of  $\geq 1/40$ . All ANA-positive samples were tested by serial double dilution to the highest dilution that yielded fluorescence. Leptin concentration was measured with an enzyme linked immunosorbent assay (ng/mL, Biosource®) with a within-assay coefficient of variation of 3.6%, a between-assay coefficient of variation of 6.8%) and a detection limit of 0.1 ng/mL. Proportions were compared with Pearson's chi-squared test, and continuous variables with Student's t test. Logistic regression model were fitted for each measurement of obesity (independent variable), with ANA being the dependent variable.

The prevalence of ANA was 27% (34% in women,  $n = 378$ , vs 17% in men,  $n = 324$ ;  $p < 0.001$ ), this being close to the value reported in an earlier international study<sup>5</sup>. In women the bivariate analysis showed inverse association of ANA positivity with obesity only for titers  $\geq 1/80$  (Figure 1): BMI (23.4 vs 10.4;  $p = 0.02$ ), waist circumference (23.5 vs 11.5;  $p = 0.02$ ), and waist/height ratio (23.7 vs 13.2;  $p = 0.04$ ). Serum leptin concentration was also significantly lower in these women ( $8.8 \pm 6.9$  vs  $11.5 \pm 8.8$  ng/mL;  $p = 0.01$ ). This analysis did not detect any associations between ANA titers and obesity in men.

After adjustment for age, the multivariate models confirmed the rela-

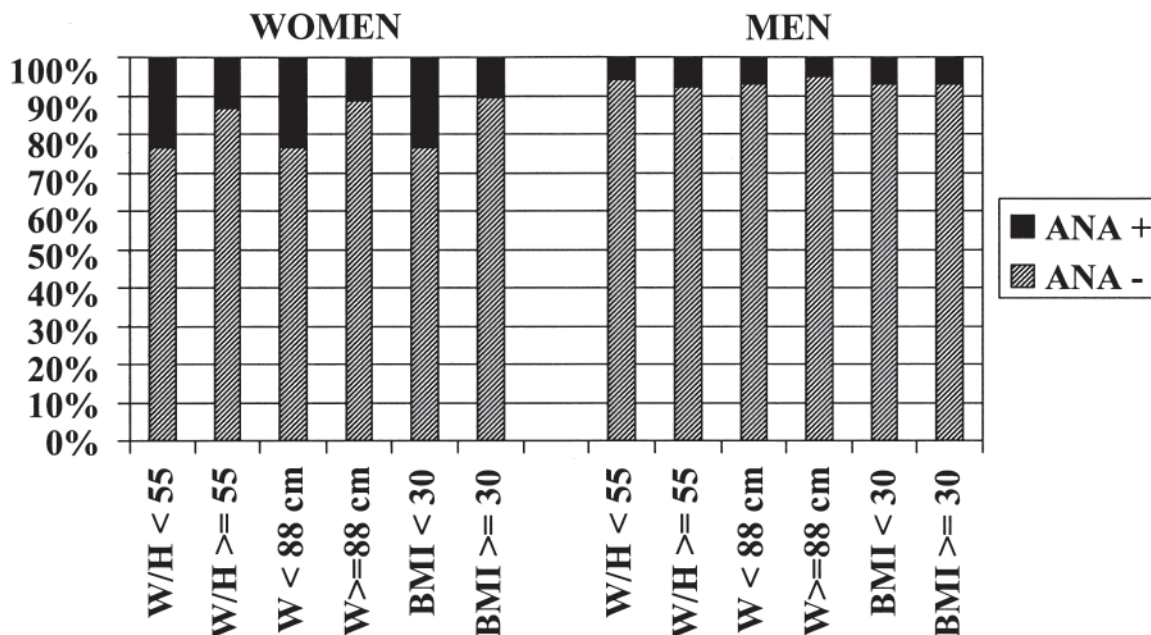


Figure 1. Differences in the proportions of men and women with obesity according to anthropometric criteria and a positive ANA titer  $\geq 1/80$ . W/H: Waist to height ratio. W: waist circumference. BMI: body mass index ( $\text{kg}/\text{m}^2$ ).

tionship between positive ANA titer and obesity in women, and the absence of this relationship in men (Table 1). In multivariate analyses to contrast ANA-negative persons against ANA-positive participants in whom the titer was  $\geq 1/80$ , the inverse association between ANA titer and obesity in women was stronger (odds ratio further from the null value) than in models that included ANA titers  $\geq 1/40$  (Table 1).

This inverse relationship we found between ANA and obesity in women from the general population has not been reported previously. Improvements in nutritional status have been paralleled by an increase in the susceptibility to autoimmune diseases<sup>6,7</sup>. Given that leptin accelerates the onset or progression of some autoimmune diseases, and that it also stimulates the secretion of autoantibodies *in vitro*<sup>8</sup>, it might be predicted that obesity and elevated leptin concentrations would be associated with an increase in ANA. However, we found no such association in men, and in contrast to our expectations, in women we observed that leptin concentration and obesity correlated inversely with ANA. This finding was bolstered by the fact that the association became stronger at higher ANA titers.

One possible explanation for the low prevalence of ANA in women with overweight or obesity is related to the lack of response to leptin in obese individuals. Obesity in humans presents hyperleptinemia together with both central and peripheral resistance to the action of this hormone. Leptin resistance has been well documented<sup>9</sup>: as BMI increases, the diminishing response to leptin can impair ANA production by B lymphocytes. To understand why the inverse relationship between obesity and ANA titer appears only in women, we may speculate whether sex hormones play a role in leptin resistance<sup>10</sup>. The main limitation of our study is its cross-sectional design; this prevents us from establishing a causal relationship for the variables we analyzed. The main strength of our study, in contrast, lies in the large sample of individuals drawn randomly from the general population. We conclude that in women in the general population there is an inverse association between positive ANA titer and obesity defined on the basis of anthropometric criteria or serum leptin concentration.

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Table 1. Relationship between antinuclear antibody (ANA) status and anthropometric and biochemical indicators of obesity in men and women. Each row shows results for the logistic regression model with ANA status as the age-adjusted dependent variable. Rows in boldface type show the results with same model as the preceding row for an ANA titer  $\geq 1/80$ .

