MR of head and neck adenopathy in asymptomatic HIV-seropositive men.

D W Chakeres, L J Zawodniak, R A Bornstein, R B McGhee, Jr and C C Whitacre

AJNR Am J Neuroradiol 1993, 14 (6) 1367-1371
http://www.ajnr.org/content/14/6/1367

MR of Head and Neck Adenopathy in Asymptomatic HIV-Seropositive Men

Donald W. Chakeres,[1] Leonard J. Zawodniak,[1] R. A. Bornstein,[2] Robert B. McGhee, Jr,[1] and Caroline C. Whitacre[3]

PURPOSE: Adenopathy is a well-known component of AIDS-related complex. Our goal was to determine whether asymptomatic HIV-infected persons have characteristic findings of head and neck adenopathy on MR imaging and whether there is an association between the MR findings and the CD4 lymphocyte counts. **METHODS:** We blindly and retrospectively evaluated the distribution and size of lymphadenopathy seen on screening MR examinations that were performed on 50 asymptomatic HIV-positive male subjects and 50 age-matched HIV-negative control subjects. We also correlated the imaging findings in HIV-seropositive and -seronegative subjects with their CD4 counts. **RESULTS:** The HIV-positive subjects had a higher incidence of adenopathy compared with the controls. Statistically significant differences were found between the groups in size and number of neck lymph nodes, thickness of the adenoids, size of high, deep cervical-retropharyngeal lymph nodes, and presence of parotid abnormalities. We found a correlation between increasing lymph node size and decreasing CD4 levels. **CONCLUSION:** We conclude that HIV-positive asymptomatic patients have a high incidence of head and neck abnormalities including lymphadenopathy, and alteration in their CD4 counts not commonly seen in seronegative control subjects.

Index terms: Acquired immunodeficiency syndrome (AIDS); Neck, abnormalities and anomalies; Neck, magnetic resonance

AJNR 14:1367–1371, Nov/Dec 1993

Many reports on the clinical and imaging studies of symptomatic patients infected with human immunodeficiency virus (HIV) have shown a high incidence of head and neck abnormalities (1–4). A wide range of causes and appearances of these head and neck findings has been described. However, there have been few reports on the incidence of head and neck abnormalities on magnetic resonance (MR) in asymptomatic HIV-seropositive patients (without acquired immunodeficiency syndrome [AIDS]) when blindly compared with healthy control subjects (5). This study compares the frequency and size of head and neck adenopathy of both control seronegative and asymptomatic HIV-positive men as seen with MR.

The clinical manifestations of HIV infection are closely associated with progressive depletion of the CD4 T lymphocyte (6–8). The CD4 T lymphocyte is the cell type critical in antigen recognition. The CD4 cell releases many cytokines, including interferon gamma (which is an important activator of the macrophage that acts to kill intracellular organisms). We also compared CD4 lymphocyte levels with the size and extent of adenopathy. The goal of this study is to determine whether there are characteristic findings of head and neck adenopathy associated with asymptomatic HIV infection and whether there is an association between CD4 lymphocyte counts and the degree of adenopathy.

Subjects and Methods

One hundred homosexual or bisexual male subjects were studied. Fifty asymptomatic HIV-infected patients and 50 HIV-negative control subjects were randomly selected from

Received March 23, 1992; revision requested July 23, received November 16, and accepted November 20.

This study was supported by a grant (MH45649) from the National Institute of Mental Health to Dr. Bornstein and by a grant (AI 25924) from the National Institute of Allergy and Infectious Disease.

[1] Division of Neuroradiology, Department of Radiology, [2]Department of Psychiatry, and [3]Department of Medical Microbiology and Immunology, Ohio State University College of Medicine, Columbus, Ohio 43221.

Address requests for reprints to: Donald W. Chakeres MD, Department of Radiology, S-209 Rhodes Hall, Ohio State University Hospital, 410 West 10th Avenue, Columbus, OH 43221.

