Chronic otitis media: a new extra-articular manifestation in ankylosing spondylitis?

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Abstract

Following a study reporting a fourfold increase in the occurrence of chronic otitis media in patients with ankylosing spondylitis, this prospective study examines this association with respect to severity, duration of disease, and acute phase in ankylosing spondylitis. Forty two consecutive patients with classical ankylosing spondylitis seen at the rheumatology clinic of a teaching hospital where the features of ankylosing spondylitis were recorded had an otological examination by an otolaryngologist. The occurrence of chronic otitis media (all categories) was 12/42 (29%). The acute phase serum markers (C reactive protein and IgG) were increased in patients with active or inactive chronic otitis media. Extra-articular manifestations were significantly more common in the chronic otitis media group than in those with no history of chronic otitis media. The results of this study suggest that chronic otitis media may be another extra-articular manifestation of ankylosing spondylitis. Alternative explanations, however, include similar aetiological factors for the two conditions or a previously unrecognised increased occurrence of HLA-B27 in patients with chronic otitis media.

We have previously reported a fourfold increase in the occurrence of chronic otitis media in a group of patients with ankylosing spondylitis[1] compared with the general population. The occurrence of active or inactive chronic otitis media in the study group was 19% (8/42) compared with 5% in the control population ($p<0{\cdot}01$).[2] There was no difference in the number of patients with healed chronic otitis media in the two groups. The explanation for the relationship of these two conditions was not immediately apparent and it was suggested that chronic otitis media may have a previously unrecognised association with the HLA-B27 histocompatibility antigen.

In this study, we have attempted to clarify further the nature of this relation by examining which, if any, of a variety of clinical and laboratory features of ankylosing spondylitis were associated with the occurrence of chronic otitis media.

Patients and methods

Forty two consecutive patients with classical ankylosing spondylitis[3] were seen at the rheumatology clinic where the following information was recorded from the patient's history and medical notes: social class, age, sex, use of non-steroidal anti-inflammatory drugs (NSAIDs), second line drug treatment, age of onset of ankylosing spondylitis, duration of ankylosing spondylitis, HLA-B27 status, peripheral joint disease, erythrocyte sedimentation rate, wall to tragus distance, spondylometry, presence of extra-articular manifestations (uveitis and aortic incompetence), duration of early morning stiffness, presence of rheumatoid factor, and serum levels of C reactive protein, IgA, IgG, and IgM. All serum levels and measurements were current or within the previous three months. Clinical otological examination was carried out after cleaning the external auditory canals where necessary to allow inspection of the whole tympanic membrane.

Chronic otitis media was categorised as active, inactive, or healed.[4] Active chronic otitis media was defined as a chronic perforation of the tympanic membrane with signs of inflammation, such as mucopus or oedema, present in the middle ear. Inactive chronic otitis media was defined as a chronic perforation of the tympanic membrane with no signs of inflammation in the middle ear. Healed chronic otitis media was defined as an intact tympanic membrane with evidence of previous perforation or marked tympanosclerosis.

Statistical analysis was performed by examining the variation in features of ankylosing spondylitis between patients with and without chronic otitis media (all categories). As our previous study had only shown a significant increase in the occurrence of active or inactive chronic otitis media in patients with ankylosing spondylitis, a second analysis examined the same features in patients with active or inactive chronic otitis media compared with the normal group, i.e. excluding the healed group from the analysis. A third analysis examined the same features in patients with active or inactive chronic otitis media compared with the healed or normal group.

The discrete variables (social class, sex, history of use of NSAID second line drug treatment, HLA-B27 status, presence of peripheral joint disease, extra-articular manifestations and rheumatoid factor) were cross tabulated using the χ^2 test with and without Yates's correction. Conover argues that Yates's correction reduces the power of the analysis and thus hides biologically significant associations.[5] Mantel and Greenhouse consider it prudent to use Yates's correction in all 2×2 contingency tables.[6] In view of the controversy over the use of Yates's correction for 2×2 tables, both values are quoted in the analysis of extra-articular manifestations.

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Accepted for publication 19 September 1991

Table 1 Categories of patients with chronic otitis media

Status of tympanic membrane*	No of patients (%)
Normal	30 (71)
Healed COM	4 (10)
Inactive COM	7 (17)
Active COM	1 (2)
Total	42 (100)

*COM=chronic otitis media.