Indicator	Dependent Variable: ANA					
	Women (n = 378)*			Men (n = 324)*		
	OR	95% CI	p	OR	95% CI	p
Waist circumference, cm	0.978	0.960, 0.997	0.023	0.988	0.962, 1.015	0.386
<b>Waist circumference, cm</b>	<b>0.971</b>	<b>0.948, 0.995</b>	<b>0.020</b>	<b>0.992</b>	<b>0.955, 1.030</b>	<b>0.668</b>
Abdominal obesity ATPIII <sup>†</sup>	0.575	0.359, 0.919	0.021	1.118	0.577, 2.167	0.740
<b>Abdominal obesity ATPIII<sup>†</sup></b>	<b>0.445</b>	<b>0.247, 0.804</b>	<b>0.007</b>	<b>1.074</b>	<b>0.420, 2.748</b>	<b>0.882</b>
Waist/height ratio, cm	0.969	0.944, 0.995	0.020	0.992	0.947, 1.039	0.736
<b>Waist/height ratio, cm</b>	<b>0.962</b>	<b>0.930, 0.996</b>	<b>0.028</b>	<b>1.016</b>	<b>0.951, 1.085</b>	<b>0.638</b>
Abdominal obesity/height <sup>††</sup>	0.460	0.280, 0.770	0.003	0.992	0.947, 1.039	0.736
<b>Abdominal obesity/height<sup>††</sup></b>	<b>0.393</b>	<b>0.206, 0.752</b>	<b>0.005</b>	<b>1.157</b>	<b>0.435, 3.079</b>	<b>0.770</b>
Abdominal obesity IDF**	0.550	0.322, 0.940	0.029	0.872	0.451, 1.686	0.685
<b>Abdominal obesity IDF**</b>	<b>0.462</b>	<b>0.235, 0.909</b>	<b>0.025</b>	<b>0.831</b>	<b>0.346, 1.996</b>	<b>0.678</b>
Body mass index, kg/m <sup>2</sup>	0.941	0.898, 0.986	0.010	0.988	0.923, 1.057	0.717
<b>Body mass index, kg/m<sup>2</sup></b>	<b>0.921</b>	<b>0.866, 0.979</b>	<b>0.009</b>	<b>1.002</b>	<b>0.912, 1.101</b>	<b>0.965</b>
Obesity body mass index***	0.553	0.344, 0.888	0.014	1.231	0.646, 2.347	0.527
<b>Obesity body mass index***</b>	<b>0.502</b>	<b>0.274, 0.921</b>	<b>0.026</b>	<b>1.38</b>	<b>0.555, 3.430</b>	<b>0.489</b>
Leptin	0.760	0.593, 0.975	0.031	0.952	0.761, 1.192	0.668
<b>Leptin</b>	<b>0.629</b>	<b>0.465, 0.852</b>	<b>0.003</b>	<b>1.057</b>	<b>0.744, 1.501</b>	<b>0.758</b>

\* For models that included all participants with a positive ANA titer: n = 378 in women (248 negative, 138 positive) and n = 324 in men (268 negative, 56 positive). For models that included only ANA-positive titers  $\geq 1/80$ : n = 318 women (248 negative, 70 positive) and n = 292 men (368 negative, 24 positive). <sup>†</sup> Abdominal obesity according to NCEP ATPIII criteria: > 88 cm in women, > 102 cm in men. <sup>††</sup> Waist/height ratio: < 0.55 = 1;  $\geq 0.55 = 2$ . \*\* Abdominal obesity according to International Diabetes Federation criteria: > 80 cm in women, > 94 cm in men. \*\*\* Body mass index: < 30 = 1;  $\geq 30 = 2$ .

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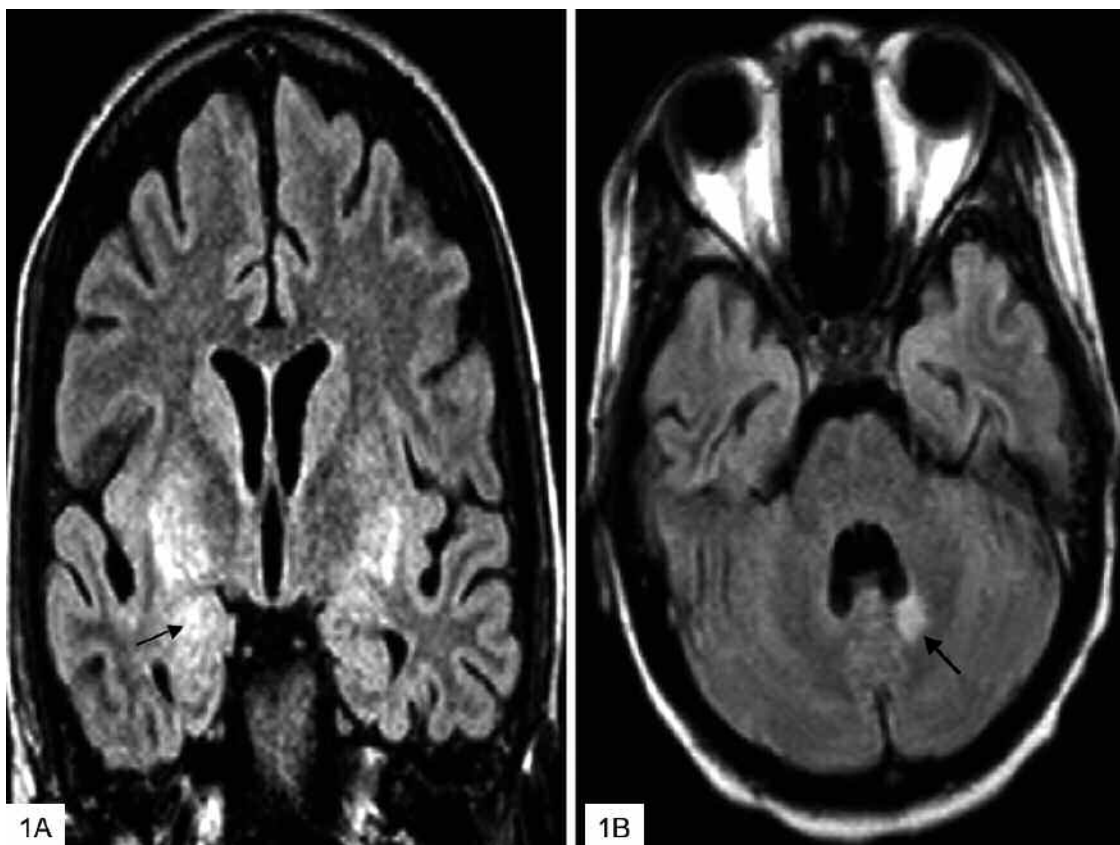
## Reversible Basal Ganglia and Amygdala Lesions in Central Nervous System Lupus

*To the Editor:*

Central nervous system (CNS) involvement in systemic lupus erythematosus (SLE) is common, with 25% to 60% of patients having neurological symptoms, and a higher percentage displaying CNS pathology in imaging

studies or on post mortem examination<sup>1,2</sup>. The most common clinical manifestations are cognitive decline, psychosis, seizures, and strokes. Abnormalities on magnetic resonance imaging (MRI) scans are usually nonspecific, such as cortical atrophy or scattered focal high-intensity white-matter signals<sup>3</sup>. Occasionally, larger infarcts or hemorrhages may be seen. We describe a young girl with CNS lupus who presented with the very uncommon MRI findings of hyperintense lesions in the basal ganglia, amygdala, and cerebellum, which resolved completely after immunosuppressive treatment, and discuss the implications for the pathogenesis of CNS involvement in SLE.

