SHORT REPORT

Correlation of MRI and neuropathology in AIDS

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Abstract

***Objective*—To assess the correlation between findings on radiological and neuropathological examinations of the brain.**

***Methods*—The formalin fixed brains of 19 patients who had died of AIDS were examined by MRI and neuropathology.**

***Results*—The rate of identification of cerebral atrophy was similar radiologically and neuropathologically. However, only in half of these cases were the two examinations concordant in the diagnosis. Furthermore, in the 15 brains which had radiological diffuse white matter lesions, the underlying pathology was heterogeneous.**

***Conclusion*—The possible reasons for the inconsistencies, and their relevance to the interpretation of imaging studies, are discussed. The study suggests that the qualitative identification of atrophy in the postmortem brain is problematical and that diffuse white matter lesions seen on MRI are not indicative of a specific pathological process.**

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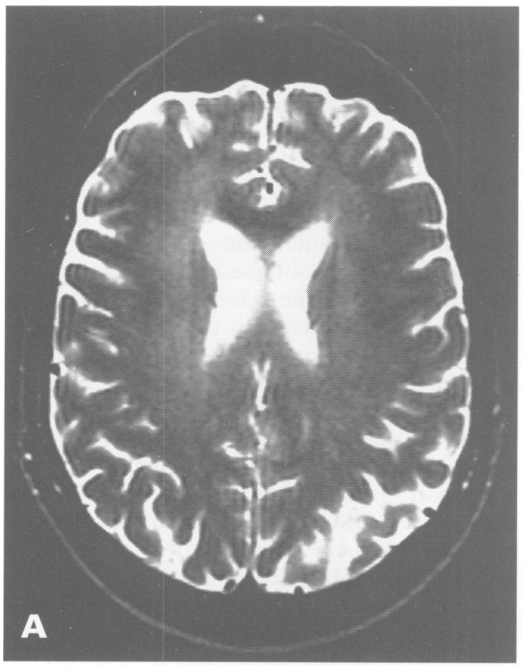
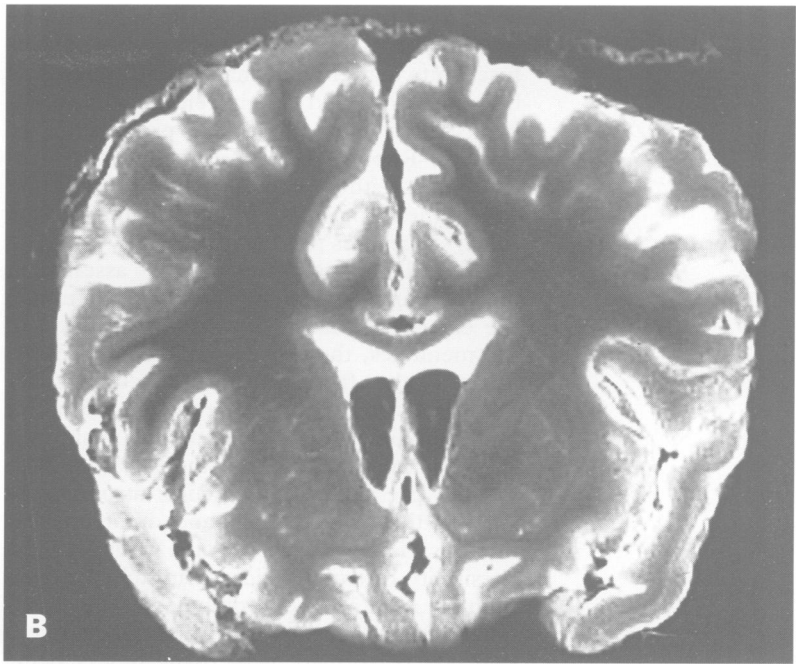
In AIDS the brain can be affected by secondary opportunistic infections and neoplasms, as well as primary disorders due to human immunodeficiency virus (HIV). The primary disorders include HIV encephalitis, leukoencephalopathy, and diffuse poliodystrophy.[1] Histologically, in HIV encephalitis, there are multiple collections of macrophages, microglia, and multinucleated giant cells, which are especially prominent in the cerebral white matter and subcortical grey structures. In HIV leukoencephalopathy these are accompanied by diffuse myelin damage. Abnormalities on CT have been found in about 60% of patients with AIDS.[2] On MRI only 35% of asymptomatic HIV infected patients were found to have normal scans,[3] and 97% had mild or moderate cerebral atrophy, regardless of the stage of the disease.[4] Moreover, up to 20% also had white matter hyperintensities.[3-5] Pathologically verified HIV encephalitis is accompanied, on CT or MRI, by cortical atrophy in 90% and white matter abnormalities in 50% of cases.[6] Yet as a sole investigation MRI is insensitive to histological changes including the presence of multinucleated giant cells and microglial nodules.[7]

