Audiovestibular Manifestations in Patients With Ankylosing Spondylitis

Juan C. Amor-Dorado, MD, PhD,* Maria P. Barreira-Fernandez, MD, Tomas R. Vazquez-Rodriguez, MD, Ines Gomez-Acebo, PhD, Jose A. Miranda-Filloy, MD, Teresa Diaz de Teran, MD, Javier Llorca, MD, PhD,* and Miguel A. Gonzalez-Gay, MD, PhD*

Abstract: Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown origin affecting up to 1% of the population. Little is known about audiovestibular impairment in patients with AS, especially the presence of cochleovestibular dysfunction in these patients. To investigate audiovestibular manifestations in AS, we studied a series of 50 consecutive patients who fulfilled the modified New York diagnostic criteria for AS and 44 matched controls. Individuals with history of cardiovascular disease, cerebrovascular complications, peripheral artery disease, renal insufficiency, syphilis, Meniere and other vestibular syndromes, infections involving the inner ear, barotrauma, or in treatment with ototoxic drugs were excluded. Most patients with AS were men (80%). The mean age at the time of study was 52.5 years, and mean age at the onset of symptoms was 34.4 years. Twenty-nine (58%) patients showed abnormal hearing loss in the audiogram compared to only 8 (18%) controls (p < 0.001). Values of audiometric tests (pure-tone average and speech reception threshold) yielded significant differences between patients and controls (p < 0.001). It is noteworthy that the audiogram shape disclosed a predominant pattern of high-frequency sensorineural hearing loss in AS patients (50%) compared to controls (18%) (p = 0.002). Also, AS patients exhibited abnormal vestibular tests more commonly than controls. AS patients had an increased frequency of head-shaking nystagmus (20%) compared to controls (0%) (p < 0.001). Moreover, patients (26%) showed a significantly increased frequency of abnormal caloric test compared to controls (0%) (p < 0.001). Finally, a significantly increased frequency of abnormal clinical test of sensory integration and balance with a predominant vestibular loss pattern was observed in patients (36%) compared to controls (5%) (p < 0.001). In conclusion, the current study demonstrates strong evidence for inner ear compromise in patients with AS.

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of unknown origin affecting up to 1% of the population.17 This rheumatic disease typically affects the sacroiliac joints and spine, leading to eventual fusion of the involved joints.70 AS can also cause peripheral joint synovitis. The pathologic process can also involve the eyes, heart, lungs or gut.

Audiovestibular manifestations have been observed in different rheumatic diseases. Sensorineural hearing loss (SNHL) and acute audiovestibular dysfunction were reported in individuals with rheumatoid arthritis.43,47 An obliterator vasculitis of the labyrinthine artery or its branches has been implicated in the pathogenesis of deafness in patients with relapsing polychondritis.35 Vasculitic and autoimmune mechanisms have been considered to play a role in the pathogenesis of the frequently subclinical sensorineural dysfunction observed in patients with systemic lupus erythematosus,1 and Sjögren syndrome.26 Audiovestibular dysfunction and benign paroxysmal positional vertigo due to vasculitis have also been found in patients with biopsy-proven giant cell arteritis.5,6 Moreover, we recently reported the presence of both auditory and vestibular dysfunction in patients with scleroderma,3,4 even in the limited form of this connective-tissue disease.3 However, information on auditory manifestation in patients with AS is limited,1,2,17,24,26,27 and in most cases is related to small series of patients.1,2,17,24,26 Information is particularly limited when we specifically search for the presence of cochleovestibular dysfunction in patients with AS.26

Because of these considerations, in the present study we assessed whether the frequency of SNHL was increased in a cohort of patients with AS in a community hospital. We aimed to establish whether vestibular abnormalities were more common in AS patients compared to matched controls. Finally, we sought to determine whether an association of audiovestibular manifestations with demographic and clinical variables of patients with AS might exist.

PATIENTS AND METHODS

Patients and Controls

We assessed a series of patients with AS and matched controls.

Patients

The patient group comprised consecutive patients attending hospital outpatient clinics seen over a period of 4 months (March through June 2008), who fulfilled the modified New York diagnostic criteria for AS.57 They were treated by the same

Abbreviations: AS = ankylosing spondylitis, BASDAI = Bath Ankylosing Spondylitis Disease Activity Index, BASFI = Bath Ankylosing Spondylitis Functional Index, CI = confidence interval, CRP = C-reactive protein, CTSIB = clinical test of sensory integration and balance, daPa = decapascal, dB = decibels, ESR = erythrocyte sedimentation rate, HL = hearing level, MRI = magnetic resonance imaging, NSAID = nonsteroidal antiinflammatory drug, OCR = oculocephalic response, OR = odds ratio, PTA = pure-tone average, SDT = speech discrimination test, SNHL = sensorineural hearing loss, SRT = speech reception threshold.
group of rheumatologists and were recruited from the Hospital Xeral-Calde, Lugo, Spain. This hospital is the single referral center for rheumatic diseases for a well-defined, stable, and ethnically homogenous, mixed rural and urban, white population living in the region of Lugo, central Galicia (northwestern Spain). The main characteristics of the Lugo population have previously been reported. Based on previous studies on other rheumatic diseases in the Lugo region of northwestern Spain, we feel that results derived from the present study may be extrapolated to other individuals of European background.

Inclusion and Exclusion Criteria

Only patients with AS who had been treated for at least 1 year at the outpatient rheumatology clinic at the time of study were included. Since degeneration of the cochlea has been found in young adults with generalized arteriosclerosis to minimize the potential influence of atherosclerosis in the development of SNHL and/or vestibular abnormalities, as previously reported, we excluded all AS patients who had experienced cardiovascular disease, including ischemic heart disease (angina or myocardial infarction electrocardiographically confirmed), heart failure, cerebrovascular events (transient ischemic attacks or strokes confirmed by magnetic resonance imaging [MRI] and/or computed tomography brain scan) or peripheral arterial disease (confirmed by Doppler and/or arteriography), or renal insufficiency. (Serum creatinine values in all individuals included in the study had to be <1.3 mg/dL, which is considered the upper normal range in our laboratory.)