A 17-year-old girl was admitted in status epilepticus. She had a history of SLE diagnosed 4 months previously when she developed a butterfly malar rash, joint pain (knees, wrists, fingers), and fatigue. She was maintained on 60 mg prednisone daily. On examination, blood pressure was 115/75 mm Hg and there were no focal neurological findings. An erythematous malar rash was noted. Blood tests [positive antinuclear antibodies (ANA) and anti-dsDNA antibodies] confirmed a diagnosis of SLE. Cranial MRI scan done the next day was normal. Cerebrospinal fluid examination revealed elevated protein (270 mg/dl; normal 20–40), normal glucose, and mild lymphocytic pleocytosis (18 leukocytes, predominantly lymphocytes). A diagnosis of neuropsychiatric lupus (NPSLE) was made; seizures were rapidly controlled with intravenous lorazepam (4 mg) and fosphenytoin (1 g loading dose, maintenance 100 mg 8-hourly). Immunosuppressive therapy was continued with prednisone 80 mg per day. An electroencephalogram (EEG) 1 week after initial seizures showed diffuse slowing, but no epileptogenic activity. There were no further seizures from the second day of admission. Three weeks later she had new complaints of fatigue and generalized body weakness. There were no neurological symptoms and neurological examination was normal. A repeat EEG 4 days before these



**Figure 1.** MRI scan 4 weeks after seizure control when neurological examination was normal. A. Coronal FLAIR image shows hyperintense lesion in right amygdala (arrow). Bilateral hyperintense basal ganglia lesions can also be seen. B. Axial FLAIR image shows left cerebellar hyperintense lesion (arrow). All lesions disappeared after 6 weeks of immunosuppressive treatment (not shown).

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new symptoms showed some improvement with mild diffuse slowing, but no epileptogenic activity. There was generalized muscle pain but no weakness. There was no joint swelling. Investigations revealed that she had increased levels of creatine kinase (CK), from 3656 U/l to 4370 U/l (normal 24–195), myoglobinuria, and proteinuria (300 mg/dl). An electromyographic study revealed early recruitment of low-amplitude, polyphasic motor unit potentials, with frequent denervation potentials consistent with an acute myopathic process such as myositis. She was treated with 1 g intravenous methylprednisolone for 5 days and continued on 80 mg oral prednisone; CK levels gradually decreased over the following 3 weeks.

Although she had no new neurological symptoms or signs, a followup cranial MRI scan was done 4 weeks after the initial admission for seizures. It unexpectedly revealed hyperintense lesions in bilateral basal ganglia, right amygdala, and left cerebellum (Figure 1 and 2A). The basal ganglia involvement was striking, with involvement of the caudate nucleus, globus pallidus, putamen, and external capsule bilaterally (Figure 2A). There was no evidence of restricted diffusion to suggest infarction. Erythrocyte sedimentation rate was 120 mm/h (normal 0–20); CK level was still markedly elevated at 1800. ANA, anti-dsDNA antibodies, antiribonucleoprotein, and anti-SM serum antibodies were positive. Lupus anticoagulant, antiphospholipid, and anti-SSB antibodies were negative. Serum complement C3, C4, and CH50 levels were normal. She had proteinuria (300 mg/dl); renal and hepatic function tests were normal. Mycophenolate mofetil 1 g twice daily was added to prednisone 80 mg daily, and she had an uneventful clinical recovery from myositis over the next month. A repeat cranial MRI scan after 6 weeks showed complete resolution of all hyperintense lesions in basal ganglia, amygdala, and cerebellum (Figure 2B).

Our patient was unique because of the bilateral involvement of basal ganglia and right amygdala and cerebellum. Involvement of the basal gan-

glia<sup>4–6</sup> and amygdala<sup>7</sup> has very rarely been reported in SLE. Basal ganglia involvement was described in one patient with seizures<sup>4</sup> and in patients with chorea or parkinsonian symptoms<sup>5,6</sup>. In contrast, in our patient basal ganglia and amygdala lesions were noted 4 weeks after seizures, while there was an exacerbation of lupus with myositis and proteinuria, but with no neurological symptoms or signs. Conversely, the cranial MRI scan at the time she presented in status epilepticus was completely normal. Normal MRI scans following seizures or psychosis in SLE has been noted<sup>3</sup>, and may reflect that small high-intensity lesions due to edema may be rapidly reversible and hence are not detected. More commonly, transient cortical hyperintense lesions can be seen for the first few days on brain MRI scans after multiple seizures<sup>8</sup>. However, in our patient the initial MRI scan done the day after seizures was normal, and abnormalities were noted on the brain MRI scan 4 weeks later, when she had no neurological symptoms or signs and had had no seizures for 4 weeks. As well, the location of lesions in the basal ganglia and cerebellum (rather than in cortical gray matter) suggested that the brain MRI abnormalities were not related to the prior episode of seizures.

Reversible brain lesions can be seen in NPSLE<sup>9–11</sup> secondary to cases of reversible posterior leukoencephalopathy syndrome<sup>9</sup>, multiple seizures, or reversible edema secondary to ischemic lesions. The absence of restricted diffusion on brain MRI scan and absence of any lesion on followup brain MRI scans makes ischemic lesions less likely in our patient. Reversible posterior leukoencephalopathy syndrome has been described in many conditions including acute hypertension, eclampsia, chemotherapy, and SLE, and is characterized by headaches, seizures, blindness, and parietooccipital vasogenic edema on MRI scans<sup>9</sup>. This diagnosis should always be considered in lupus patients with reversible brain lesions. However, in