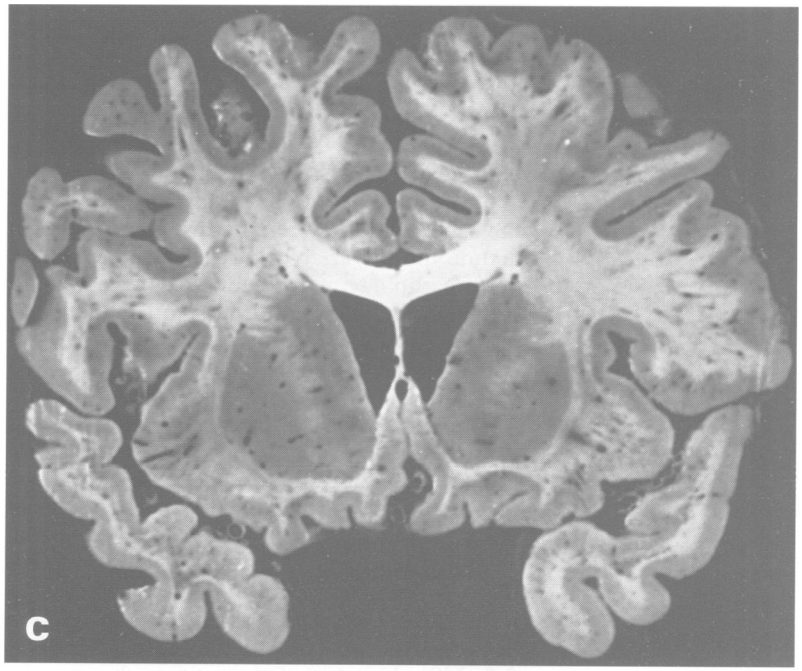
Currently, there seems to be a discrepancy with atrophy being more commonly reported on neuroimaging, leading to the suggestion that the current neuropathological examination may not be a sensitive technique.[8] The difference may be due to several factors, including, firstly, the interval between imaging and necropsy examination; secondly, the effects of formalin fixation; and thirdly, the qualitative manner in which both assessments arrive at the diagnosis of atrophy. However, the reliability of the qualitative diagnosis of atrophy at necropsy has been reported to be strongly concordant with the planimetric measurements of the brain, thus validating the established method of neuropathological diagnosis.[9] The aim of the current study was to compare the rates of atrophy, as identified by MRI and neuropathological examination, and to assess the underlying pathology of diffuse white matter abnormalities.

