pathy associated with nucleoside reverse-transcriptase inhibitor (NRTI) therapy and mitochondrial dysfunction.

Patient 1. A 52-year-old, homosexual, male patient with HIV infection diagnosed since eight years, was admitted owing to a four-month history of intermittent myalgia, muscular fatigue, and progressive muscle weakness in his upper and lower limbs, but maximal in proximal muscles of the legs. Antiretroviral therapy was started since five years, and the most recent antiretroviral regimen included zidovudine, lamivudine and lopinavir/ritonavir, and was administered since ten months.

The admission laboratory workout revealed increased serum levels of creatine phosphokinase or CK (622 U/L), lactate dehydrogenase or LDH (705 U/L), aspartate aminotransferase or AST (82 U/L), and aldolase (14.3 U/L). Immunological and virological tests demonstrated a CD4+ lymphocyte count of 541 cells/mm^3, with a plasma viral load (HIV RNA) lower than 50 copies/mL. Physical examination showed diffuse muscle hypotrophy and asymmetric hyposthenia affecting the proximal and distal muscle groups in both upper and lower extremities, associated with raising tendon reflexes. Sensory examination and coordination were normal.

An electromyogram revealed myopathic motor unit potentials showing early recruitment and full interference patterns, as well as fibrillation potentials and positive sharpe waves, indicative of an irritative process. A biopsy specimen of quadriceps muscle showed diffuse necrotic and degenerative alterations of muscle fibers in association with broad interstitial inflammatory infiltrates, including mostly macrophages, lymphocytes, and plasma cells. HIV-associated polymyositis was diagnosed and therapy with oral prednisone (0.5 mg/Kg daily) was begun.

Six months later, the patient reported a mild subjective benefit and the dose of prednisone was decreased to 0.25 mg/Kg daily. One year later, he did not report any symptoms of myositis; physical examination, electromiography and laboratory workout were normal.

Patient 2. A 51-year-old drug abuser male patient with advanced HIV infection recognized since 13 months and Graves' disease diagnosed since six months, was admitted owing to the persistence of asthenia and progressive muscle weakness in his upper and lower extremities, associated with dysphagia to solids and liquids. Physical examination revealed muscle hypotrophy and asymmetric hyposthenia affecting mostly proximal muscle groups in both upper and lower limbs and neck, while sensory evaluation and coordination did not show any alteration. Swallowing assessment confirmed severe oropharingeal muscle weakness. Ongoing antiretroviral theraphy included zidovudine, lamivudine, and nelfinavir, and was started 12 months before the ospitalization.

The laboratory workout showed increased serum levels of CK (485 U/L), LDH (692 U/L), AST (91 U/L), and aldolase (13.2 U/L). Immuno-virological tests showed a CD4+ lymphocyte count of 348 cells/mm^3 and a plasma HIV viral load lower than 50 copies/mL. Electromyography revealed diffuse fibrillation and severe reduction of muscle action potential amplitudes bilaterally. A biopsy specimen of quadriceps muscle showed frank necrotic changes of muscle fibers infiltrated by inflammatory cells, mainly lymphocytes and plasma cells. HIV-associated polymyositis was diagnosed and therapy with oral prednisone (0.5 mg/Kg daily) was started.

Six months later, the patient referred a remarkable improvement of muscle weakness and dysphagia. One year later, he was asymptomatic and electromiography was normal, such as the serum levels of muscular enzymes.

Polymyositis is considered the most common of the HIV-associated myopathies and usually shows clinical course, laboratory and electromyographic findings similar to the idiopathic form observed in HIV-negative subjects.

The pathophysiology of HIV-associated polymyositis is unknown still today. Several studies suggested that HIV-associated myositis is not attributable to persistent HIV infection of the muscle cells (5). However, other authors have found amplified HIV nucleic acids in myocyte nuclei, leading to the opposite conclusion (6).

At the same time, the rapid onset of HIV-associated polymyositis during the immune restoration following the use of combination antiretroviral therapy which has described in some reports supports the immunopathological mechanism of HIV-related myositis, similarly to other autoimmune manifestations seen in HIV-positive patients receiving HAART(3, 7).

HIV-polymyositis is often difficult to distinguish from the NRTI-related myopathy. Ragged-red fibers, abnormal mitochondrial levels in muscle tissue, concurrent manifestations of mitochondrial toxicity (such as hyperlactataemia, peripheral neuropathy, liver toxicity, acute pancreatitis, or pancytopaenia), and the disease reversibility after the discontinuation of drug therapy suggest a diagnosis of NRTI-associated myopathy. Particularly, a recent report highlights the importance of muscle biopsy in HIV-positive subjects whose myopathy persists despite withdrawal of antiretroviral therapy (8, 9).

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Multiple sclerosis and the antiphospholipid (Hughes) syndrome: Acommon differential diagnosis?

Sirs,

The antiphospholipid (Hughes) syndrome (APS), a prothrombotic disorder, is characterised by prominent neurological involvement. In addition to stroke, headache and memory loss, other features can include ataxia, diplopia, visual loss and myelopathy (1). It is not surprising therefore that some patients with Hughes syndrome are misdiagnosed as multiple sclerosis (MS).

