The Paraneoplastic Limbic Encephalitis: MRI Characterization of a Deceiving Neurological Disorder

ALAA M. ELORABY, M.D.
The Department of Radiology, National Cancer Institute, Cairo University, Egypt.

ABSTRACT

Objective: Establishing diagnostic MRI criteria for such a pathological entity to enable the oncologist to modify the treatment plan combating the neurological deficits from a different diagnostic prospective, hence improving the quality of life of cancer patients.

Material and Methods: Sixty patients from the National Cancer Institute (Cairo University) diagnosed with different types of cancer at time interval of one year were included in the study pool. Twenty patients were known to have lung cancer, 15 patients with breast cancer, 10 patients with lymphoma and 15 patients with leukemia. No age or sex predilection. All patients performed cranial MRI before and after intravenous contrast media injection, backed by the clinical assumption of encephalopathy and wide spectrum of neurological symptoms as seizures, dementia and behavioral disorders. Some of the patients with positive MRI studies performed serological test to detect onconeuronal antibodies. The study was carried out from January till December 2007.

Results: Thirty three patients' revealed definite MRI signal abnormality involving the limbic system proper and further temporal lobes affection while five patients revealed mixed pattern of regional encephalitic changes including the cerebellum, frontal lobes and brain stem. The rest of the study group exhibited no signs of encephalitis.

Conclusion: Specific MRI appearance could be traced in paraneoplastic limbic encephalitis thus establishing diagnostic pattern for such entity that could help characterizing the disease with subsequent impact upon the treatment protocol resulting in regaining normal brain faculties and better life quality for such cancer patients.

Key Words: Paraneoplastic – Limbic encephalitis – MRI.

INTRODUCTION

The identification of antibodies against neuronal proteins in the serum and cerebrospinal fluid of patients with both cancer and a specific neurologic disorder (paraneoplastic syndrome) has uncovered the existence of antigens, (onconeuronal antigens) shared by some tumors and the nervous system [1].

Paraneoplastic syndromes usually precede detection of the tumor, may affect any part of the nervous system, and are often more debilitating than the cancer itself [2].

The detection of antibodies against onconeuronal antigens points to the diagnosis of a paraneoplastic syndrome and focuses the search for an underlying tumor to a few organs [3].

Paraneoplastic limbic encephalitis is a syndrome consisting of irritability, depression, seizures, severe memory deficit, and dementia [4].

The symptoms are due to dysfunction of the limbic system (hippocampus, amygdala, hypothalamus, insular and cingulated cortex), which is the area of the nervous system where most of the pathological changes that characterize the syndrome occur. Brain-stem encephalitis and abnormalities in other areas of the nervous system are frequent, but they may be clinically silent [5-6].

Paraneoplastic limbic encephalitis is probably under diagnosed, because of the diversity of its symptoms and the lack of specific diagnostic markers. In patients known to have cancer, symptoms of this paraneoplastic syndrome may be attributed to metastases to the brain, toxic or metabolic encephalopathies, infections, or toxic effects of cancer therapy [2].

In approximately 60% of patients with paraneoplastic limbic or brain-stem encephalitis,
the syndrome precedes the detection of the tumor, further complicating the diagnosis of the neurologic disorder [6-7].

MR imaging can aid in establishing the diagnosis of paraneoplastic limbic encephalitis, especially in those cases in which no characterized antineuronal antibody can be detected in serum or CSF. T2 weighted imaging and fluid-attenuated inversion recovery imaging techniques are useful in revealing the encephalomyelitis of the mesial temporal lobes and other areas of the brain. These imaging techniques should be used whenever hippocampal pathologic abnormality is likely [8].

The aim of this study was to solidify the utility of MRI in the diagnosis of paraneoplastic limbic encephalitis by establishing specific imaging criteria that could be linked to the clinical status, and backed by the detection of antineuronal antibodies in the patients’ sera; a solid diagnostic possibility could be postulated.

MATERIAL AND METHODS

The study population consisted of 60 patients receiving treatment in the National Cancer Institute of Cairo University for Different Types of cancer.