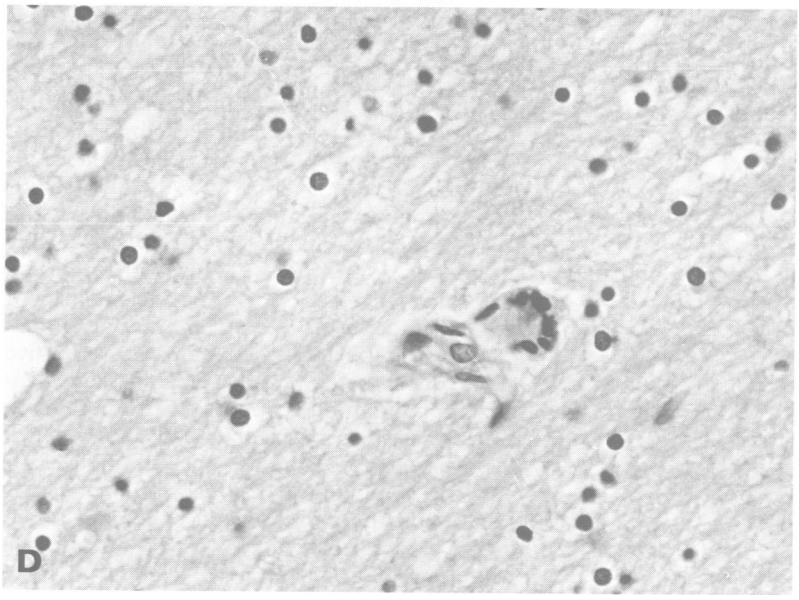
Materials and methods

The brains of 19 consecutive patients who had died of AIDS were fixed in 10% formalin for one month and then assessed. Seventeen were men. The mean age was 44 (SD 11), range 26 to 67 years. Brain MRI was performed in a whole body imager operating at 1·5 T (Siemens 63SP, Erlangen, Germany). Each brain was placed within a standard circularly polarised head coil for radiofrequency transmission and reception with their convexities face down and a marking cannula inserted into the surface of the temporal lobe in the same plane as the mamillary bodies. A spin echo sequence (TR = 1200 ms; TE = 20 ms; ave = 4, FOV = 15 cm; matrix = 512 × 512) produced contiguous 5 mm coronal proton density images. A dual spin echo sequence (TR = 3500 ms; TE = 20,90 ms; ave = 1, FOV = 18 cm; matrix = 256 × 256) produced contiguous 5 mm T2 and proton density weighted transverse images. Two radiologists jointly assessed these scans, blind to the clinical and neuropathological details









Example of the variability of the findings between different examinations from one of the study cases. (A) MRI T2 image in the transverse plane obtained during life which shows bilateral diffuse white matter hyperintensities. (B) MRI image obtained from the postmortem brain of the same patient in the coronal plane of the frontal lobe which has little or no evidence of diffuse white matter hyperintensities. This difference may be the result of variation over time or formalin fixation. (C) Coronal slice at the same level obtained during macroscopic neuropathological examination. The frontal lobe white matter is unremarkable apart from prominent vascular markings. (D) Microscopical examination of the same region of the frontal white matter showed florid HIV encephalitis and leukoencephalopathy, with multinucleated giant cells as demonstrated here; p24 immunopositive cells and myelin pallor were also present.

apart from the patient's age. The findings were organised as to the presence or absence of diffuse white matter abnormalities, atrophy, focal brain lesions, and when relevant, miscellaneous findings, such as the prominence of Virchow-Robin spaces. Atrophy was defined as being either central, with ventricular enlargement, or sulcal, when widening of the sulcal spaces was prominent.

Clinical neuropathological assessment included firstly, weighing the brain, examining the external surfaces and noting the state of the meninges, the presence of sulcal atrophy, and any other findings; secondly, coronal slicing of the brain, initially through the plane of the mammillary bodies and the positioned cannula, then every 5 mm thereafter, recording the presence of ventricular atrophy, the state of the white matter, and other relevant findings. The marking cannula optimised the possibility of similar slices being obtained on both the MRI and neuropathological examinations. Finally, diagnostic histological examination was performed, with tissue blocks being obtained exhaustively from all regions of the brain. Histological staining included haematoxylin and eosin and Luxol fast blue with Nissl, together with immunocytochemistry when diagnostic confirmation was necessary, using antibodies against HIV structural proteins gp41 or p24, cytomegalovirus (CMV), and toxoplasma gondii. Statistical analysis of the correlation between the two assessments of dichotomous variables, from both MRI and neuropathology, was performed by calculation of the φ coefficient and its significance by χ^2 test.

Results

Atrophy was reported in 10 cases on MRI and eight at neuropathological examination. However, in only five of these were the two investigations concordant for the presence of atrophy, and three were noted as being atrophic neuropathologically but not on MRI. Thus although the rates of detection were similar, there was no significant correlation between the two assessments ($\varphi = 0{\cdot}17$, $\chi^2 = 0{\cdot}5$, NS). In most of these cases the atrophy was central, with only two cases per assessment noting accompanying sulcal atrophy. These were not concordant between the two examinations. There was no significant difference in the mean formalin fixed brain weight of those without atrophy (1342 (SD 108) g), and those with atrophy (1310 (SD 93) g). Fifteen brains were noted to have diffuse white matter lesions, of which four were in the absence of atrophy. Neuropathologically, there were five cases of multinucleated giant cell encephalitis, two of which were accompanied by HIV leukoencephalopathy, and five cases of microglial nodular encephalitis, without demonstrable opportunistic infection. There was no significant correlation between these findings and the presence of either atrophy or radiological diffuse white matter lesions. Furthermore, myelin pallor was noted in three cases, of which two also had diffuse white matter lesions on MRI.

The figure gives an example of the variable findings between the different examinations. The case was chosen for illustration as, uniquely, MRI obtained during life was available and this showed diffuse white matter hyperintensities, especially throughout the frontoparietal region. On the postmortem coronal MRI of the frontal area these changes were not noticeable, and on an equivalent coronal brain slice obtained at neuropathological examinations the white matter appeared unremarkable, apart from prominent vascular markings. However, microscopical examination disclosed pronounced HIV encephalitis and leukoencephalopathy as characterised by multinucleated giant cells, immunopositive cellular staining for p24, and myelin pallor.