AJNR 14:1367–1371, Nov/Dec 1993 0195-6108/93/1406–1367

a sample of 325 volunteers for a longitudinal study of neurobehavioral and MR changes associated with HIV infection. All of the control subjects and HIV-positive patients were asymptomatic with no manifestations of HIV infection. No patients were receiving medical therapy for their HIV infection. All of the participants signed informed consents approved by a Human Subjects Research Committee.

The mean average age was similar for both groups: 33.4 years (standard deviation [SD], 7.7) for the HIV-positive group and 32.3 years (SD, 7.8) for the controls. All patients enrolled in the study were homosexual or bisexual males with no history of intravenous drug use. The CD4 cell count (percentage of total lymphocytes) was measured for all of the controls and patients.

All MR examinations were performed on a 1.5-T system (General Electric Medical Systems, Milwaukee, WI). Spin-echo images were obtained with the following parameters: T1-weighted images (617/20/1 [repetition time/echo time/excitations]) were acquired in the sagittal and coronal planes (acquisition time, 2 minutes 16 seconds). Axial (3017/30 and 3017/80) images with flow-compensating gradients were also acquired (acquisition time, 7 minutes 45 seconds). All sections were 5 mm thick, with a 1-mm intersection gap in the axial and sagittal planes and a 1.5-mm gap in the coronal plane. The image matrix was 256 × 192. The field of view was 24 cm. All of the images were acquired with a standard quadrature head coil. The lowest imaging range varied according to the subjects' body habitus and positioning. The lowest section usually crossed at approximately the inferior portion of the third cervical vertebrae.

The studies were interpreted jointly by two neuroradiologists (D.W.C. and L.J.Z.) with no knowledge of the patients' HIV status. A random sample of 22 of the studies were reinterpreted separately by both authors, and the results were evaluated for reproducibility. The mean reliability coefficient was 0.80, and all coefficients were significant at less than the 0.0001 level.

Nasopharyngeal soft tissue (adenoids) thickness was measured in millimeters on the T1-weighted sagittal images in the midline, perpendicular to the clivus (Fig 1). Specific lymph nodes of the high, deep cervical retropharyngeal region seen just anteromedial to the carotid arteries at the skull base were evaluated (Fig 1). These high, deep cervical retropharyngeal nodes were measured along their longest axis on the axial T2-weighted images at the skull base. Lymph nodes included in the field of view in the posterior and anterior triangles and in the suboccipital and submental regions were also measured along their longest axis and were counted if they measured more than 5 mm in diameter (Fig 2). The parotid glands were considered abnormal if they demonstrated signal abnormalities consistent with cysts or intraparotid lymph nodes larger than 8 mm in largest dimension (Fig 3). They were usually low signal intensity on the T1-weighted images and high signal intensity on the T2-weighted images.

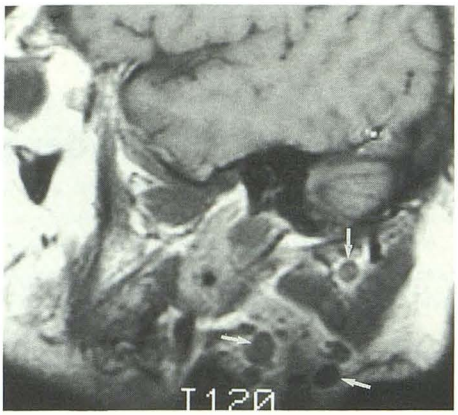

Fig. 2. Cervical adenopathy in an asymptomatic HIV-positive patient. This sagittal T1-weighted image demonstrates multiple rounded structures representing lymph nodes (*arrows*) in the posterior triangle and suboccipital region surrounded by high-signal-intensity fat.