Twenty patients had lung cancer of small and non small cell type. Fifteen patients had breast cancer, all were females. Ten patients had lymphoma and fifteen patients had leukemia.

No sex or age group predilection. The age of the study group ranged from 25 years to 65 years old.

All the patients were diagnosed as cancer patients since one year back and all were under current standard treatment protocols including systemic chemotherapy and radiotherapy excluding all patients with history of cranial irradiation.

The study group fulfilled clinical criteria that could indicate the presence of encephalopathy standardized as signs of memory and psychiatric disorders, seizures and focal cerebellar as well as hypothalamic and brain stem symptoms.

Full laboratory profiling of the patients was attained with special emphasis on tests that could help excluding inflammatory process such as cerebro-spinal fluid cytological evaluation.

Special serological studies using the immunofluorescence technology were performed for a sample of ten patients with different kinds of cancer targeting the antineuronal antibodies namely, (anti-Hu, anti-Ta and anti-Ma), which are considered as fingerprints of paraneoplastic auto-immune reaction involving the central nervous system.

All our patients performed cranial MRI studies in the radiology department of the National Cancer Institute of Cairo University using General Electric, Signa, 1.5 Tesla, superconductive magnet.

The study protocol was aiming at obtaining multi-planar images in T1 [pre contrast], T2, FLAIR (fluid attenuation inversion recovery) and post intravenous contrast T1 weighted images. The slice thickness, gap, number of excitations (NEX) and the matrix size were fixed parameter as shown in the Table (1).

The data collected from the MRI images was analyzed regarding the following items:

- Presence of brain parenchymal signal abnormality.
- Proper anatomical localization of the abnormal signal.
- Signal characterization in each pulse sequence.
- Presence of contrast uptake and its magnitude if present.
- Detection of hemorrhage or calcification signal.
- Evaluating the effect upon the anatomical structures near the abnormal signal.

<table>
<thead>
<tr>
<th>Pulse Sequence</th>
<th>TR</th>
<th>TE</th>
<th>IT</th>
<th>NEX</th>
<th>Slice thickness</th>
<th>Slice gap</th>
<th>Matrix Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>480</td>
<td>15</td>
<td>1</td>
<td>1</td>
<td>6.5 mms</td>
<td>1 mm</td>
<td>256X192</td>
</tr>
<tr>
<td>T2</td>
<td>4000</td>
<td>104</td>
<td>1</td>
<td>1</td>
<td>6.5mms</td>
<td>1 mm</td>
<td>256x192</td>
</tr>
<tr>
<td>FLAIR</td>
<td>7152</td>
<td>148</td>
<td>1787</td>
<td>1</td>
<td>6.5mms</td>
<td>1 mm</td>
<td>256x192</td>
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The MRI results and laboratory data; namely the antibodies serological studies, were utilized to prove the link between both and to reach a convincing diagnostic MRI criteria of the paraneoplastic encephalitis.

RESULTS

The inclusion criteria of the work were applied for 60 cancer patients with 20 patients having lung cancer including small cell and non small cell subtypes, 15 patients with breast cancer, all were females, 10 patients with non-Hodgkin lymphoma and 15 patients with leukemia.

The study population exhibited wide spectrum of neurological clinical presentations as mentioned in Table (2).

Table (2): The different clinical presentations of the patients sharing in the study pool taking in consideration that many patients had a combination of symptoms.

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Loss of short term memory</td>
<td>32 patients</td>
</tr>
<tr>
<td>Fits</td>
<td>25 patients</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>7 patients</td>
</tr>
<tr>
<td>Hypothalamic symptoms</td>
<td>8 patients</td>
</tr>
<tr>
<td>Brain stem manifestations</td>
<td>10 patients</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>16 patients</td>
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</tbody>
</table>

Table (3): The different signal criteria of the limbic system lesions detected in the MRI pulse sequences used in this study.