All AS patients and controls were questioned about any history of previous audiostebular disturbances, cranial trauma, exposure to noise, ear infection, metabolic disease, renal failure, ototoxic drug use, and familial history of hearing impairment. We excluded patients with a known cause, such as trauma, Meniere disease and other audostebular disorders, ear surgery, previous history of cerebrovascular complications, infections involving the inner ear, syphilis, barotrauma, acoustic schwannoma, or those in treatment with ototoxic drugs.

All patients included in the study had begun treatment with nonsteroidal antiinflammatory drugs (NSAIDs) immediately after the disease diagnosis. Most were still being treated with these drugs at the time of study. They were treated with ibuprofen (1800–2400 mg/d), naproxen (500–1000 mg/d), diclofenac (100–150 mg/d), or indomethacin (100–150 mg/d). At the time of study, 14 were on treatment with tumor necrosis factor (TNF)-alpha blockers (13 with infliximab and 1 with adalimumab) because of severe disease refractory to at least 3 NSAIDs. However, none of the patients was taking salicylates at the time of study. Most were still being treated with antiinflammatory disease-modifying agents (AIDs), and 12 were on treatment with anti-TNF agents. Only patients with AS who had been treated for at least 1 year at the outpatient rheumatology clinic at the time of the audiovestibular study. At that time, clinical information on hip involvement, history of synovitis or enthesis in other peripheral joints, history of anterior uveitis, presence of syndesmophites, and HLA-B27 status (typed by cell cytotoxicity) was assessed. C-reactive protein (CRP), by a latex immunoturbidity method, and erythrocyte sedimentation rate (ESR), Westergren method, were assessed in all patients at the time of study. We also reviewed information about CRP by nephelometry and ESR at the time of disease diagnosis.

Clinical Definitions of Rheumatologic and Laboratory Data

A clinical index of disease activity (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], range of 0–10) and functional status (Bath Ankylosing Spondylitis Functional Index [BASFI], score of 0–10) were evaluated in all patients at the time of the audiovestibular study. At that time, clinical information on hip involvement, history of synovitis or enthesis in other peripheral joints, history of anterior uveitis, presence of syndesmophites, and HLA-B27 status (typed by cell cytotoxicity) was assessed. C-reactive protein (CRP), by a latex immunoturbidity method, and erythrocyte sedimentation rate (ESR), Westergren method, were assessed in all patients at the time of study. We also reviewed information about CRP by nephelometry and ESR at the time of disease diagnosis.

Clinical Definitions of Otolaryngology Data

We used the following definitions for otolaryngology data:

1. Subjective hearing loss: if a patient described subjective deafness at the time of study.
2. Tinnitus: subjective perception of noise in 1 or both ears or sometimes into the head. Hearing illusion without meaning for the patient at the time of study.
4. Dizziness: sensation like that of being drunk or having motion sickness.
5. Dysequilibrium: if at the time of study the patient was unable to walk in tandem even with open eyes. Dysequilibrium was also considered to be present if, standing in Romberg position, the patient fell to 1 or both sides.
6. Quantitative hearing loss was evaluated by audiometric tests:
   6.1. Pure-tone audiometry: Audiometry is the term used to describe the formal measurement of hearing. It is a subjective test not an objective measurement. The basic audiometric test battery began with behavioral pure-tone threshold testing to compare a subject’s hearing sensitivity to norms at selected frequencies (the audiogram), for bone and air-conducted signals. A frequency range for octave frequencies from 250 to 8000 Hz was assessed. In our study, when hearing loss was observed the next step was to determine whether the hearing loss was caused by a sensory problem (SNHL) or a mechanical problem (conductive hearing loss). This distinction was made using a bone vibrator, which bypasses the mechanical parts of the middle ear. If hearing was better using bone than air, this suggested a conductive hearing loss.

Control Group

A list of potential controls was obtained from the cooperating health centers. Once a case was recruited, we randomly selected his or her control from the patients included in that list that matched the age and sex criteria.

Controls (n = 44) were community based. They were recruited from family physician health centers of the Lugo region. They were age ± 2 years and sex and ethnically matched controls without family history of AS, psoriasis, psoriatic arthritis, rheumatoid arthritis, or any other inflammatory rheumatic diseases. As required for patients with AS, none of the controls had a history of cardiovascular disease such as heart failure, myocardial infarction, angina, cerebrovascular events and peripheral arteriopathy, or renal insufficiency.

Informed consent was obtained from all cases and controls. The local institutional committee approved the study.
For calculating hearing impairment, we used the 4 pure-tone average (PTA), arithmetic mean of 0.5, 1, 2, and 3 kHz used in the Academy formula and The Committee on Hearing and Equilibrium guidelines for Meniere disease. PTA was the representative value of hearing thresholds, as decibels hearing level (dB HL), in the spectrum of conversational frequencies. PTA was reported to be a valid and accurate measure to assess audiometric outcomes.\cite{48,49} For calculating hearing handicap in high frequencies, an arithmetic media of 4, 6, and 8 kHz was applied. Data were expressed as decibels hearing level (dB HL).

Pure-tone air and bone conduction thresholds were obtained in a sound isolation chamber with a clinical computer audiometer (MAICO, MA 52, Eden Prairie, MN).

Hearing loss (hypacusia) was considered to be present when the audiometric tests disclosed pure-tone thresholds ≥25 dB HL in 2 frequencies of the audiogram. SNHL and mixed hypacusia, with the air-bone gap, were registered and assessed in the audiogram. A hearing loss difference >15 dB HL between each ear in at least 1 frequency (0.5–3 kHz) was rated as asymmetrical.

