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Clinical Study

Failure of radiation therapy for brain involvement in Erdheim Chester disease

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Summary

A patient with suprasellar and brain stem involvement in Erdheim Chester disease (ECD) underwent magnetic resonance (MR) imaging and proton MR spectroscopy (^{1}H MRS) of the ventral pons before and 1, 4 and 18 months after external whole-brain (24 Gy) radiotherapy. By revealing a decrease of the *N*-acetyl-aspartate/choline ratio in the pons, ^{1}H MR spectroscopy anticipated lesions growth on MR imaging. In line with the results in four patients reported in the literature, our observation indicates that external radiation therapy is not effective for intracranial involvement in ECD.

Introduction

Erdheim Chester disease (ECD) is a systemic form of histiocytosis [1]. Central nervous system (CNS) involvement in ECD is uncommon and its treatment is controversial [2–5]. We report a patient with brain involvement in ECD who underwent magnetic resonance (MR) imaging and proton MR spectroscopy (^{1}H MRS) before and after external radiation therapy and reviewed the literature.

Case report

A 52-year-old man was admitted to hospital for progressive gait unsteadiness. History included polydipsya, polyuria and mood depression since 20 years. The neurological examination showed cerebellar ataxia and defective smooth pursuit eye movements. Blood and CSF laboratory analysis were normal. Cranial MR imaging showed mild thickening and signal change and contrast enhancement of the infundibulum. Further small areas of signal change and contrast enhancement were present in the pons, right middle cerebellar peduncle and right peridentate regions (Figure 1A).

^{1}H MRS was performed on a 1.5 T system using point resolved spectroscopy sequence (PRESS) with repetition time of 2000 msec and echo time of 272 and 136 msec. Water suppression was obtained with a selective excitation pulse. A volume of interest of $20 \times 20 \times 20\,mm^3$ was placed in the pons in order to include the widest area of signal change. Post-processing included zerofilling (2048 points), exponential broadening (−3 Hz), Gaussian filter (4 Hz), and Fourier transformation and phase correction. The ratios of the areas corresponding to the resonance peaks at 2.02, 3.0 and 3.2 ppm assigned respectively to *N*-acetyl-aspartate (NAA), creatine/phosphocreatine (Cr) and choline (Cho) were computed and compared with those obtained in 10 healthy volunteers using the same sequence, voxel size, localisation and post-processing. The patient's initial spectrum (Figure 1B) revealed low NAA/Cr (2.65) and NAA/Cho (0.93) ratios and normal Cho/Cr ratio (2.75) as compared to control values (NAA/Cr = 4.16 ± 0.53; NAA/Cho = 1.61 ± 0.29; Cho/Cr = 2.64 ± 0.25) (Figure 1C and D). No abnormal peaks at 1.2–1.3 ppm consistent with lactate or lipids were observed. Skeletal scintigraphy with ^{99}Tc diphosphonate showed increased uptake in the distal parts of the femurs which corresponded to sclerotic areas on X-ray films. Bone biopsy from the left distal femur revealed spindle shaped cells, multinucleated giant cells and spumous histiocytes. Immunohistochemical study of the foam cells allowed the diagnosis of ECD.