<table>
<thead>
<tr>
<th>MRI pulse sequence</th>
<th>Signal pattern</th>
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<tbody>
<tr>
<td>T1 weighted images</td>
<td>Hypo intense</td>
</tr>
<tr>
<td>T2 weighted images</td>
<td>Hyper intense</td>
</tr>
<tr>
<td>Fluid attenuation inversion recovery [FLAIR] weighted images</td>
<td>Hyper intense</td>
</tr>
<tr>
<td>Post contrast T1 weighted images</td>
<td>No appreciable enhancement</td>
</tr>
</tbody>
</table>

All of the positive MRI cases showed no evidence of parenchymal hemorrhage or calcification. The entire positive group revealed an element of mass effect accompanying the parenchymal signal abnormality ranging from subtle focal swelling to moderate compression of the nearby anatomical structures. No brain herniation syndromes were recorded.

None of the positive MRI patients scored isolated parietal or occipital lobes involvement. Seven patients showed non compressive myelopathic signal manifestations in spinal MRI studies done for other clinical situations within the clinical course of their illness.

Out of the 33 patients with positive MRI studies encountered in this work, 25 patients were known to have malignant lung neoplasm scoring about 75% of the cases, 20 of them were proven small and non small cell lung cancer patients while the rest were under reassessment being initially diagnosed as non-Hodgkin's lymphoma outside the National Cancer Institute (Cairo University). 7 patients were suffering from breast cancer scoring about 20% of the pool, one patient was diagnosed as abdominal B-cell non Hodgkin lymphoma representing about 5% of the positive MRI studies.
Fig. (1): Thirty five years old Female patient with history of non small cell lung cancer under chemotherapy.

A- T1 and T2 weighted images with bilateral hippocampal T1 hypo density which turned to hyper intense T2 pattern being more pronounced on the left side with minimal focal swelling.

B- FLAIR and post contrast T1 weighted images of the same patient showing hyper intense FLAIR signal and no contrast uptake.

Fig. (2): 30-year-old patient with metastatic cancer breast.

T1 and T2 weighted images showing dominant left hippocampal T1 hypo intensity changing to hyper intense T2 pattern with mild mass effect partially trapping the temporal horn of left lateral ventricle.

The FLAIR and Post contrast T1 weighted images of the same patient revealing hyper intense FLAIR signal in the left hippocampus and subtle, suspected right sided hyper intensity with no contrast enhancement.
Fig. (3): 35 years old male patient with history of non small cell lung cancer.

T1 and T2 weighted images with subtle limbic, temporal and frontal T1 hypo intensity changing to T2 hyper intensity with no frank mass effect.

FLAIR and post contrast T1 weighted images of the same patient exhibiting bright FLAIR signal of bilateral temporal, thalamic and frontal configuration. No contrast uptake.

Fig. (4): Thirty eight years old female patient with breast cancer.

FLAIR weighted images revealing abnormal high signal seen involving the hippocampus region on either side as well as the cerebellar dentate nucleus.

FLAIR weighted images for the same patient at a lower cerebellar level with dentate hyper intensity.
DISCUSSION

Patients with paraneoplastic limbic encephalitis present with sub acute cognitive dysfunction, severe memory impairment, seizures, and psychiatric features including depression, anxiety, and hallucinations. Other causes of encephalopathy, metastases, drug neurotoxicity, infectious diseases such as herpes encephalitis, and meningeal carcinomatosis must be excluded. Sometimes, antineuronal antibodies such as anti-Hu or anti-Ma2 are found in the CSF in patients with paraneoplastic limbic encephalitis [9].

In this study, the inclusion criteria of the patients were designed to gather diagnosed cancer patients with different types of cancer under multi-facetted treatment protocols with symptoms suggestive of encephalopathy ranging from memory loss, psychological disorders up to focal neurological deficits of central configuration.

Paraneoplastic limbic encephalitis is frequently associated with bronchial carcinoma and is considered a particular manifestation of paraneoplastic encephalomyelitis, which includes involvement of other areas in the central (pyriform cortex, frontal orbital surface of the temporal lobe, insula, cerebellum, brain stem) and peripheral nervous system [10].