Since audiogram shapes represent the frequency predominance of hearing loss, the specific audiogram configuration was described regarding the shape of hearing loss in audiograms. To characterize the shape of the audiogram in each ear, a classification was applied taking into account both the curvature and the slope of the audiogram. This led to 2 categories for the audiogram shape:

6.1.1. High-frequency SNHLLs were considered present when pure-tone audiometric thresholds were at least 25 dB HL or greater in 1 of the frequencies: 4, 6, or 8 kHz. In this case the remaining audiometric thresholds in the frequencies of the audiogram (0.25–3 kHz) could be normal or abnormal.

6.1.2. A flat pattern was considered present when audiometric thresholds were 25 dB HL or greater in each different frequency of the audiogram (0.25–8 kHz) and differences between them were not greater than 15 dB HL.

6.2. Speech reception threshold (SRT): Like the speech discrimination test described below, this test is used to determine central auditory processing and central hearing deficits. It shows the lowest intensity level expressed in dB HL at which the patient can correctly identify 50% of common 2-syllable Spanish words from a phonetically balanced list of 2-syllable words.\cite{50} The correlation between SRT and PTA was also studied. It was considered abnormal if the differences between SRT and PTA were >5 dB HL. Therefore, in our study SRT evaluated the central auditory system.

6.3. Word recognition test, also known as the speech discrimination test (SDT): The person’s ability to understand speech when presented at a loudness that is well above the threshold was assessed without earphones (free field) in all individuals of the study. It was considered abnormal if individuals were unable to identify at least 85% of common 2-syllable Spanish words from a phonetically balanced list of 2-syllable words. Loudness discomfort (recruitment) was also assessed.

7. Impedance study for middle ear disease: 7.1. Tympanometry: A method of measuring the stiffness (or its inverse, compliance) of the ear drum (tympanic membrane), to establish how much sound is reflected back while pressure is swept through the ear canal. Tympanometry is mainly useful to determine if there are problems with eardrum movement. The tympanometer scale used was in decapascal (daPa). If the eardrum is under no positive or negative pressure, its maximum compliance will be at 0. Static admittance (or compliance) and peak pressure were measured in cm\(^2\). Peaks under 0.1 cm\(^2\) (a reduced peak height or a flattened curve) and over 1.5 cm\(^2\) were considered abnormal.\cite{46} On the other hand, if the eardrum is under negative or positive pressure, the peak will move to the left or to the right or it will be flat. In this study, pressures under ~125 or greater than 100 daPa and a flat curve were considered abnormal.

7.2. The stapedius reflex: The tympanometer was also used to measure the stapedius reflex. The purpose was to deliver a sound to either ear and to measure the admittance of the tympanic membrane (GSI TymStar Version 1, Guymark, UK). Ipsilateral reflexes were elicited at 500, 1000, and 2000 Hz using 105 dB HL and at 4000 Hz using 100 dB HL. The amplitude of the reflex, the latency, and timing (sustained or rapidly decaying) were quantified (reflex decay). In this study, the absence of reflex, latencies <40 or >180 milliseconds, or the presence of decay in any ear were considered abnormal.\cite{22} We also assessed whether a stapedius reflex was present when the auditory stimulus was <60 dB HL (auditory recruitment).\cite{22}

8. Quantitative and qualitative oculographic tests: 8.1. Smooth pursuit (tracking test): This test is used to establish the integrity of the neural brainstem pathways implicated in the extrinsic ocular motility. The ability of study subjects to match eye movement to visual target movement was measured by this test. While 1 eye was occluded with the goggles, a sinusoidal pursuit was elicited in the other eye using the explorer finger like a target at 50 cm in front of the subject, then the finger was displaced at a constant velocity and continuously, first laterally to the right and then to the left alternating the side and the eye, during 60 seconds. Only the last 30 seconds registered during the test were assessed in this study.

Since sinusoidal smooth pursuit is reduced by age and sex (elderly people and women have poorer pursuit than young individuals and men),\cite{60} for the purpose of this study, the presence of catch-up saccades and pursuit gains <0.2 Hz was considered abnormal. Moreover, since symmetrical reduction of smooth pursuit (reduced gain) is commonly found in the general population, and in our study none of the patients or controls had an asymmetrical pursuit, individuals with symmetrical pursuit were classified into those with perfect pursuit (normal) and those with moderately impaired pursuit (abnormal). This classification was done by eye from the position trace, where a reasonable sinusoidal stimulus (for example, 0.5 Hz, ±20 degree amplitude) was used.\cite{55}

8.2. Saccades: In some cases cerebellar and degenerative disorders of the central nervous system may be unveiled by saccadic testing. In the present study saccadic eye movements were tested at the bedside by instructing the subject to fixate alternately upon 2 targets: the tip of the examiner’s finger and the examiner’s nose, noting saccadic latency, trajectory, accuracy, and conjugacy. The 3 saccadic parameters most relevant to clinicians were studied: peak velocity, latency, and accuracy. The saccades were classified into the following patterns: inappropriate, inaccurate (hypermetric or hypometric), too slow or too fast, or saccades that are poorly initiated. Individuals showing 1 of these patterns were considered to have abnormal saccades. All patients and controls were questioned and encouraged
not to use anticonvulsants and benzodiazepines before the test was performed.

9. Quantitative and qualitative vestibular function tests:

9.1. Spontaneous nystagmus: This is assessed to determine the presence of vestibular dysfunction, either central or peripheral: the presence of spontaneous nystagmus suggests a nonspecific vestibular dysfunction. In most cases spontaneous nystagmus is caused by a peripheral vestibular imbalance. Nystagmus in primary eye position was assessed by asking the patient to look ahead with open eyes. Eye movements were recorded for at least 20 seconds without visual fixation and 20 seconds allowing visual fixation.23

9.2. Evoked nystagmus: The presence of gaze-evoked nystagmus in the clinical examination is generally related to central nervous system pathology. With visual fixation, the nystagmus beats to the right on rightward gaze and to the left on leftward gaze. This nystagmus disappears with eyes closed or when visual fixation is not allowed.