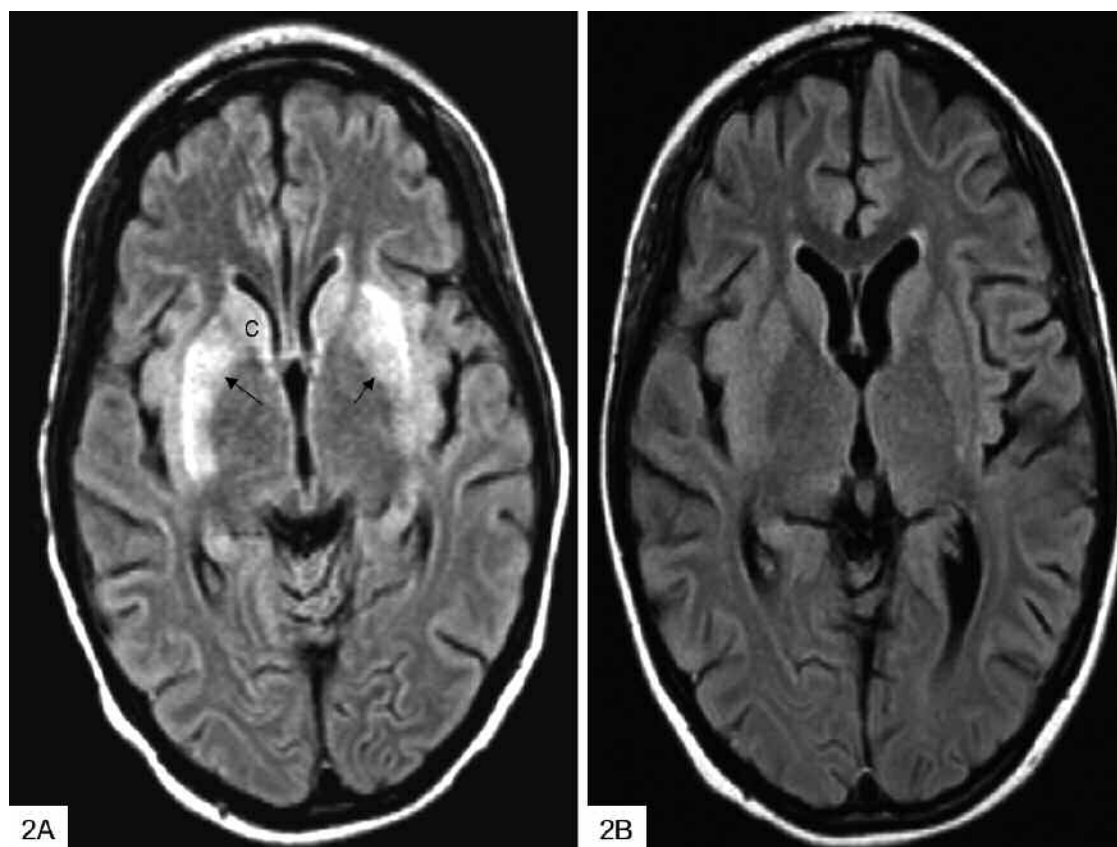


Figure 2. A. Axial MRI FLAIR image 4 weeks after seizure control when neurological examination was normal shows bilateral, extensive, hyperintense lesions in basal ganglia [globus pallidus, putamen (arrows) and in caudate nucleus (C)]. B. Axial MRI FLAIR image after 6 weeks of immunosuppressive treatment is normal, with resolution of all lesions.

our patient the absence of hypertension and the distribution of lesions in basal ganglia and cerebellum (without more typical posterior parietooccipital involvement on MRI scan) makes it less likely. Further, immunosuppressive therapy can trigger and should be avoided in reversible posterior leukoencephalopathy syndrome. However, our patient improved while under immunosuppression with high-dose prednisone and mycophenolate mofetil, making this diagnosis less likely.

The pathogenesis of neuropsychiatric lupus is not well understood<sup>12</sup>. Vascular compromise in lupus from an embolus or thrombus has been associated with antibodies that bind cardiolipin or phospholipids and may occur in any organ including the CNS<sup>13</sup>. However, CNS involvement can also occur, as is likely in our patient, with no evidence of ischemia<sup>2</sup>. It has been hypothesized that for CNS disease to occur the pathological agent, which may be an antibody or cytokine or cells capable of producing these molecules, has to cross the blood-brain barrier<sup>12</sup>. Specifically, CNS lupus has been linked to autoantibodies to ribosomal P proteins<sup>14</sup> and more recently to antibodies to double-stranded DNA, which have been shown to crossreact with the neuronal NMDA glutamate receptor and produce neuronal injury<sup>15</sup>. It is likely that many other still undiscovered autoantibodies exist that can crossreact with different brain proteins. The location of these proteins may determine the specific region of the brain that gets involved. For example, mice injected with anti-NMDA receptor antibodies have been reported to develop specific damage to the amygdala<sup>16</sup>, as seen in our patient.

Under normal circumstances antibodies cannot cross the blood-brain barrier. However, anti-NMDA receptor antibodies have been found in lupus brain<sup>15</sup>, implying that breaches of blood-brain barrier do occur in patients with SLE. Many factors, such as status epilepticus<sup>17</sup>, infection, stress, hypertension, or nicotine exposure, are known to disrupt the blood-brain barrier<sup>18</sup>. We speculate that in our patient breaches of the blood-brain barrier at the time she was undergoing an acute systemic exacerbation of lupus (with presumed higher levels of autoantibodies) allowed entry of pathogenic autoantibodies to the brain. The disruption of the blood-brain barrier may have been secondary to the prior status epilepticus (even though it occurred 4 weeks before brain lesions were first detected). Further, the absence of clinical neurological abnormalities and the complete resolution of all cerebral lesions on MRI scans suggest that autoantibodies can sometimes cause nonlethal reversible damage to neurons. It is also likely that early immunosuppression may have reduced the severity of neuronal damage.

We conclude that cranial MRI scans should be obtained during acute exacerbations of lupus or following events that may disrupt the blood-brain barrier. This may reveal unexpected CNS lesions, which could assist more effective planning of dosage and duration of immunosuppressive therapy. More research is needed to determine the significance and prognosis of findings obtained by MRI FLAIR studies, and careful clinical correlation for new neurological abnormalities is important and should be taken into consideration before any decisions about therapy are made.

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## Blockade of Interleukin 1 Receptor in Still's Disease Affects Activation of Peripheral T-Lymphocytes

To the Editor:

Adult-onset Still's disease (AOSD) is a rare systemic inflammatory disease characterized by arthralgias, transient cutaneous eruption, and high fluctuating fever<sup>1</sup>. No pathognomonic biological marker has yet been identified, making diagnosis difficult.

Recent pathophysiological findings showed that AOSD is characterized by a particular cytokine profile, suggesting implication of Th1 immune response. The overwhelming implication of interleukin 1 (IL-1) in the systemic inflammatory reaction seen during the course of AOSD has justified the administration of agents blocking IL-1 receptor (anakinra), which gave

some good results<sup>3,4</sup>. We describe a case of AOSD with an activated macrophage syndrome that responded to anakinra. The progression of activated T cells was associated with AOSD activity.

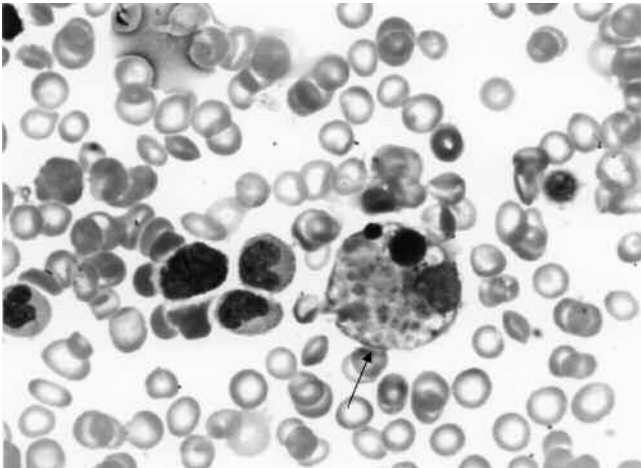


Figure 1. Bone marrow aspiration; cytopathology shows macrophages (arrow) that have active hemophagocytosis with intracellular blood cells, confirming the diagnosis of macrophage activation syndrome (Wright-Giemsa stain, original magnification  $\times 400$ ).

A 41-year-old woman presented in April 2001 with a history of intermittent fever, arthralgias, and cutaneous lesions progressing since 1986. AOSD was diagnosed in 1999 according to Yamaguchi's criteria<sup>5</sup>. Since 1999 she had received hydroxychloroquine and corticosteroids, resulting in remission for 2 years until January 2001. She presented with spiking fevers up to 39°C, polyarthritits, and an evanescent rash. Biological findings were white blood cell (WBC) count 30,000/mm<sup>3</sup> (90% neutrophils), elevated liver enzyme (5 times the normal level), and high ferritin level (2000 ng/ml, normal 10–240 ng/ml; 9% glycosylated). C-reactive protein and erythrocyte sedimentation rate were elevated to 60 mg/dl and 85 mm/h, respectively. Immunologically, she exhibited strong and permanent T-lymphocyte activation, with 25%–60% of CD3+ T cells expressing the HLA DR+ cluster (N < 15%). The latter are usually 80% CD8+ cytotoxic T cells expressing perforin and granzyme B, and being CCR7– CD45RA+.