Cancer of the lung, particularly small cell lung cancer, and testicular germ cell tumors are the most frequently found neoplasms associated with paraneoplastic limbic encephalitis, such a pathological entity may be rarely associated with thymoma, adenocarcinoma of the colon, renal cell cancer, esophageal cancer, bladder cancer, breast cancer, small cell carcinoma of the prostate, ovarian carcinoma, neuroblastoma, testicular seminoma, or Hodgkin disease [9].

In accordance with the above mentioned opinion about the frequency of para-neoplastic limbic encephalitis association with lung cancer; twenty patients out of 60 in our work were lung cancer cases scoring 33% of the study pool followed by 15 female patients with breast cancer and 15 patients with leukemia scoring 25% each and 10 patients with non-Hodgkin’s lymphoma scoring 16% of the study pool.

The first step to reach the conclusion was to establish characteristic MRI criteria in the positive cases regarding the anatomical regions of disease predilection and the signal criteria of the pathological process. All our patients scored bilateral limbic system affection within the context of selective temporal lobes involvement. In addition to the temporal lobes lesions 10 patients exhibited other anatomical areas involvement as the cerebellum.

Pathologic changes of the brain are found not only in limbic structures but also in the pyriform cortex, frontal orbital surface of the temporal lobe, and insula [10].

Gultekin et al. [2] mentioned that typical MRI findings of paraneoplastic encephalitis include unilateral or bilateral mesial temporal lobe abnormalities that are best seen on T2-weighted images. On T1 sequences, the temporal-limbic regions may be hypo intense and atrophic, and may sometimes enhance with contrast injection. They also mentioned that 64% of their patients with paraneoplastic encephalopathy had abnormal MRI studies, which in 89% of the cases showed the changes indicated above.

Dirr et al. [11] and Lacomis et al. [12], has mentioned that the abnormalities although well known has not been examined in a large series of patients.

Thuerl et al. [6], mentioned that MR imaging-based diagnosis of paraneoplastic limbic encephalitis requires depiction of signal intensity changes of the temporo-basal region. It is important to observe the initial subtle finding of increased signal intensity of both medial temporal lobes on T2-weighted images, and this was visible only on the fluid-attenuated inversion recovery images.

Conventional T2-weighted turbo spin echo images failed to reveal the abnormalities, the advantage of fluid-attenuated inversion recovery imaging in diagnosing hippocampal disease was shown by Jack et al. [10], who reported significantly higher accuracy of fluid-attenuated inversion recovery imaging in identification of increased signal intensity of the hippocampus in cases of mesial temporal sclerosis as compared with conventional spin echo imaging.
The fluid-attenuated inversion recovery sequence might be more appropriate for identification of increased signal intensity of the hippocampus because of complete suppression of the high signal intensity of the CSF while yielding T2-weighted contrast properties. The use of conventional T2-weighted turbo spin-echo sequences might be a reason for the fairly high rate of negative MR imaging findings in cases of paraneoplastic limbic encephalitis reported by Gultekin et al. [2].

In our work, all the positive MRI cases revealed hypo intense T1 signal and hyper intense T2 and FLAIR pattern of the lesions however the lesions exhibited more intense FLAIR signal compared to the T2 making the detection of the pathological change easier.

None of our case showed contrast uptake which is in agreement with Thuerl et al. [6] mentioning; contrast enhancement is very rare and only single cases are published.

Contrast enhancement of the mesial temporal lobes was observed for a patient with testicular seminoma, a patient with testicular carcinoma and a patient with Hodgkin disease [6].

One point of argument is differentiating the paraneoplastic encephalitis from the herpetic encephalitis which is characterized by selective temporal lobes affection. All our positive cases revealed no contrast uptake in addition to the clinical back up of being cancer patients and the presence of antineural antibodies in the patient’s sera.

In conclusion, paraneoplastic limbic encephalopathy can accompany several types of cancer however lung cancer patients are more prone to such illness; the syndrome expresses itself with characteristic MRI pattern regarding the anatomical distribution and signal abnormality of the lesion with FLAIR pulse sequence superiority. The MRI pattern could be used to solidify the clinical assumption of the disease with better design of the treatment protocol.

REFERENCES