9.3. Oculolabyrinthic response (OCR) also called "head thrust test" or Halmagyi test: This is a simple office test that assesses the vestibulo-ocular reflex. The examiner was seated directly in front of the subject and grasped his or her head with both hands. The subject was visuallyfixating on the examiner's nose. The head was rapidly turned in the horizontal (yaw) plane to 1 side approximately 30° while an assessment was made to determine whether the subject was able to maintain fixation on the examiner's nose. The distance between the subject's eyes and examiner's nose was approximately 18 inches. The head was then turned to the opposite side to evaluate the contralateral OCR. The test was repeated several times until the subject was accustomed to the test and was able to maximally suppress neck muscle guarding before an OCR evaluation was done.37,38

A normal response was recorded when the subject was able to maintain visual fixation without ocular drift during the head rotation. An abnormal response was recorded when the eyes drifted in the same direction as the head and clinically evident compensatory reflexion saccades were necessary to reset gaze on the stationary target.

9.4. Head shaking nystagmus: This nystagmus is an abnormal finding that may be detected in individuals with unilateral vestibular lesions. The head was shaken passively and horizontally by the examiner with a rapid 30-second head shake at approximately 45° of 2–3 Hz followed by a sudden stop. Head-shaking nystagmus was considered to be present when a jerk nystagmus in 1 direction of at least 10 seconds' duration was observed.31,36

9.5. Positional nystagmus: This is assessed in several positions to establish gravity's effect on vestibular receptors of the inner ear. Horizontal and vertical eye movements were monitored using videoystagmography and video-ystagmography with open eyes without fixation during 60 seconds in 4 different positions: supine lying, right lateral lying, left lateral lying, and head hanging position. For this evaluation, only the last 30 seconds of the study were registered. The presence of positional nystagmus in any direction in at least 1 of the 4 positions mentioned above was considered abnormal.11,16

9.6. Dix-Hallpike test: This test assesses the presence of otoliths (debris) in the posterior and anterior semicircular canals. The presence of linear-rotatory (torsional) nystagmus accompanied by symptoms of vertigo evoked by this test was considered an abnormal response. The patient was seated near the end of an examining table with the head rotated 45° to right or left and then moved to the head hanging position (head rotated) as fast as possible. No visual fixation was allowed, and, to assess nystagmus both videonystagmography and videoystagmography were performed. After 30 seconds, or once nystagmus abated, the patient was returned to the sitting position.10,16,25

9.7. Cephalic rotational test: This test assesses the presence of otoliths in the horizontal semicircular canal. The presence of pure horizontal nystagmus without latency that was accompanied by symptoms of vertigo evoked by cephalic rotation was considered an abnormal response. While a subject was lying in a supine position in a 30° cervical flexion, the examiner grasped his or her head with his hands, then the head was first quickly turned to the left and then to the right laterally.5,46

9.8. Static postural study: To assess static equilibrium and before performing bithermal water caloric test, the clinical test of sensory integration and balance (CTSIB) ("foam and dome test") was conducted in all patients. CTSIB was performed as described by Horak and Shumway-Cook.40,53 (CTSIB is an inexpensive test useful in differentiating between individuals with and without vestibular disorders. The technique uses combinations of 3 visual and 2 support-surface conditions. Visual conditions include the use of a blindfold for eliminating visual input and a visual-conflict dome for producing inaccurate input. The 6 test conditions of the sensory organization were performed in a manner that attempted to simulate the 6 conditions of dynamic posturography. All of them were performed with the individual in a standing position: conditions 1–3 were done standing on the floor, on a firm surface (condition 1 with open eyes, condition 2 blindfolded, and condition 3 wearing a visual-conflict dome with a modified Japanese lantern). Conditions 4–6 were replicated on a 24 × 24-inch piece of medium-density SunMate foam (Boston, MA) with the subject standing on a foam and repeating the visual conditions described for conditions 1 through 3 (condition 4 with open eyes, condition 5 blindfolded, and condition 6 with a modified Japanese lantern).

As explained before, a modified large Japanese lantern was placed over the head to provide visual conflict information for eyes-open conditions 3 and 6 (situations to assess the somatosensory compromise).

The score on each of the 6 conditions was measured by the length of time (in seconds) that the subject was able to maintain upright posture without assistance from the examiner and without a fall reaction. A patient's postural sway was observed in each of the 6 conditions always in the same sequence, while standing with feet together and hands on the hips for a maximum period of 30 seconds. Three trials were given for each condition, and the average determination was expressed in seconds. To quantify sway, a stopwatch was used to record the amount of time the patient maintained erect standing without excessive swaying in each condition.

Healthy young adults are able to maintain balance for 30 seconds under all 6 conditions with minimal amounts of body sway. The examiner uses the first condition (condition 1) as a baseline for comparing sway under the other 5 conditions. In conditions 5 and 6, healthy adults sway 40% more than they do in condition 1. For this reason, for each specific condition individuals were considered to have abnormal CTSIB when they were not able to maintain the position for more than 50% of the time.33 The patterns of postural disorientation are classified...
as “visually dependent” when conditions 3 and 6 fulfill criteria of abnormality, and conditions 2 and 5 may or not show abnormality; “surface dependent” if conditions 4, 5, and 6 are abnormal; “vestibular loss” when abnormality is found in conditions 5 and 6; and “sensory selection” when the abnormal conditions are 3, 4, 5, and 6.