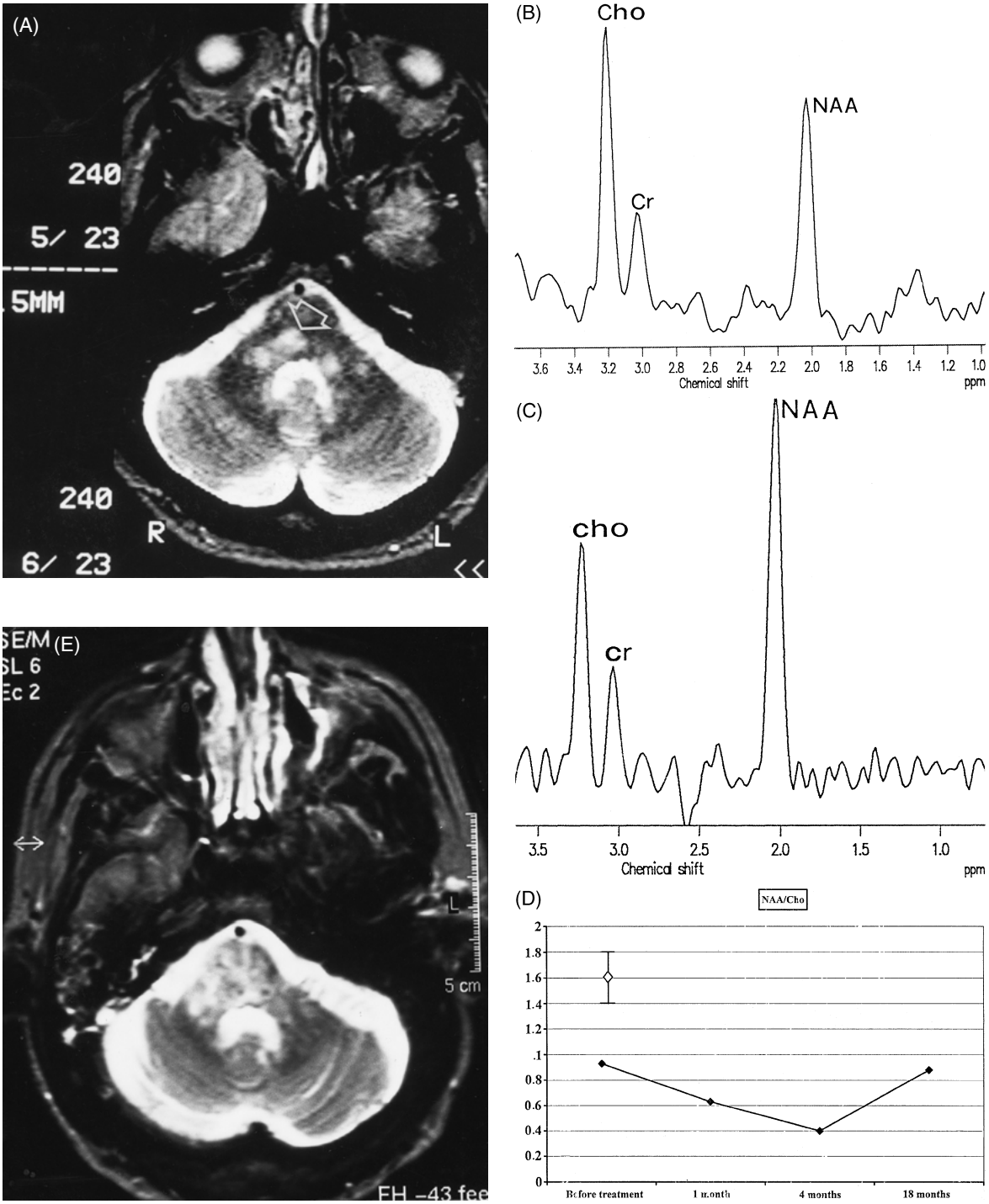

Figure 1. (A) Axial T2 weighted (TR 2500 msec, TE 100 msec) spin echo image at presentation demonstrates multiple partially confluent focal areas of high signal intensity in the pons (arrow). (B) Pre-treatment ^{1}H MR of the ventral pons in the patient with PRESS (TR 2000 msec TE 272 msec) demonstrates low NAA and high Cho as compared to the pontine spectrum in a healthy volunteer (C). (D) Serial changes of the NAA/Cho ratio in the pontine spectrum obtained before and 1, 4 and 18 months after completion of whole-brain external (24 Gy) therapy. The mean and one standard deviation of the pontine NAA/Cho ratio in 10 healthy volunteers is indicated by the empty rhomb and the error bar. (E) Axial T2 weighted (TR 2500 msec, TE 100 msec) spin echo image 18 months after completion of radiation therapy shows extension of the areas of signal change in the brain stem.

The patient was initially treated with corticosteroids which were interrupted after few days because of severe hyperglycaemia. He then received whole-brain fractionated external radiation therapy with a total dose of 24 Gy in 12 fractions over two-and-half weeks. MR imaging findings one month after completion of radiation therapy were unchanged. ^{1}H MRS of the pons with TE of 272 msec showed decrease of NAA/Cr (1.82) and NAA/Cho (0.63) (Figure 1D) without change of Cho/Cr (2.8) ratios as compared to the first ^{1}H MRS. Three months later MR imaging findings were unchanged, but ^{1}H MRS of the pons showed further reduction of NAA/Cho (0.41) ratio, a remarkable increase of Cho/Cr (5.4) ratio and a ratio of NAA/Cr of 2.23. Eighteen months after completion of radiation therapy the neurological examination showed worsening of cerebellar ataxia and MR imaging revealed growth of the infundibular lesion which obstructed the third ventricle and extension of the areas of signal changes in the brain stem (Figure 1E). ^{1}H MRS of the pons showed decrease of the NAA/Cr (1.74) and Cho/Cr (1.94) ratios and relative increase of the NAA/Cho (0.88) ratio as compared to the 4 months control (Figure 1D) without lactate or lipids.