The antimalarial drug was stopped in April 2001 and methotrexate (15 mg/wk) was started, with no response. She received different therapeutic agents — intravenous immunoglobulins, azathioprine, thalidomide, infliximab, etanercept, adalimumab — with no improvement.

In October 2002, while she was taking corticosteroids (20 mg/day), azathioprine, and thalidomide, she developed severe pancytopenia (WBC count 1100/mm<sup>3</sup>, hemoglobin 9.3 g/dl, platelets 35,000/mm<sup>3</sup>) in the context of macrophage activation syndrome, documented by a bone marrow examination (Figure 1). Cyclosporine was started and resulted in improvement of pancytopenia within 10 days, but not lymphocyte activation (45% CD3+DR+). In January 2003, infliximab was reintroduced because of clinical and hematological relapse. This treatment was considered partially efficient.

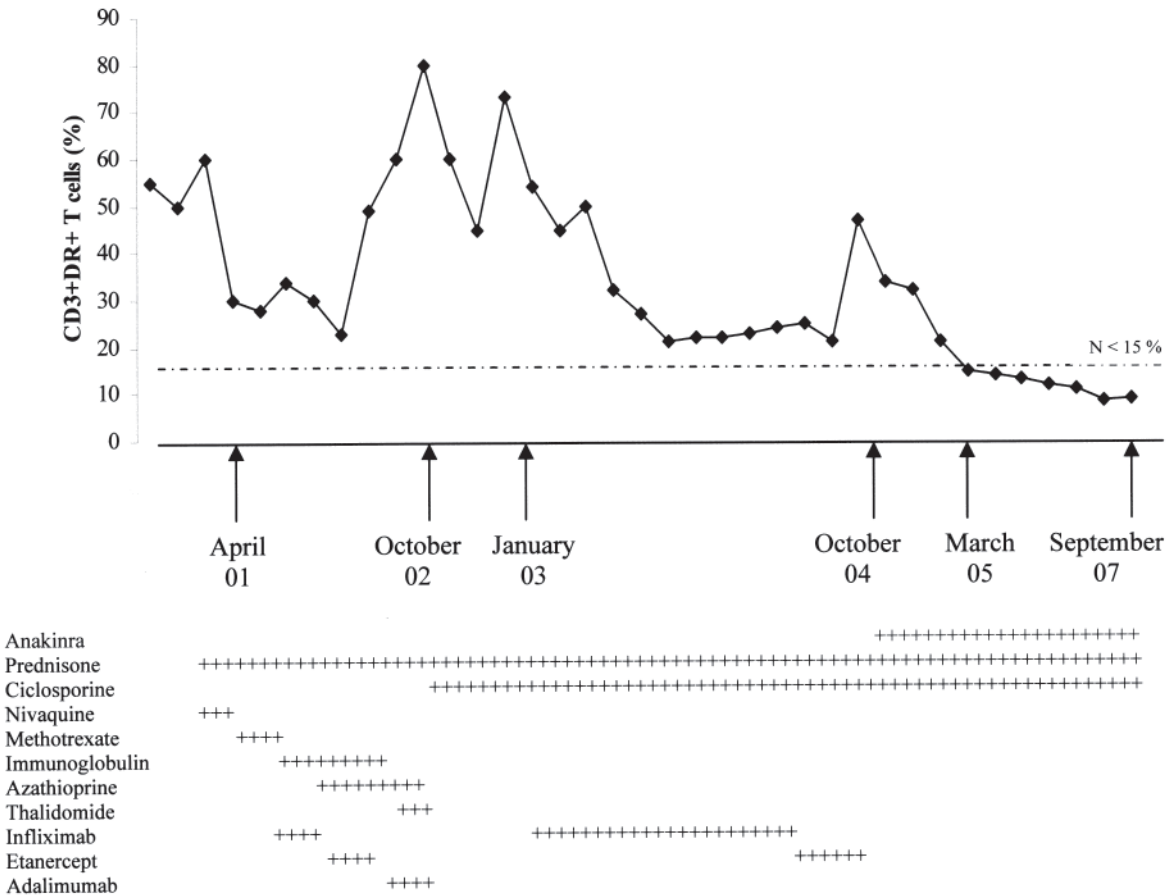


Figure 2. Expression of peripheral CD3+DR+ T lymphocytes (as percentages of total lymphocytes) as a function of time and the different therapeutic agents (indicated below). CD3+DR+ T-lymphocyte levels seemed to parallel disease activity, with generally high rates until October 2004, when the patient was clinically symptomatic; October 2002 and January 2003 correspond to AOSD flares. Normal levels were attained only after introduction of anakinra, October 2004, which achieved complete clinical and biological remission. N: normal value.

In October 2004, anakinra (100 mg/day) was started, in combination with cyclosporine and corticosteroids. Ferritin level was 344 ng/ml and the percentage of T-lymphocytes expressing HLA-DR was 34%. Great improvement was observed during the first weeks of treatment. Clinical symptoms regressed completely, and the percentage of circulating peripheral activated T-lymphocytes was normal within 6 months (Figure 2). In September 2007, she was still asymptomatic taking daily prednisone (5 mg), cyclosporine (120 mg), and anakinra (100 mg). We planned to taper the dosage of cyclosporine and prednisone until we could stop it.

The notable efficacy of anakinra and use of the percentage of peripheral activated T-lymphocytes to monitor disease activity make this case unusual. The decision to treat AOSD with an IL-1 receptor antagonist was based on recent pathophysiological findings<sup>6</sup>. Indeed, IL-1 plays a major role in the systemic inflammation observed during AOSD. This cytokine, secreted mainly by monocytes and macrophages, has dual activity: it binds to specific hypothalamic receptors responsible for temperature dysregulation and it targets the vascular endothelium, explaining cutaneous lesions, hyperleukocytosis, and IL-6 secretion responsible for liver involvement<sup>6</sup>. Several patients have been successfully treated with anakinra<sup>3,4,7,9</sup>; in conjunction with our experience with this patient, this further highlights the importance of biotherapy in AOSD treatment. Infliximab, etanercept, and adalimumab achieved only partial biological and clinical remission, and were clearly less effective than anakinra.

The Th1/Th2 disequilibrium in favor of Th1 responses was demonstrated in patients with untreated AOSD. IL-18, a cytokine synthesized by activated macrophages and playing an important role in Th1 polarization, is found at a very high concentration in AOSD, whereas the level of IL-4 is usually low, which supports the Th1/Th2 disequilibrium in favor of Th1 lymphocytes. Th1 activation induces the secretion of numerous proinflammatory cytokines, including IL-6 and tumor necrosis factor- $\alpha$ , that are able to exert positive feedback control on T-lymphocytes, leading to the overactivation of the immune system<sup>10</sup>.