9.9. Caloric test: This test was performed to discover the degree to which the vestibular system was responsive and how symmetric the responses were between left and right ears. This test assesses only the lateral semicircular canal. Each ear was irrigated alternatively with a constant flow of water, at temperatures of 30°C and 44°C, for a constant period of time of 40 seconds. The recording of the response was made for 3 minutes. A 5-minute interval between each stimulus was allowed, to avoid cumulative effects. A videonystagmography-based system was used for the acquisition and analysis of the eye response. Correct head positioning was checked before irrigation to maintain the horizontal semicircular canal close to earth-vertical. Patient alertness was maintained by having the patient do mental arithmetic calculations throughout the recording. The irrigation was delivered randomly in temperature and side, and no fixation was allowed while recording. Maximum slow-phase velocity of nystagmus after irrigation was calculated, and canal paresis was determined according to the formula of Jongkees et al. In our laboratory a canal paresis over 25% is considered to be a pathologic sign. Thus, a value over 25% defines an abnormal result in the caloric test.

A subject was considered to have abnormal vestibular tests if at least 1 of the vestibular tests mentioned above except CTSIB was abnormal.

In all patients and controls with nystagmus, an ocular fixation test (measured by red-light-emitting diode fixation) was performed. A diagnosis of central vestibular disorder was suspected when 1 of the following situations was observed: nystagmus on the gazed evoked nystagmus test, hypometric or hypermetric saccades in the oculographic test, an ataxic smooth pursuit, or a persistent nystagmus when the ocular fixation test was performed. Following the study protocol, an MRI of the central nervous system should be done to any individual with suspicion of central vestibular disorder.

Data Collection
Clinical data at the time of study for the patients with AS were extracted from their clinical records. Besides demographic features, data on the following items were analyzed: age at time of disease diagnosis, disease duration from the onset of symptoms. BASDAI and BASFI at the time of study, hip involvement, synovitis or enthesitis in other peripheral joints, anterior uveitis, presence of syndesmophites, HLA-B27 status, CRP at time of disease diagnosis and at time of study, ESR at time of disease diagnosis and at time of study.

Audiologic and Vestibular Assessment: Protocol
We analyzed data obtained from patients and controls in the audologic, oculographic, and vestibular studies. Patients and controls were asked whether they had hearing loss, vertigo, tinnitus, dizziness, or dysequilibrium symptoms at the time of study. All patients and controls underwent a complete ear, nose, and throat examination, including pneumatic otoscopy and otomicroscopic examinations, and the following audiologic tests: pure-tone audiometric test (0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz), both aerial and bone conduction stimulus, and SRT and SDT. Tympanometry and stapedius reflex threshold were also performed.

MRI of the posterior fossa and brainstem was performed in those individuals with asymmetric sensory-neural hypacusia to exclude central nervous system involvement.

Qualitative vestibular studies in patients and controls were evaluated by videonystagmography and videonystagmography (Ulmer VNG, Version 5.5 SYNAPSIS, Marseille, France). The equipment consisted of a modified diving mask (goggles) in which the eyes were illuminated by infrared light-emitting diodes placed on 1 side of the camera lens. The sealed-mask carried 1 infrared-sensitive video camera, allowing observation of 1 eye in a monitor while the other was closed.

In all patients and controls spontaneous nystagmus, gazet evoked nystagmus, ocularographic tests (saccades and slow smooth pursuit evaluation), OCR, head shaking nystagmus, and positional nystagmus in supine, lying on the right, lying on the left, and cervical hyperextension positions (head hanging) were performed. Then, the cephalic rotational test in the supine position and the Dix-Hallpike test were done. Later, a static postural evaluation with CTSIB was conducted. Finally, a bithermal water caloric test was performed.

Statistical Analysis
Continuous data were expressed as mean ± standard deviation, and categorical variables as percentages. Continuous variables were compared using the Student t test or Mann-Whitney U test. Categorical variables were compared using the Fisher exact test. Association between audiovestibular tests and epidemiologic and clinical features in patients with AS was measured as odds ratio (OR) and 95% confidence interval (CI) adjusting for age at the time of study via multiple logistic regressions. Two-sided p values < 0.05 were considered to indicate statistical significance. Analyses were performed with the package Stata 8/SE (Stata Corporation, College Station, TX).

RESULTS
Main Clinical Features of AS Patients
We studied 50 patients with AS and 44 matched controls. All patients fulfilled classification criteria for AS. The main

| TABLE 1. Main Demographic and Clinical Findings of 50 Patients With Ankylosing Spondylitis |
| Variable | Men/Women | Mean age (yr) ± SD | At time of study | At time of onset of symptoms | Delay to diagnosis (yr) ± SD | Mean disease duration (yr) ± SD | Mean BASDAI ± SD at time of study | Mean BASFI ± SD at time of study | Hip involvement | Synovitis or enthesitis in other peripheral joints | Anterior uveitis | Syndesmophites | HLA-B27 | CRP ± SD (mg/L) at time of disease diagnosis | ESR ± SD (mm/1 h) at time of disease diagnosis | CRP ± SD (mg/L) at time of study | ESR ± SD (mm/1 h) at time of study |
|--------|-----------|-------------------|-----------------|-----------------------------|--------------------------|--------------------------|-----------------------------|-----------------------------|----------------|---------------------------------|----------------|----------------|-----------|---------------------------------|----------------|----------------|----------------|----------------|
epidemiologic and clinical features of this series of patients are shown in Table 1. Most patients with AS were men (80%). The mean age at the time of study was 52.5 years, and the mean age at the onset of symptoms was 34.4 years. Patients included in this study had long disease duration (mean, 18.7 yr). A history of anterior uveitis was found in 20%. HLA-B27 was positive in 74% of patients.

**Audiovestibular Symptoms and Auditory Differences Between AS Patients and Controls**

While 20% of the patients complained of subjective audiovestibular symptoms, none of the matched controls reported audiovestibular manifestations (p < 0.001) (Table 2).

We compared auditory findings of patients with AS at the time of study with those of matched controls (Table 2). Audiometric tests were more sensitive than clinical symptoms in disclosing subclinical hearing loss. Twenty-nine (58%) of the 50 patients with AS showed abnormal hearing loss in the audiogram, compared to only 8 (18%) of the 44 controls (p < 0.001). Values of audiometric tests (PTA and SRT) also yielded significant differences between patients and controls (p < 0.001).