Blood samples were collected in ethylenediaminetetraacetic acid tubes and transported to the AIDS Clinical Trials Unit, hematology and immunology laboratories. Whole blood cell counts and differentials were performed electronically (Coulter STKR, Coulter Electronics, Hialeah, FL). For determination of CD4 values, whole blood samples were stained with two-color monoclonal reagents (Coulter Immunology, Hialeah, FL), followed by lysis of red blood cells and fixation by use of the Q-Prep Immunology workstation (Coulter). Immediately thereafter, processed samples were analyzed by dual color analysis on a flow cytometer (Epics

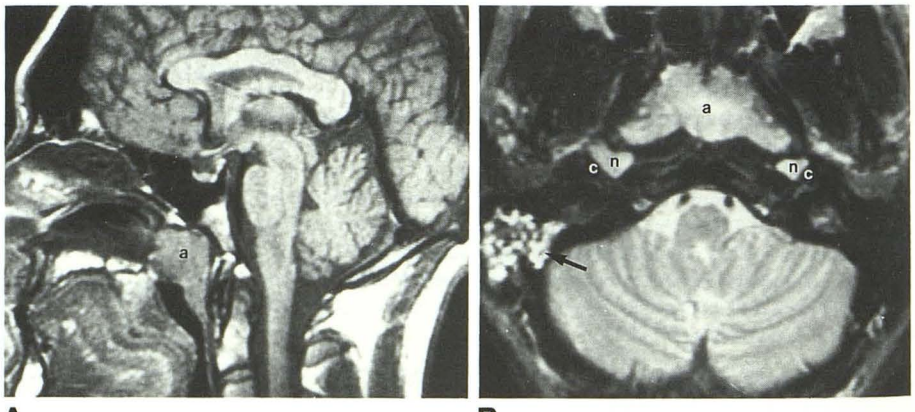

Fig. 1. Enlarged adenoids and deep cervical retropharyngeal lymph nodes in an asymptomatic HIV-positive patient.

A, sagittal T1-weighted image shows enlargement of the adenoids (*a*), which measure 22 mm in thickness.

B, axial T2-weighted image in the same patient also demonstrates symmetric enlargement of the adenoids (*a*). Enlarged deep cervical retropharyngeal lymph nodes (*n*) are seen just below the skull base, medial to the vessels of the carotid sheath (*c*). There is opacification of unknown cause of mastoid air cells (*arrow*) on the right.

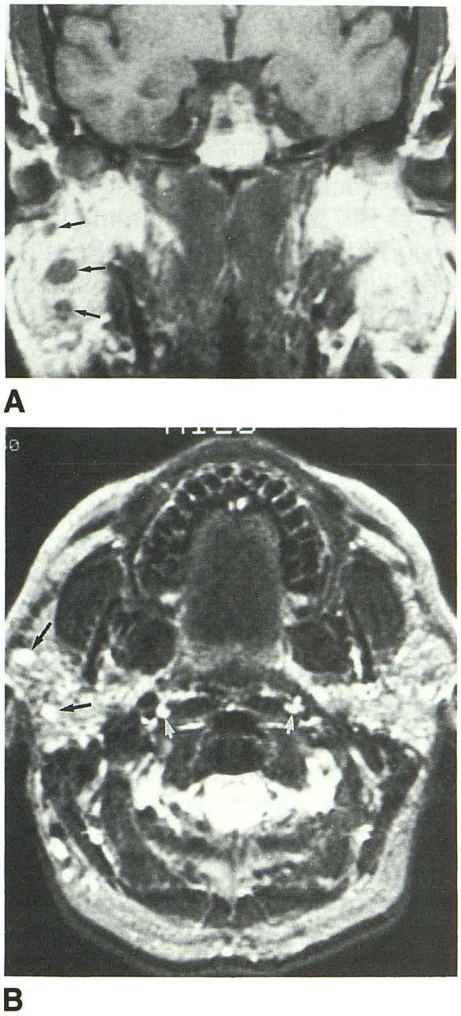

Fig. 3. Parotid abnormalities in an asymptomatic HIV-positive patient.