Biological markers routinely used to monitor disease activity are needed. Ferritin and glycosylated ferritin are commonly used. However, they do not directly reveal abnormalities of the immune system. Cytokine measurement

is not used routinely, although this might be relevant. Measurement of the percentage of circulating peripheral activated T-lymphocytes, found to be useful in followup of various inflammatory diseases, can be used routinely<sup>11</sup>. Interestingly, we found an increase of activated T-lymphocyte CD3+CD8+HLADR+ that is closely associated with disease activity. Levels declined markedly to normal after introduction of anakinra. As described by Koeller, *et al*<sup>12</sup> and confirmed by Chen, *et al*<sup>2</sup>, the association between CD3+DR+ T cells and disease activity strongly suggests that activated T-lymphocytes could be implicated in disease pathogenesis.

Moreover, our observation may establish the rationale to measure the percentage of activated T-lymphocytes in followup of activity of Still's disease and to monitor treatment efficacy.

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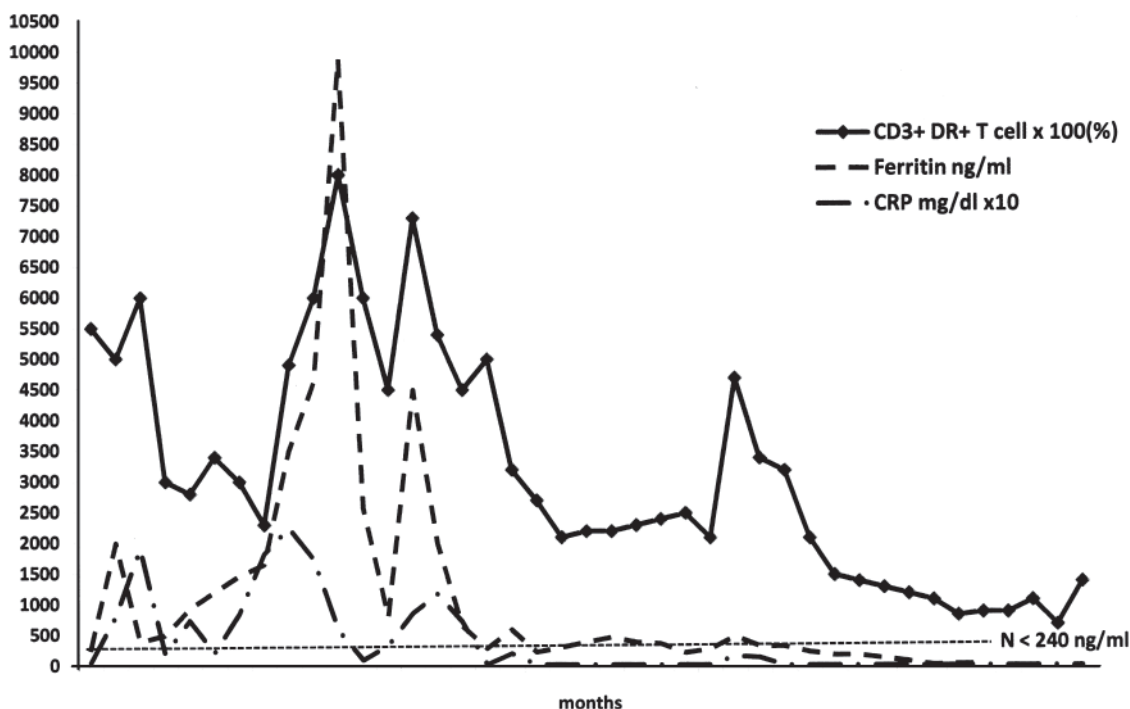


Figure 3. Expression of peripheral CD3+DR+ T-lymphocytes (as percentage of total lymphocytes), in parallel to ferritin and C-reactive protein (CRP) levels. N: normal ferritin value.



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## Efficacy of Infliximab in Cogan's Syndrome

*To the Editor:*

Cogan's syndrome is a rare chronic inflammatory disease that most commonly affects adults in the third decade, with no gender predominance. Interstitial keratitis is the characteristic ocular feature, although this is not mandatory for the diagnosis; moreover, ocular manifestations such as scleritis, episcleritis, and uveitis may occur. The vestibuloauditory manifestations consist of a Ménière's-like disease including vertigo, nausea, vomiting, tinnitus, and hearing loss. The diagnosis is made upon the association of eye disease and vestibuloauditory dysfunction, with or without systemic features (fever, asthenia, weight loss, arthritis, arthralgias, aortitis, and abdominal pain)<sup>1–4</sup>.

A 48-year-old woman was admitted to our hospital in May 2001 following a sudden bilateral hearing loss with vertigo and tinnitus. One year previously, she had had a history of polyarthritis of the wrists and metacarpophalangeal joints, without morning stiffness, which was treated as a seronegative arthritis with nonsteroidal antiinflammatory drugs and low-dose oral prednisone. She also had an episode of painful red eye for which no medical attention had been given. She had tapered the prednisone from 10 mg/day to 7.5 mg/day 3 weeks before the appearance of the vestibuloauditory manifestations.

Upon admission, the clinical examination was not significant. She complained of polyarthralgia without arthritis. Otolaryngeal examination confirmed a bilateral sensorineural hearing loss predominantly on the right side (Figure 1A). The ophthalmologic examination showed signs of prior anterior uveitis. Chest radiograph, cerebral and auditory conduct magnetic resonance imaging (MRI), electroencephalogram, electrocardiogram, transthoracic cardiac echography, and thoracic MRI were all normal. Laboratory tests showed normal complete blood count, erythrocyte sedimentation rate, C-reactive protein, renal function, and complements. Treponemic pallidum serologies, rheumatoid factors, antinuclear antibodies, anti-DNA antibodies, antiphospholipid antibodies, and antineutrophil cytoplasm antibodies were all negative.

The diagnosis of Cogan's syndrome was established upon the association of vestibuloauditory, ocular, and systemic manifestations. The patient did not fulfil the classification criteria for any other systemic disease such as rheumatoid arthritis, spondyloarthropathy, or inflammatory bowel disease. Treatment with prednisone 60 mg/day was started, which resulted in improvement in the audiogram and the polyarthralgias. Prednisone was

slowly tapered, but a relapse with acute bilateral worsening of hearing loss occurred at a dose of 14 mg/day. She was admitted again and started pulse therapy of methylprednisolone 240 mg/day for 5 days. This resulted in a partial improvement. Then methotrexate (MTX) 17.5 mg weekly was added. She continued to have progressive hearing loss of the right ear until she lost hearing completely in October 2002, while being treated with steroids (60 mg/day initially and slowly tapered) and MTX. A new relapse with acute hearing loss on the left side occurred with prednisone therapy of 18 mg/day in March 2003 (Figure 1B).

Because of continued hearing loss despite steroids and MTX, pulse therapy of intravenous cyclophosphamide 750 mg was started in June 2004, for 6 months, along with methylprednisolone 250 mg/day for the first 5 days. The auditory acuity improved after 2 perfusions of cyclophosphamide (Figure 1C). Azathioprine 150 mg/day was started after the sixth perfusion of cyclophosphamide. Although the patient was treated with azathioprine and prednisone, relapses continued to occur, with a progressive hearing loss every time the prednisone was tapered to a dose less than 20 mg/day (Figure 1D).