A bilateral SNHL was registered in 19 of the 29 patients with hearing impairment. It was asymmetrical in 7 and symmetrical in the other 12 patients. In contrast, SNHL was bilateral in all controls (n = 8) with hearing impairment. Unlike AS patients, only 1 of the 8 controls with bilateral SNHL showed asymmetrical hearing impairment (p < 0.001) (see Table 2). It is noteworthy that the audiogram shape disclosed a predominant pattern of high-frequency SNHL in AS patients (50%) compared to controls (18%) (p = 0.002).

Abnormal tympanogram and absence of stapedius reflex were more commonly observed in patients than controls: 8% and 10%, respectively, in AS patients compared with 0% in controls, but the difference did not achieve statistical significance (p = 0.12 and p = 0.06, respectively) (see Table 2). There was no abnormal correlation between SRT and PTA, as differences between SRT and PTA were ≤5 dB HL in all patients and controls. None of the patients and controls had abnormal SDT.

MRI was performed in all patients who had asymmetrical or unilateral SNHL, and excluded the presence of degenerative and tumoral lesions of the central nervous system in all these patients.

**Oculographic, Vestibular, and Postural Differences Between Patients With AS and Controls**

No statistically significant differences in the frequency of abnormal oculographic tests between AS patients and controls were found (Table 3). However, AS patients had abnormal

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Patients With AS (n = 50) No. (%)</th>
<th>Controls (n = 44) No. (%)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Sex (no. men/no. women)</td>
<td>40/10</td>
<td>33/11</td>
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<tr>
<td>Proportion men (%)</td>
<td>80</td>
<td>75</td>
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<td>Age at time of study (yr ± SD)</td>
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<td>50.7 ± 16.3</td>
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<td>Individuals with abnormal audiovestibular symptoms</td>
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<td>Hearing loss</td>
<td>20 (40)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
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<td>Tinnitus</td>
<td>13 (26)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vertigo</td>
<td>7 (14)</td>
<td>0 (0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (14)</td>
<td>0 (0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Dysequilibrium</td>
<td>6 (12)</td>
<td>0 (0)</td>
<td>0.03</td>
</tr>
<tr>
<td>Individuals with abnormal hearing loss in audiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilaterally</td>
<td>29 (58)</td>
<td>8 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symmetrical</td>
<td>12 (24)</td>
<td>7 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asymmetrical</td>
<td>7 (14)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>10 (20)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Audiogram shape</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-frequency SNHL</td>
<td>25 (50)</td>
<td>8 (18)</td>
<td>0.002</td>
</tr>
<tr>
<td>Flat pattern SNHL</td>
<td>4 (8)</td>
<td>0 (0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Abnormal tympanogram</td>
<td>4 (8)</td>
<td>0 (0)</td>
<td>0.12</td>
</tr>
<tr>
<td>Absence of stapedius reflex</td>
<td>5 (10)</td>
<td>0 (0)</td>
<td>0.06</td>
</tr>
<tr>
<td>PTA at 0.5–3 kHz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear</td>
<td>21.2 ± 15.8</td>
<td>9.3 ± 5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ear</td>
<td>20.2 ± 15.1</td>
<td>7.9 ± 4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTA at 4–8 kHz</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear</td>
<td>32.9 ± 23.1</td>
<td>13.3 ± 9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ear</td>
<td>30.9 ± 21.1</td>
<td>13.3 ± 9.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SRT in dB HL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right ear</td>
<td>23.7 ± 19.1</td>
<td>12.2 ± 6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ear</td>
<td>22.6 ± 15.4</td>
<td>9.8 ± 4.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abnormal SRT and PTA correlation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abnormal SDT</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*See Patients and Methods section for definitions and descriptions.
TABLE 3. Oculographic, Vestibular, and Postural Variables in Patients With AS and Controls

<table>
<thead>
<tr>
<th>Variable*</th>
<th>Patients With AS (n = 50) No. (%)</th>
<th>Controls (n = 44) No. (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth pursuit</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Abnormal saccades</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Spontaneous nystagmus</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Evoked nystagmus</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abnormal OCR</td>
<td>5 (10)</td>
<td>0 (0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Head-shaking nystagmus</td>
<td>10 (20)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Patients with positional nystagmus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With ≥1 abnormal position</td>
<td>4 (8)</td>
<td>2 (5)</td>
<td>0.68</td>
</tr>
<tr>
<td>Dix–Hallpike test</td>
<td>4 (8)</td>
<td>1 (2)</td>
<td>0.37</td>
</tr>
<tr>
<td>Abnormal cephalic rotation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>Abnormal caloric test</td>
<td>13 (26)</td>
<td>0 (0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Individuals with Abnormal CTSIB</td>
<td>18 (36)</td>
<td>2 (5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patterns of CTSIB in individuals with abnormal CTSIB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vestibular loss</td>
<td>14 (28)</td>
<td>0 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Visually dependent</td>
<td>3 (6)</td>
<td>2 (5)</td>
<td></td>
</tr>
<tr>
<td>Surface dependent</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Sensory selection</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

*See Patients and Methods section for definitions and descriptions.

Association of Abnormal Audiovestibular Symptoms With Demographic and Clinical Features of AS

An association between the presence of audiovestibular symptoms and age at the time of study was observed (OR, 1.06; 95% CI, 1.01–1.10; p = 0.01). However, when results were adjusted for age at the time of study, no significant association between age at time of disease diagnosis or disease duration and the presence of abnormal audiometric tests was observed (Table 4). An increased risk of hypoacusia was observed in patients with severe extraspinal manifestations, such as hip involvement (OR, 1.56) and anterior uveitis (OR, 2.39). This was also the case for HLA-B27 (OR, 1.78). Although these associations did not achieve statistical significance, our observations suggest that the presence of severe extraspinal manifestations may be a positive “signal” for the presence of hypoacusia in audiometric tests.