Table 2 Association between extra-articular manifestations (EAM) and chronic otitis media (COM)

Status of middle ear COM	EAM present	EAM absent	χ^2 test with Yates's correction	χ^2 test without Yates's correction
Active Inactive Healed	7	3		
			p=0·048	p=0·017
Normal	8	21		
Active Inactive	5	2		
			p=0·084	p=0·030
Normal	8	21		
Active Inactive	5	2		
			p=0·121	p=0·048
Normal Healed	10	22		

The Mann-Whitney U test was used for the non-parametric continuous variables (age of onset of ankylosing spondylitis, C reactive protein, erythrocyte sedimentation rate, wall to tragus distance, spondylometry, IgG, duration of early morning stiffness, and duration of ankylosing spondylitis) and the two sample *t* test was used for continuous variables (age, IgA, IgM) with a normal distribution.

Results

The occurrence of chronic otitis media (all categories) was 12/42 (29%). Table 1 shows the number of patients in the various categories. There was a significant increase in IgG levels (p=0·035) and there was a trend towards an increase in C reactive protein (p=0·078) in the patients with active or inactive chronic otitis media compared with normal subjects (which included the patients with healed chronic otitis media).

Extra-articular manifestations were significantly more common in the chronic otitis media group in all three analyses. Table 2 shows the 2×2 contingency tables for the three analyses, including the p values for each with and without Yates's correction.

None of the other features were significantly related to either the chronic otitis media or normal groups. Missing data accounted for 1·8% of the total data required when analysing the features of ankylosing spondylitis.

Discussion

The presence of an association between active or inactive chronic otitis media and increased levels of C reactive protein and IgG is not surprising as this probably reflects the acute phase response to such an episode. It shows that any increase in the acute phase serum markers in patients with ankylosing spondylitis may be due to factors other than rheumatological disease and full examination should be carried out before specific management is planned.

The more interesting finding is the association between chronic otitis media and the subset of patients with extra-articular manifestations. Our original study[1] showed an increase in the occurrence of active or inactive but not healed chronic otitis media in patients with ankylosing spondylitis. The current analysis seems to indicate that the extra-articular manifestations of ankylosing spondylitis are more associated with all categories of chronic otitis media than just the active or inactive group. This apparent anomaly may be due to the small sample size used in the original study.

Ankylosing spondylitis is known to be strongly associated with the presence of HLA-B27. It is not known if the incidence of HLA-B27 in chronic otitis media is different from the general population and we are currently undertaking a further study to assess the occurrence of HLA-B27 in an unselected group of patients with chronic otitis media. If there is an association between chronic otitis media and HLA-B27, this could explain both the increased incidence of chronic otitis media in ankylosing spondylitis and the particular association with extra-articular manifestations as uveitis, the most common extra-articular manifestation seen in our group of patients, is known to be more common in HLA-B27 positive subjects without ankylosing spondylitis. Brewerton found that 58% of 100 patients presenting to an eye department with acute anterior uveitis were positive for HLA-B27 compared with 7% (22/300) of asymptomatic control subjects.[7]

A further explanation for these findings may be that chronic otitis media is, in fact, a previously unrecognised extra-articular manifestation of ankylosing spondylitis. It may be relevant in this regard that a combination of topical steroid and antibiotic drugs has been shown to be more effective than antibiotics alone in treating patients with active chronic otitis media.[8]

An alternative explanation for the apparent association between ankylosing spondylitis and chronic otitis media would be if the two conditions shared aetiological factors. Gram negative bacteria, particularly *Klebsiella pneumoniae*, have been suggested as possible bacterial triggers in ankylosing spondylitis. Further evidence to support this has come from the finding that there is some cross reactivity between an epitope of HLA-B27 and *Klebsiella pneumoniae*.[9] The bowel has previously been thought to be the portal of entry for any bacterial trigger but it is interesting that coliform bacteria are the most common organisms to be cultured from the ears of patients with chronic otitis media.[10] It could therefore be suggested that chronic middle ear infection acts as a trigger for ankylosing spondylitis in susceptible subjects. Ebringer *et al* found that episodes of acute anterior uveitis were associated with faecal carriage of klebsiella. Our study may be detecting a similar phenomenon with middle ear infection rather than

gastrointestinal colonisation acting as a trigger for episodes of uveitis.

In summary, we present a new association between chronic otitis media and ankylosing spondylitis, particularly those patients with ankylosing spondylitis who have extra-articular manifestations.

The authors thank Dr S Gatehouse, MRC Institute of Hearing Research (Scottish Section) for advice on statistical analysis and the staff of the rheumatology department for their assistance during the course of this study.

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