A, On this coronal T1-weighted image, several small, rounded, low-signal-intensity structures that may represent lymph nodes or cystic lesions (*black arrows*) are surrounded by the high-signal-intensity fatty parotid gland.

B, On an axial T2-weighted image at the level of the parotid glands in the same patient, the round structures (*black arrows*) have high signal intensity compared with the fatty parotid gland. Small deep cervical retropharyngeal lymph nodes are also seen (*white arrows*).

TABLE 1: Lymphadenopathy measures in HIV-positive subjects and control subjects

	HIV Positive	Controls	*t*	*P*
	Mean, SD	Mean, SD		
Adenoids (mm)	3.6, 4.8	1.4, 3.5	2.60	.01
Left retropharyngeal node (mm)	2.4, 2.8	0.8, 1.5	3.58	.001
Right retropharyngeal node (mm)	3.2, 2.8	0.8, 1.5	5.21	.001
Cervical lymph nodes (n)	4.1, 3.3	2.6, 2.5	2.58	.01

C; Coulter). Because of the known variability in absolute CD4 counts, CD4 levels in this study were expressed as a percentage of total lymphocytes in addition to the absolute number. The normal range for the CD4 percentage is 41 to 57%.

Results

The results of the measurements of adenoid thickness, high cervical retropharyngeal lymph node size, total number of head and neck lymph nodes (larger than 5 mm in diameter), and presence of parotid cysts or lymph nodes are shown in Table 1. A wide range of thickness of the adenoids was found in both the control and HIV-positive groups. None of the control group had adenoids thicker than 10 mm; 36% of the HIV-positive group did.

The HIV-positive patients had a wide range of findings related to the degree of cervical adenopathy. A significantly higher percentage of HIV-seropositive subjects had more than five nodes compared with the controls (29 versus 10%). Also, there were far more control subjects (32%) with no adenopathy, compared with only 14% of the HIV-positive group ($\chi^2 = 7.78$; $P < .02$). None of the control group had more than 10 nodes; 6% of the HIV-positive patients did.

None of the control subjects had high deep cervical retropharyngeal nodes larger than 6 mm in size; 16% of the HIV-positive group did. This finding was noted in the left ($\chi^2 = 5.98$; $P < .015$) and right ($\chi^2 = 8.70$; $P < .003$) high deep cervical retropharyngeal nodes.

Only two control patients (4%) had visible parotid pathology compared with 21 (42%) of the HIV-positive group ($\chi^2 = 20.38$; $P < .0001$).

These data indicate that there are differences in the prevalence of these indicators of adenopathy when viewed individually. It also was of interest to examine whether the overall extent of these markers would be of potential clinical value. Therefore, a summary measure of lymphadenopathy was generated on the basis of the four criteria described previously (adenoids thicker than 10 mm, high deep cervical retropharyngeal nodes larger than 6 mm in diameter, more than eight lymph nodes larger than 5 mm in the head and neck region, and evidence of parotid pathology). It was found that 42% of the HIV-seropositive patients and 0% of the control subjects had two or more of these abnormalities ($\chi^2 = 38.96$; $P < .0001$).

The mean CD4 count for the control subjects was 51.6% (SD = 5.2). The mean CD4 count for

the HIV-positive subjects was 28.4% (SD = 7.1). The HIV subjects with evidence of lymphadenopathy on the basis of two or more positive findings of the imaging algorithm had significantly lower CD4 counts compared with the HIV-positive subjects without lymphadenopathy (30.5 versus 25.0%; $t = 2.5$; $P < .017$).

To further demonstrate the relationship of these lymphadenopathy measures to the effects of HIV infection, correlation coefficients were computed with CD4 counts in the HIV-seropositive subjects. It was found that the number of cervical lymph nodes was strongly related to CD4 counts ($r = -.45$; $P < .005$). CD4 counts were also strongly correlated with the presence of parotid pathology ($r = -.46$; $P < .002$). A lesser relationship was observed with the presence of enlarged high deep cervical retropharyngeal adenopathy ($r = -.32$; $P < .05$). In all cases, greater lymphadenopathy was related to greater levels of CD4 decline.