TABLE 4. Association of Abnormal Audiovestibular Symptoms With Demographic and Clinical Variables in 50 Patients With AS

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) at time of study (by yr)</td>
<td>1.06 (1.01–1.10)</td>
<td>0.01</td>
</tr>
<tr>
<td>Age (yr) at time of disease diagnosis (by yr)</td>
<td>0.99 (0.93–1.05)</td>
<td>0.70</td>
</tr>
<tr>
<td>Disease duration</td>
<td>1.00 (0.95–1.06)</td>
<td>0.88</td>
</tr>
<tr>
<td>BASDAI at time of study</td>
<td>1.11 (0.81–1.53)</td>
<td>0.52</td>
</tr>
<tr>
<td>BASFI at time of study</td>
<td>1.14 (0.83–1.58)</td>
<td>0.41</td>
</tr>
<tr>
<td>Hip involvement</td>
<td>1.32 (0.26–6.59)</td>
<td>0.74</td>
</tr>
<tr>
<td>Synovitis or enthesis in other peripheral joints</td>
<td>1.49 (0.38–5.83)</td>
<td>0.57</td>
</tr>
<tr>
<td>Anterior uveitis</td>
<td>1.76 (0.39–7.98)</td>
<td>0.46</td>
</tr>
<tr>
<td>Syndesmophites</td>
<td>0.91 (0.22–3.73)</td>
<td>0.90</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>0.33 (0.08–1.46)</td>
<td>0.15</td>
</tr>
<tr>
<td>CRP (mg/L) at time of disease diagnosis</td>
<td>0.98 (0.93–1.05)</td>
<td>0.69</td>
</tr>
<tr>
<td>ESR (mm/1 h) at time of disease diagnosis</td>
<td>1.01 (0.99–1.04)</td>
<td>0.35</td>
</tr>
<tr>
<td>CRP (mg/L) at time of study</td>
<td>1.01 (0.96–1.07)</td>
<td>0.63</td>
</tr>
<tr>
<td>ESR (mm/1 h) at time of study</td>
<td>1.03 (0.96–1.10)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

As expected, a significant association between hypoacusia in audiometric tests and age at the time of study was found (OR, 1.11; 95% CI, 1.05–1.18; p < 0.001). However, when results were adjusted for age at the time of study, no significant association between age at time of disease diagnosis or disease duration and the presence of abnormal audiometric tests was observed (Table 5). An increased risk of hypoacusia was observed in patients with severe extraspinal manifestations, such as hip involvement (OR, 1.56) and anterior uveitis (OR, 2.39). This was also the case for HLA-B27 (OR, 1.78). Although these associations did not achieve statistical significance, our observations suggest that the presence of severe extraspinal manifestations may be a positive “signal” for the presence of hypoacusia in audiometric tests.
To our knowledge, the current study encompasses the largest series of patients with AS assessed for the presence of audiologic, vestibular, and postural abnormalities. Our results show that patients with AS have an increased frequency of abnormal vestibular tests and anterior uveitis (OR, 1.78) did not reach statistical significance (Table 6).

**Association of Abnormal Vestibular Tests, Excluding CTSIB, With Demographic and Clinical Variables in 50 Patients With AS**

No association of age at time of study, age at time of disease diagnosis, or disease duration with abnormal vestibular tests was observed (Table 6). Apart from an association with BASFI at time of study (OR, 0.64; 95% CI, 0.44–0.89; p = 0.02), no associations between abnormal tests and specific features of AS were found. In this regard, the presence of HLA-B27 was associated with an increased risk of abnormal vestibular tests (OR, 4.64), but such an association had a broad CI (0.89–24.2), and it remained slightly out of the range of significance (p = 0.07). However, the implication of a positive HLA-B27 and abnormal vestibular tests is definitely worth further investigation, and the present data may be a very important "signal" that was detected as a result of this study. It was also the case that the association between abnormal vestibular tests and anterior uveitis (OR, 1.78) did not reach statistical significance (Table 6).

**Association of Abnormal CTSIB With Demographic and Clinical Variables in Patients With AS**

Apart from an association with age at time of study and ESR at time of disease diagnosis (Table 7), no associations between specific clinical features of AS and the presence of CTSIB abnormalities were observed.

**DISCUSSION**

The current study confirms the presence of auditory impairment in patients with AS. We found a significantly increased frequency of patients with abnormal hearing loss in the audiogram compared to matched controls. AS patients exhibited significantly higher values of PTA and SRT than controls. Moreover, a predominant pattern of high-frequency SNHL was observed in patients with AS.

Little is known about cochleovestibular dysfunction in AS. To our knowledge, the current study encompasses the largest series of patients with AS assessed for the presence of oculographic, vestibular, and postural abnormalities. Our results show that patients with AS have an increased frequency of abnormal vestibular tests. We observed an increased frequency of head shaking-nystagmus and abnormal caloric tests in these patients compared to matched controls, and an abnormal CTSIB with a predominant pattern of vestibular loss was more frequently found in patients than controls.

In 1979, McCabe described a syndrome of SNHL that was often accompanied by vertigo and tinnitus. More recently,
Stone and Francis emphasized that this syndrome may be observed in autoimmune disorders and some vasculitides. In keeping with this statement, audiovestibular dysfunction was reported in vasculitides, both in patients with primary small and middle-sized blood vessel systemic vasculitides, such as Wegener granulomatosis, or polyarteritis nodosa, and in patients with vasculitides secondary to other underlying conditions, such as Behçet disease.

They also found an increased auditory and vestibular impairment in patients with scleroderma. Another typical connective tissue disease is Sjögren syndrome and relapsing polychondritis. We have recently confirmed the presence of auditory and vestibular dysfunction in patients with biopsy-proven giant cell arteritis, a primary vasculitis involving large-sized blood vessels.