Opportunistic infections were identified in three cases and these also had focal MRI lesions. Two were radiologically diagnosed as progressive multifocal leukoencephalopathy, but only one was confirmed neuropathologically, the other was identified as pontine CMV encephalitis. In the third case, which affected the brainstem, the radiological diagnosis of CMV was found to be *Toxoplasma gondii* encephalitis. Furthermore, the MRI in two further cases had noticeable focal lesions but no identifiable focal pathology on neuropathological examination. There were other inconsistencies between the two subjective examinations. These included five cases with prominent Virchow-Robin spaces on MRI but no identifiable neuropathological lesions. One case had small well defined areas of high signal in the left internal capsule, thalamus, and cerebellum whereas neuropathologically there was only moderate gliosis, diffuse moderate myelin pallor, and a mild degree of vessel mineralisation in the globus pallidus, but no consistent focal abnormality to explain the noted lesions. Furthermore, whereas on macroscopic neuropathological assessment the leptomeninges of six brains appeared somewhat thickened or opaque, on microscopical examination apart from some lymphocytic infiltration no other changes were found to explain this appearance. Finally, in another case the frontal lobe white matter was noted to appear abnormal but microscopically there was diffuse HIV encephalitis but no other abnormality which would explain this apparent alteration in the appearance of the white matter.

Discussion

This study has investigated MRI and neuropathological findings in 19 brains fixed in formalin at necropsy from patients who died of AIDS, with the aim of identifying atrophy and the underlying pathology of diffuse white matter lesions. Discrepancies due to the interval between examinations and differences between the living and postmortem brain were excluded by limiting the study to necropsy material. T2 and proton density images were examined in this study because, unlike T1 values, they are little affected by formalin.[10 11] T2 images are also more sensitive to white matter lesions, especially those resulting from the

introduction of water, areas of myelin loss, infarction, or demyelinating disease.[11]

The rates for the identification of atrophy were comparable for both the MRI and neuropathological examinations—53% and 42% respectively. These rates were similar to those reported by Gelman and Guinto,[9] but higher than the 30% noted by Jarvik *et al.*[12] None the less, in this study the finding of atrophy was not concordant between the two investigations. Thus either the criteria for atrophy were inappropriately applied in the present investigation, or published estimates of atrophy on MRI or neuropathology studies cannot be assumed to relate to the same cases. With regard to our methodology, both the radiologists and the neuropathologists independently examined the cases for atrophy as defined by clinical experience and with reference to age. Apart from ventricles appearing larger with rounded angles, and prominent gaps appearing between sulci, no further criteria were specified, as this would have introduced quantitative standards. Qualitative diagnosis on imaging and brain slices has previously been demonstrated to have a high concordance,[9] and on MRI has also been validated against a quantification of brain volume.[13] It is likely that formalin fixation results in such alterations in the shape and size of the sulci and ventricles that the criteria for diagnosis of atrophy used for in vivo studies are inappropriate.

Previous investigations have confirmed that MRI of formalin fixed brains is a useful component of the neuropathological assessment, especially as it can provide a three dimensional perspective of lesions lost during brain slicing and tissue sampling.[11 14] However, its application in confirming the microscopical pathology is still unclear. Recently, a quantitative MRI study failed to show any association between brain MRI and cortical volumes and the presence of gliosis.[15] This study confirms prior reports that MRI is insensitive to microscopical pathology,[7 16] as the underlying pathology of the radiological diffuse white matter lesions was heterogeneous. Furthermore, radiological diagnosis of focal lesions was either not always accompanied by discernible opportunistic or focal pathology, or the radiological diagnostic labels were not confirmed pathologically. Importantly, there were other inconsistencies in findings between the two examinations; these related to explaining isolated findings. Whereas individual variation between brains may possibly explain these differences, the formalin fixation in these brains may have also contributed to alter the typical appearance and exacerbate inconsistencies. Finally, the relevance of the presence of cerebral atrophy or diffuse white matter lesions to neurological or psychiatric disorders remains uncertain. There are differing views as to whether they are associated with the development of dementia.[17] Better clinical correlation with imaging changes may help elucidate the recognition and relevance of atrophy and white matter changes as they do appear reliably predictive of histological damage.

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