Discussion

AIDS is associated with a severe defect in cell-mediated immunity (3, 6, 9). The major abnormality is depletion of helper-inducer CD4 T lymphocytes. There is a slow decline of the CD4 population. Lower CD4 counts are associated with progressive symptoms. For example, patients with less than 200/mm or approximately 15% of total lymphocytes are susceptible to *Pneumocystis carinii*, cytomegalovirus, or atypical mycobacteria infections (6).

Patients infected with HIV have shown a wide array of clinical findings, including opportunistic infections or of neoplasms that can produce many unusual symptoms. A subgroup of HIV-positive patients with persistent generalized lymphadenopathy, but without symptoms of overt AIDS, has been described (3, 10, 11). These patients have unexplained adenopathy of more than 3 months' duration involving two or more extrainguinal sites. Most nodes are larger than 1 cm in diameter. Many of these patients may initially be asymptomatic, but others may have vague constitutional symptoms, including chronic fatigue, fever, night sweats, diarrhea, pharyngitis, sinusitis, and weight loss. Because our patients were asymptomatic, we could not assess the percentage with persistent generalized lymphadenopathy.

The initial site of presentation of persistent generalized lymphadenopathy is most commonly the head and neck region (12–16). Histopathologic analysis of tissue biopsies is usually nonspecific. Findings include follicular hyperplasia and increased number and size of lymph follicles. None of these findings is specific for HIV. With time, more-specific findings develop that are suggestive of HIV infection, including lymphocyte depletion and follicular involution. Routine lymph node biopsy in HIV-seropositive patients is not recommended because only 3 to 15% of these patient have significant findings (such as tumors or opportunistic infections).

In symptomatic patients with AIDS, a wide range of pathologic findings in the head and neck has been reported, including multifocal head and neck adenopathy, cystic parotid lesions (13), bacterial and fungal infections, and neoplasms (Kaposi sarcoma, lymphoma, squamous cell carcinoma, and other sarcomas) (16). The radiographic findings are quite diverse and nonspecific. In general, the findings in symptomatic patients are more severe than in our study of asymptomatic HIV-seropositive patients.

This study demonstrates that there is a very high incidence of adenopathy of the head and neck region in asymptomatic HIV-positive men. The individual imaging findings of any one lymph node group cannot be considered in isolation as clearly pathologic and indicative of HIV infection because isolated adenopathy of this nature is commonly seen.

Although there were differences between the HIV-positive and control groups on several of the adenopathy measures, the most potentially important data were obtained from combining the data across measures. The presence of two or more of the four criteria described in this report was found in 42% of the HIV-positive subjects and 0% of the control subjects. Although sensitivity is less than might be desired for an ideal clinical marker, the exceptionally low false-positive rate (specificity) is encouraging. These data also demonstrate that the observed adenopathy may be a reflection of alterations in immune status.

The CD4 lymphocyte count is currently recognized as the most useful surrogate marker for monitoring the progression of HIV infections in the early stages of disease. HIV seroconversion has been shown to be accompanied by a wave of CD4 destruction, followed by a rather slow prolonged decline in CD4 numbers (over a period often lasting several years). In this study, MR adenopathy measures were significantly related

to lower CD4 cell counts, which suggests that the adenopathy is somehow related to immune suppression. The importance of these data is further emphasized because the HIV-positive subjects in the study were at a relatively early stage of immune decline.