Vasculitic and autoimmune mechanisms have been considered to play a role in the pathogenesis of the frequently subclinical sensorineural dysfunction observed in patients with systemic lupus erythematosus. SNHL has been observed in patients with Sjögren syndrome and relapsing polychondritis. We have recently confirmed the presence of auditory and vestibular impairment in patients with scleroderma, another typical connective tissue disease.

AS is a common chronic inflammatory rheumatic disease. Previous studies, in most cases based on small series of patients, disclosed an auditory impairment in AS. In this regard, Caselin et al. assessed 22 consecutive patients with AS. They observed a higher frequency of SNHL in patients with AS aged 45-59 years old compared with healthy controls. Alatas et al. found SNHL in 28.6% of 28 AS patients compared to 4.35% in 23 matched controls. Dagli et al. studied 28 patients with AS and 25 controls; they found SNHL in 10 patients (35%), bilateral in 7 and unilateral in 3. In keeping with these findings, in the current series, where PTA was used to assess hearing impairment, we observed 29 (58%) AS patients with abnormal hearing loss in the audiogram compared to only 8 (18%) controls. In 19 of these 29 patients the SNHL was bilateral. Dagli et al. observed significant differences in pure-tone threshold levels for hearing levels at 250–500 Hz and 4000–8000 Hz between patients and controls, but not at 1000 and 2000 Hz. Those results are in keeping with our data, as we found a predominant pattern of high-frequency SNHL in AS patients in the current series.

Likewise, as observed in our study, Eryilmaz et al. reported significant differences in the pure-tone thresholds between 59 patients with AS and 52 controls. Such differences were more prominent in the higher frequencies.

In line with the above, Adam et al. studied 45 consecutive patients with AS and 31 controls. These authors did not observe statistically significant differences between the 2 groups with respect to conventional frequency air conduction threshold and bone conduction threshold. However, they found a statistically significant difference at 14,000–16,000 Hz at extended high frequencies in 32 (71.1%) patients with AS compared to 12 (40%) controls. They also found an increased frequency of SNHL, especially at extended high frequencies, in patients with extraspinal involvement.

Despite the absence of statistical significance, in our study individuals with severe extraspinal manifestations had an increased risk of having hypoacusis. The presence of hip involvement, anterior uveitis, and HLA-B27 in patients with AS appears to be a signal for SNHL that deserves further investigation.

In the current series of patients with AS, SRT was in accordance with PTA results (within a range of difference between SRT and PTA ≤5 dB HL). Indeed, a significant difference between the 2 thresholds was noted, raising doubts about the validity of the pure-tone thresholds. Furthermore, SDT yielded good discrimination scores and correlation between the type and degree of hearing loss, suggesting the presence of a cochlear impairment. The absence of a stapedius reflex in 5 patients and a SDT >85% may also suggest that abnormalities in our patients with AS may be due to a cochlear lesion in the inner ear.

Besides sensorineural damage, in our series middle ear dysfunction, manifested by an abnormal tympanometry, was found in 8% of patients with AS compared to none of the controls. A flattened tracing is considered the most specific sign of abnormal tympanometry. We note that a flattened tracing was more commonly observed in our series of AS patients than in the control group (4 [8%] patients vs. none in controls). Also, although in the general population the most common cause of flattened tracing in tympanograms is a decreased mobility of the tympanic membrane secondary to middle ear fluid, none of the AS patients from our series had otitis media with effusion. All our patients and controls were evaluated by otomicroscopic examination. In the 4 AS patients with flattened pattern in the tympanogram, the otomicroscopic examination was normal. This finding could be explained by an increased rigidity of the tympanosascular system in these 4 patients.

These observations suggest that not all abnormal tympanic membranes in these patients are an indication of an infectious or a serious effusion—they may be due to increased rigidity of the tympanosascular system.

Information on cochleovestibular dysfunction in AS is scarce. Erbek et al. studied 32 patients with AS and 30 controls. Besides a significant difference between the 2 groups with regard to PTA at high frequencies, the rates of reproducibility in transient evoked otoacoustic emission testing were significantly lower in patients with AS than controls. Moreover, the signal-to-noise rates of the response values were lower at all frequencies in patients with AS, but a statistically significant difference was found only at 2, 3, and 4 Hz. Electronystagmography disclosed pathologies in 11 patients with AS (34%), 8 of which were central (25%), and 3 peripheral (9%).

In the current series we did not find significant differences between AS patients and controls when tracking or saccade tests were assessed. However, our results confirmed that the vestibule is also involved in patients with AS. Patients with AS had a marginally increased frequency of abnormal OCR and a significantly increased frequency of head-shaking nystagmus and abnormal caloric test compared to controls. The static postural study also yielded a significantly increased frequency of abnormal CTSIB in AS patients (36%) compared to controls (5%). Vestibular loss was the main pattern of abnormal CTSIB in our patients. All these findings support the presence of a peripheral vestibular lesion in patients with AS.

A potential limitation of the present study is related to the use of NSAIDs by the patients with AS. As shown in Table 1, the mean age at the time of study for patients with AS was 52.5 years, and only 9 cases from this series were aged 70 years or older. Therefore, most healthy matched controls included in this study were not taking NSAIDs. An option to minimize the potential effect of NSAIDs on audiovestibular manifestations might have been the inclusion of patients with osteoarthritis. However, we feel that the use of controls with osteoarthritis taking NSAIDs might have strongly biased the control sample toward higher ages, which was confirmed to be strongly associated with audiovestibular symptoms in our study. Another potential limitation is that the results might not be applicable to patients with severe cervical involvement, as those patients were excluded from the study due to methodologic limitations.

In conclusion, the current study demonstrates strong evidence for inner ear compromise in patients with AS. The study...
is relevant because it provides justification for rheumatologists or physicians to screen for inner ear compromise in their AS population.

REFERENCES