Treatment with infliximab 3 mg/kg (200 mg) every 3 weeks was initiated in April 2005. There was a rapid improvement of the audiogram of the left ear after 2 perfusions (Figure 1E). Treatment intervals were then extended to 8 weeks. Prednisone was successfully tapered to a daily dose of 5 mg, with a complete remission for 3 years after starting infliximab. The patient is still receiving infliximab (3 mg/kg every 8 weeks) and prednisone (5 mg/day) in June 2008. The audiogram is stable, as shown in Figure 1E.

Treatment of Cogan's syndrome is difficult, and the only information we find in the literature is based upon clinical case reports; no organized series of treatments has been published. Systemic corticosteroids are the mainstay of treatment for inner ear disease and/or systemic vasculitis, other immunosuppressive drugs being used in case of treatment failure or as corticosteroid-sparing therapy<sup>3</sup>. Failure to aggressively treat immune-mediated hearing loss may lead to profound and permanent hearing loss. Repeated disease flares lead to loss of hearing despite control of hearing damage initially<sup>1</sup>. Early treatment after onset of hearing loss was shown to give better results<sup>5</sup>. However, severe hearing loss may occur despite treatment with high-dose steroids and immunosuppressive agents<sup>1,4</sup>. So it is not clear that providing aggressive immunosuppressive treatment alters the longterm outcome.

The effect of tumor necrosis factor- $\alpha$  blockers in Cogan's syndrome was recently investigated<sup>1</sup>, and we identified 5 cases<sup>6–8</sup> of Cogan's syndrome treated with infliximab (Table 1). In our case there was a resistance and failure of steroids and other immunosuppressive agents (azathioprine, MTX, and cyclophosphamide). Although the patient was treated with high doses of methylprednisolone and immunosuppressive agents, a complete hearing loss of the right ear and progressive hearing loss on the left side occurred. Infliximab, started 29 months after the right ear hearing loss and 4 years after the diagnosis, showed good efficacy, with improvement of auditory acuity of the left ear after the second perfusion. There was no improvement in the right ear, which was already deaf 29 months before the treatment was started. Oral prednisone was successfully tapered to a daily dose of 5 mg, with no relapses and a good tolerance after 3 years of treatment with infliximab.

The effect of etanercept was investigated in an open-label prospective study<sup>9</sup> including 23 patients with bilateral immune-mediated cochleovestibular disorder or symptoms of Ménière's disease; 3 of these patients had Cogan's syndrome. Etanercept was not effective in preserving or improving hearing loss, but 2 of 3 patients who had Cogan's syndrome showed improvement in word identification and recognition<sup>9</sup>. However, etanercept was not helpful in preventing hearing loss in Cogan's syndrome.

Infliximab might be an alternative therapy for Cogan's syndrome, especially in cases of failure of corticosteroids and immunosuppressive therapy. However, treatment might be more effective when started at an early stage of the disease, and mainly for inner-ear disease, when the lesions are still reversible. The decision to consider infliximab as first-line therapy after the onset of hearing loss is worth investigating.



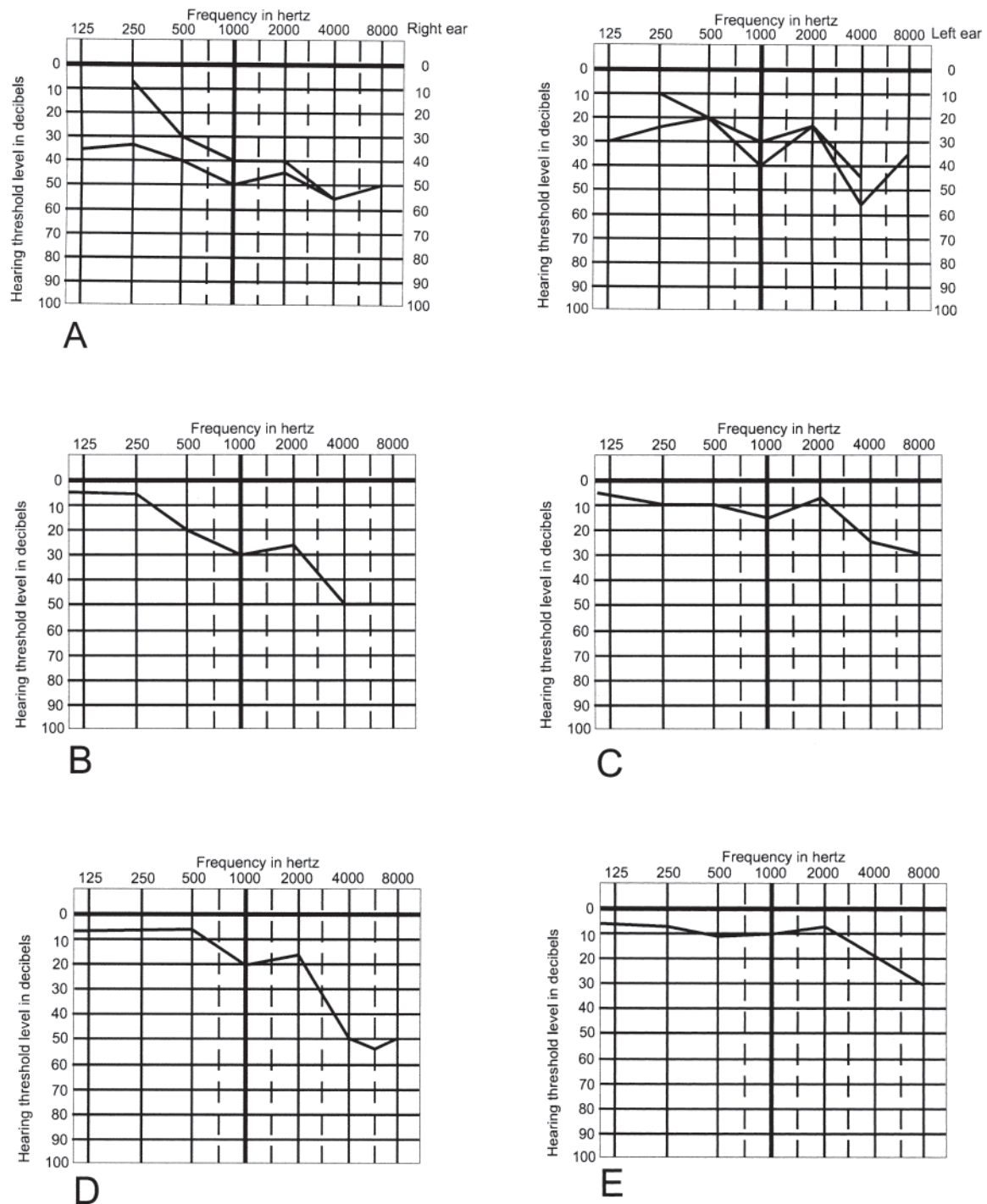


Figure 1. A. Bilateral sensorineural hearing loss predominantly on the right side. B. Acute left-side hearing loss with prednisone therapy 18 mg/day. C. Auditory acuity improved after 2 perfusions of cyclophosphamide. D. There was progressive hearing loss when prednisone was tapered to < 20 mg/day. E. Audiogram is stable: patient is receiving infliximab 3 mg/kg every 8 weeks and prednisone 5 mg/day.