In a recent study from our unit (2), 27 patients with Hughes syndrome who had been originally diagnosed as MS were analysed. The clinical similarities between APS and MS were striking, and brain magnetic resonance imaging appearance was often indistinguishable. Notably, the majority of primary APS patients, once adequately treated with aspirin or anticoagulants, suffered no further neurological episodes.

Two hundred and eighty-two consecutive patients with systemic lupus erythematosus (SLE) and/or APS were asked the standard

question "Did any of your doctors at any stage of your illness consider the diagnosis of MS ?". In all patients, antiphospholipid antibody (aPL) status was recorded.
Out of 90 patients with positive aPL tests, 26 (28.8%) recorded a positive response to the question, as compared with 10 (8.4%) of the aPL negative patients [RR: 5.5 (95 CI: 2.8-11) $p < 0.0001$].
The aims of this audit study were two-fold: firstly, to obtain an estimate of the frequency with which patients with SLE and Hughes syndrome had had a differential diagnosis of MS considered. Secondly, to determine whether the MS differential diagnosis was made more frequently in patients with aPL.
This study acknowledges the pitfalls in patient questionnaire surveys, in patient recollection of previous consultation, and in the relevance of aPL. Despite these caveats, we believe that the result of this survey serves to emphasise the importance of the APS as a neurological entity, and as a differential diagnosis from MS.

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Sensorineural hearing impairment in systemic lupus erythematosus: Sudden or progressive?

Sirs,
Sensorineural hearing loss (SNHL) in systemic lupus erythematosus (SLE) has been described by several authors, though its pathogenesis is still not clear. Sudden onset SNHL is the most frequent SLE related hearing impairment and often represents the consequence of an anticardiolipin antibody (ACL) syndrome involving the inner ear (1).
Despite the prevalence (21.5%) (2) of progressive SNHLin SLE patients at pure tone audiometry, no one ever focused on the cochlear function by using the most recent and sensible techniques, such as transiently evoked otoacoustic emissions (TEOAEs), enabling to evaluate cochlear outer hair cells' function by recording their response to transient acoustic stimulation thorough a probe placed in the external auditory canal (3).
We investigated 30 (27 F; 3 M) SLE consecutive patients (group 1), mean age 41.2 years (range 27-66). A complete rheumatological and audiological assessment was carried out. Mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (4) was 9.12 (range 2-19). Anticardiolipin IgG and IgM antibody (aCL) positivity was found in 6 (20%) subjects at elisa. SLE patients were treated with hydroxychloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), metotrexate (MTX), dehydroepiandrosterone (DHEA), and cyclophosphamide. Conductive hearing impairment was excluded by pure tone audiometry and tympanometry. $TEOAE_s$ were recorded in all 60 ears with ILO88 OAE Analyzer (Otodynamics), and results were compared with those obtained in 30 healthy age-matched controls (group 2). No patient had a history of sudden hearing loss.
TEOAEs average reproducibility was 37.08% (±18.75%) in group 1, and 44.78% (±20.89) in group 2 ($p = 0.031$); the average amplitude was 4.58 (±2.93) decibel Sound Pressure Level (dB SPL) in group 1 and 6.43 (±3.18) dB SPLin controls ($p < 0.001$). In SLE patients, a statistically significant inverse correlation ($r = -0.289$, with a corresponding $p = 0.025$) between duration of disease and TEOAEs amplitudewasfound (Fig. 1). An inverse correlation, though not statistically significant, was found between TEOAEs amplitude ($r = -0.214$, $p = 0.099$) or reproducibility ($r = -0.683$, $p = 0.604$) and SLEDAI. No relation was noticed between audiological parameters and aCL positivity or patients'therapy.
Our data confirm a progressive cochlear impairment in SLE patients, though its pathogenesis is still unclear. Vasculitis processes, fibrosis, and new bone formation in the inner ear may be involved (5). A possible role of antibodies directed against inner ear antigenic epitopes and/or an involvement of aCLin inner ear immunocomplex-mediated vasculitis (6) has been proposed, though our data do not confirm it.
The inverse correlation between duration of disease and TEOAEs amplitude suggests that progressive inner ear impairment is common in SLE patients and represents the consequence of a chronic and progressive damage to the cochlea developing during the disease. This is partially confirmed by the relation, though not statistically significant, between TEOAEs parameters and SLEDAI. Additional prospective studies are needed to elucidate the pathogenetic mechanisms of SLE related cochlear impairment.

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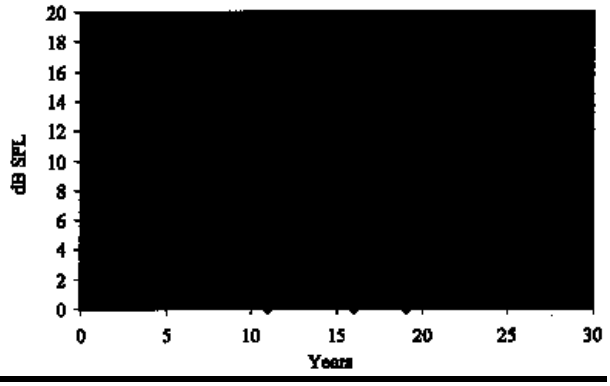

Fig. 1. Correlation between systemic lupus erythematosus duration (horizontal axis) and transiently evoked otoacoustic emission amplitude (vertical axis). The regression line approximates the relation between the variables; dB SPL = decibel Sound Pressure Level.