There have been anecdotal observations of MR-detected lymphadenopathy in HIV infection, but this study represents an early attempt to quantify these observations. These data raise the possibility that observation and quantification of head and neck lymphadenopathy may be able to generate clinical indicators that raise the index of suspicion of HIV infection. It is clear that MR is not proposed as a primary screening examination for HIV infection, but it is possible that routine measurement of head and neck lymphadenopathy in patients undergoing MR of the head and neck might identify patients for whom HIV testing could be indicated. On the basis of these data, patients with two or more of the abnormalities defined in this report could have occult HIV infection. In patients who present with unclear diagnosis, these MR findings may result in improved identification of HIV-infected patients. The public health importance of this is obvious. It is unknown whether these data are also applicable to women and children, information that will be important to determine because of the changing demographics of the HIV epidemic.

References

1. Kirshenbaum KJ, Nadimpalli SR, Friedman M, Kirshenbaum GL, Cavallino RP. Benign lymphoepithelial parotid tumors in AIDS patients: CT and MR findings in nine cases. *AJNR: Am J Neuroradiol* 1991;12:271–274
2. Olsen WL, Jeffrey RB, Sooy CD, Lynch MA, Dillon WP. Lesions of the head and neck in patients with AIDS: CT and MRI findings. *AJNR: Am J Neuroradiol* 1988;9:693–698
3. Davidson BJ, Morris MS, Kornblut AD, Macher AM. Lymphadenopathy in HIV-seropositive patients. *Ear Nose Throat J* 1990;69:478–485
4. Holliday RA, Cohen WA, Schinella RA, Rothstein SG, Persky MS, Jacobs JM, Som PM. Benign lymphoepithelial parotid cysts and hyperplastic cervical adenopathy in AIDS-risk patients: a new CT appearance. *Radiology* 1988;168:439–441
5. Cohen WA, Maravilla KR, Gerlach R, et al. Prospective Cerebral MR study of HIV seropositive and seronegative men: correlation of MR findings with neurologic neuropsychologic, and cerebrospinal fluid analysis. *AJNR: Am J Neuroradiol* 1992;13:1231–1240
6. Bird A. Monitoring of lymphocyte sub-population changes in the assessment of HIV infection. *Genitourinary Med* 1990;66:133–137
7. Philips A, Lee CA, Elford J, et al. Prediction to progression to AIDS by analysis of CD4 lymphocyte counts in a hemophiliac cohort. *AIDS* 1989;3:737–741
8. Taylor JM, Fahey JL, Detels R, et al. CD4 percentage CD4 number and CD4:CD8 ratio in HIV infection: which to choose and how to use. *AIDS* 1989;2:114–124
9. Marcusen DC, Sooy CD. Otolaryngologic and head and neck manifestations of acquired immunodeficiency syndromes (AIDS). *Laryngoscope* 1985;94:401–405
10. Osmond D, Chaison R, Moss A, et al. Lymphadenopathy in asymptomatic patients seropositive for HIV. *N Engl J Med* 1987;317:246
11. Abrams DI, Lewis BJ, Becksteak JH, et al. Persistent diffuse lymphadenopathy in homosexual men: endpoint or prodome. *Ann Intern Med* 1984;100:801–808
12. Federle MP. A radiologist looks at AIDS: imaging evaluation based on symptom complexes. *Radiology* 1988;166:533–562
13. Iaochim HL, Ryan JR, Blaugrund SM. AIDS-associated lymphadenopathies and lymphomas with primary salivary gland presentation. *Lab Invest* 1987;56:33A
14. Ryan JR, Iaochim HL, Marmer J, Loubeau JM. Acquired immune deficiency syndrome related lymphadenopathies presenting in the salivary gland lymph nodes. *Arch Otolaryngol* 1985;111:554–556
15. Morris MR, Moore DW, Shearer GL. Bilateral multiple benign lymphoepithial cyst of the parotid gland. *Otolaryngol Head Neck Surg* 1987;97:87–90
16. Rosenberg RA, Schneider KL, Cohen NL. Head and neck presentation of acquired immunodeficiency syndromes. *Otolaryngol Head Neck Surg* 1985;93:700–705