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Table 1. Efficacy of infliximab in 5 cases of Cogan's syndrome.

Features	Case 1 <sup>6</sup>	Case 2 <sup>7</sup>	Case 3 <sup>6</sup>	Case 4 <sup>8</sup>	Case 5 <sup>8</sup>
Vestibulo-auditory presenting symptoms	Bilateral sensorineural hearing loss, tinnitus, ataxia	Tinnitus	Bilateral sensorineural hearing loss	Bilateral sensorineural hearing loss, vertigo, tinnitus	Bilateral sensorineural hearing loss
Ocular presenting symptoms	Bilateral interstitial keratitis		9 months after, bilateral scleritis, arthralgias, fever	Bilateral interstitial keratitis	Interstitial keratitis
Efficacy of corticosteroids	Bilateral sensorineural hearing loss, tinnitus, ataxia	Ineffective for ocular and vestibulo-auditory manifestations	2 mg/kg PO: improvement of auditory acuity. Ineffective for ocular manifestation and fever	1 mg/kg PO and topical: improvement of ocular manifestation, worsening of left hearing loss	1 mg/kg, ineffective
Efficacy of cyclophosphamide (CYC)	Pulse therapy 1000 mg 6 mo. Improvement of left audiogram. Relapse on 20 mg prednisone. 2nd trial with CYC ineffective	Ineffective for ocular and vestibulo-auditory manifestations	Effective for ocular manifestations, but relapse of scleritis on 5 mg prednisone and CYC		
Efficacy of infliximab	300 mg 2 years after diagnosis. Improvement of hearing. Successful taper of corticoids. Infliximab stopped	Effective for ocular disease but not for tinnitus	300 mg effective for ocular disease, improvement of auditory acuity. Successful prednisone taper and discontinuation	3 mg/kg 3 weeks after diagnosis. Improvement of auditory acuity after first perfusion	3 mg/kg 30 months after diagnosis. No improvement 4 mo after beginning treatment

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## Unilateral Anterior Uveitis Complicating Zoledronic Acid Therapy in Prostate Cancer

To the Editor:

A 78-year-old man with no ocular history was admitted for low back pain. His medical history revealed prostate cancer diagnosed in August 2004 after transurethral resection. He was treated with hormone therapy with cypoterone acetate 50 mg/day and goserelin acetate 10.8 mg/3 months. From January 2005, he complained of mechanical low back pain. Initially, plain radiographs were normal. Pain increased, and new plain radiographs revealed increased density of the fifth lumbar vertebra. Lumbar resonance magnetic imaging examination confirmed metastatic bone localization. Blood samples revealed prostate-specific antigen elevation, normal calcium, and serum creatinine. Forty-eight hours after the first intravenous infusion of zoledronic acid 4 mg in normal saline, given over 15 min, he began to experience right-eye pain with decreased visual acuity, and conjunctival hyperemia. Three days later, an ophthalmological examination found unilateral fibrinous anterior uveitis of moderate severity (Figure 1). Chest radiograph was normal. He was treated with topical prednisone eye-drops and recovered slowly over several weeks. Treatment was switched from zoledronic acid to pamidronate, without any recurrence.

To assess the imputability of zoledronic acid, we used the drug imputability criteria established by French pharmacovigilance centers<sup>1</sup>. These criteria take into account both the chronology of events from the time the drug is taken until the appearance of the clinical signs (intrinsic chronological imputability), and the type of clinical signs (intrinsic semio-logic imputability). Both scores make it possible to calculate the overall intrinsic imputability score; and the data in the literature, the extrinsic imputability score. In our case, the uveitis diagnosis was confirmed by ophthalmological examination. No new treatments have recently been introduced. There were no indicators of any other diagnosis with our patient: no ocular history, clinical signs of spondyloarthropathy, or radiological sign of sarcoidosis, no oral or genital aphthosis; and to our knowledge, there has been no case report of prostate cancer-specific uveitis



Figure 1. Right-eye acute anterior uveitis.

(semiologic criterion: S3). The clinical signs of uveitis occurred 48 h after the first intravenous infusion. Uveitis was controlled with topical prednisone eyedrops with no relapse (chronological criterion: C3). The overall intrinsic imputability score (I4) strongly suggests the involvement of zoledronic acid. Bisphosphonates are widely used in patients with hypercalcemia of malignancy and cancer metastatic to bone, osteoporosis, and Paget's disease. Most frequent general side effects include clinical troubles such as influenza-like symptoms, nausea, bone pain, and biological perturbation such as transient hypocalcemia. Some previous inflammatory ocular adverse events have been reported with other bisphosphonates<sup>2</sup>, usually with the nitrogen-containing bisphosphonates (alendronate, pamidronate, zoledronate, risedronate)<sup>3-5</sup>, except in one case (clodronate)<sup>6</sup>. The mechanism of the inflammation is unclear, but may be explained by the fact that the nitrogen-containing bisphosphonates cause elevated levels of proinflammatory cytokines, including interleukin 6 and tumor necrosis factor- $\alpha$ <sup>7</sup>. No ocular or patient predisposing factors are known. Only 3 recent cases reported uveitis as a complication of zoledronic acid<sup>8-10</sup>. Zoledronic acid is characterized by its high antiresorptive potency and short infusion time<sup>11,12</sup>. In the HORIZON (Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly) trial conducted in postmenopausal women with osteoporosis<sup>12</sup>, patients treated with zoledronic acid had an absolute increase of approximately 0.69% in inflammatory ocular adverse events (mainly conjunctivitis) during the first 15 days after infusion in comparison with controls, but no case of uveitis. Finally, the extrinsic imputability score (B2) also suggests the involvement of zoledronic acid.

All physicians should be aware of uveitis as a possible complication of zoledronic acid therapy. They should instruct patients to immediately report eye trouble such as pain or decreased visual acuity in order to treat the onset of symptoms with specific therapy, after ophthalmological examination. This may be true especially after the first infusion, which is the time of occurrence in 3 of the 4 published cases. Repeating the infusions of zoledronic acid in these patients, even with prophylactic topical steroids and atropine, may not be safe. Indeed, one case report of uveitis associated with clodronate relapsed when rechallenged with the same drug<sup>6</sup>. In another case, in which the original bisphosphonate was replaced by a different drug of the same class, eye inflammation was reduced and eventually resolved with continued use, suggesting the development of immunological tolerance<sup>13</sup>. This was the rationale to switch to pamidronate, and we did not observe any relapse of uveitis.

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## Correction

Eder L, Zisman D, Rimar D, Barzilay M, Rahat M, Laor A, Bitterman H, Rozenbaum M, Rozner I, Feld J. Subclinical atherosclerosis in patients with psoriatic arthritis. Reply; letter. *J Rheumatol* 2008;35:2070-1. The correct spelling of the author's name is Rosner. We regret the error.