Discussion

ECD is a systemic non-Langerhans form of histiocytosis with distinctive immunohistochemical and radiological features [1]. In fact, the lesions of ECD are composed of foamy histiocytes which show positive reaction to CD 68 macrophage associated antigens and lack S-100 protein and intracytoplasmatic Birbeck granules, both specifically seen in Langerhans cell histiocytosis. In ECD, X-ray films often reveal symmetrical osteosclerosis in the diaphyseal and metaphyseal regions of long bones (mainly the femur, tibia and fibula) with sparing of epiphyseal region, whereas skeletal lesions in Langerhans cell histiocytosis are osteolytic and rarely located in the long bones. The clinical manifestations of ECD vary from asymptomatic or paucisymptomatic isolated bone lesions to a severe multisystem disease. Extraskeletal involvement includes orbits, retroperitoneum, kidneys, adrenal glands, liver, spleen, lungs pleura and heart. In two review articles [1,4], CNS involvement was observed in 20–38% of patients with ECD, central diabetes insipidus, cerebellar ataxia and motor deficits being the most frequent neurological symptoms and signs. MR imaging usually shows extra-axial masses in the leptomeningeal and epidural cranial and spinal spaces and intra-axial areas of abnormal signal in the hypophysio-hypothalamic region, deep lobar white matter, brain stem and cerebellum [3–9]. The lesions usually show intense enhancement after contrast administration, which is typically persistent for several weeks in the epidural lesions [6]. However some lesions do not enhance after contrast administration [3] or show a transient enhancement [8].

MR imaging features in our patient are in line with previous reports. Our is the first report of a ^{1}H MRS study of brain involvement in ECD. The initial pontine spectrum in our patient was characterised by reduction of NAA/Cr and NAA/Cho with normal Cho/Cr. The decrease of NAA, a putative neuronal marker, is presumably due to relative neuronal rarefaction in areas of neoplastic infiltration. As such, it is a non-specific finding which is observed in a variety of neoplastic and non-neoplastic brain lesions. More interestingly, the level of Cho containing compounds (acetylcholine, glycerophosphocholine and phosphocholine), as it can be inferred by the Cho/Cr ratio, was initially normal. Increased Cho, probably related to an increased membrane turnover and cell proliferation, is frequently observed in gliomas, in which it seems to correlate with histological higher grades of malignancy [10], and increased Cho/Cr was also reported in a patient with nodular non-Hodgkin lymphoma of the CNS [11]. Moreover the latter was characterised by increased amount of lipids which were not observed in our case. Further observations are obviously needed in order to confirm the spectral pattern we observed before treatment and to verify if it can be useful for the differentiation of intra-axial CNS involvement of ECD from gliomas and CNS lymphoma which can show similar MR imaging features.

Patients with ECD and intracranial CNS involvement have a poor prognosis. In fact death occurred in 13 of 21 patients in whom clinical follow-up was available [1–9], often within few months of discovery of CNS involvement [1,2,9]. There is no consensus on the optimal treatment of CNS involvement in ECD. Intravenous corticosteroids yield transient improvement of symptoms [4] without any documented case of lesion regression on radiological evaluation. Chemotherapy and immunosuppression are employed for systemic involvement [1]. Surgery is sometimes useful for diagnosis and debulking before other therapies [9]. Since ECD is histologically similar to LCH, which in the majority of cases is a radiosensitive tumor [12], radiation therapy has been proposed for brain involvement of ECD [9]. External radiation therapy

was attempted in five cases of intracranial localisation with doses of 16–18 Gy [3–5,7,8] and one case of spinal epidural involvement [9]. Short-term stabilisation of intracranial disease was achieved in two patients [3,9] whereas clinical or radiological progression occurred in other two [8,9]. Only in a patient with brain involvement [5] and in the one with spinal epidural involvement [9], lesion regression was observed after radiation therapy. In our patient, as it can be judged by the clinical and MR imaging follow-up, radiation therapy yielded a transient stabilisation of the lesions. However it has been observed [7] that growth of lesions in ECD could exhibit long periods of spontaneous stabilisation corresponding to asymptomatic or paucisymptomatic phases.

^{1}H MRS allows an *in vivo* non-invasive biochemical evaluation of brain diseases and is increasingly used to characterise brain tumours and assess their response to radiation or chemotherapy [10,11,13].

We employed ^{1}H MRS to monitor response to radiation therapy. In our case decrease of NAA/Cho anticipated lesion growth. Increase in Cho containing compounds correlates with malignant degeneration of cerebral gliomas [10] and poor response of glioblastoma to radiation therapy [13], whereas decrease of Cho containing compounds suggests transformation of glial tumours in necrotic tissue [13] and was correlated with lesion regression in a case of CNS lymphoma [11]. Our observation extends the above findings and supports the advantages of ^{1}H MRS over MR imaging to monitor response to radiation therapy. However the possible contribute of the effects of radiation therapy on the normal brain parenchyma intermixed with the tumour in the 8 ml voxel we employed has to be considered. In particular, since external brain radiation therapy determines a transient decrease of NAA and increase of Cho in normal brain regions which are maximal 4 months after therapy [14], we submit that the drop of the NAA/Cho and increase of Cho/Cr observed 4 months after completion of radiation therapy in our patient could partially reflect such effects.

In conclusion, our observation and review of the literature indicate that external whole-brain radiation therapy is not effective for the treatment of brain involvement in ECD and claim for new therapeutic strategies for this severe and often fatal disease.

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