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Case report

Fused ^{18}F-Choline PET/MRI: A potential non-invasive biomarker imaging tool in cerebral vasculitis ☆

Moheieldin Abouzied, MD[a,*], *Riyadh AlSalloum, MD*[a], *Omar AlHarbi, MD*[a], *Mohanned Al Suhaibani, MD*[a], *Ahmad AlMuhaideb, MD*[a], *Abdulaziz Al Sugair, MD*[a], *Mohammed Al Qahtani, PhD*[b]

[a] *Department of Radiology, King Faisal Specialist Hospital & Research Centre, MBC#28, P.O. Box 3354, Riyadh 11211, Saudi Arabia*

[b] *Cyclotron & Radiopharmaceuticals Department, King Faisal Specialist Hospital & Research Centre, MBC#28, P.O. Box 3354, Riyadh 11211, Saudi Arabia*

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ABSTRACT

Primary CNS vasculitis is an inflammatory brain disease commonly misdiagnosed affecting the medium and small vessels of the CNS. Due to its broad and non-specific clinical and radiological manifestations; Its diagnosis remains challenging. New diagnostic tools and biomarkers which increase specificity and facilitate the diagnosis for patients with suspected vasculitis are highly desirable to enable physicians to start therapy that can alter its potential aggressive course like immunosuppressant.

This case report highlights the potential role of ^{18}F-choline PET/MRI as a novel imaging tool that might help in the right clinical scenario in the diagnosis of this disease.

Furthermore, it speculates on its secondary role in monitoring the response to immunosuppressant therapy.

Introduction

Central nervous system vasculitis represents a heterogeneous group of inflammatory diseases affecting the walls of the blood vessels in the brain, spinal cord, and the meninges.

It has been classified as either primary confined to the CNS with no involvement of other systems; called primary angiitis of the CNS or secondary that occurs in the context of a systemic inflammatory or infectious process [1].

The primary form is rare with an annual incidence rate of 2.4 cases per million, it affects patients of all ages, but peaks at around 50 years of age, with males affected more commonly than females [2,3].

Secondary form of CNS vasculitis far exceeds the primary type; it could be part of systemic disease like SLE, or induced

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* Corresponding author.
E-mail address: mohei.abouzied@gmail.com (M. Abouzied).

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by systemic infectious process, malignancy, radiation or drug induced.

Patients present with multiple symptoms of varying duration, severity and progression, headache, and cognitive dysfunction being the commonest followed by focal deficits, seizures, and ataxia [3].

Calabrese and Mallek in 1988 suggested diagnostic criteria for primary central nervous system vasculitis. These included the development of a neurologic deficit unexplained by other processes, plus the presence of either an angiogram with characteristic features of vasculitis, or a central nervous system (CNS) biopsy showing vasculitis [4]

The diagnosis of this disease remains challenging due to its rarity, its diverse clinical and imaging manifestations, and the multiple differential diagnoses (including reversible cerebral vasoconstriction syndrome [5].

Brain biopsy remains the only definite diagnostic confirmation procedure [6].

Nonetheless, brain biopsy is invasive and thus is only performed on a small proportion of patients in which it has a limited sensitivity [7].

Imaging findings for primary angiitis of the CNS are usually non-specific with ischemic infarction being the most common lesions. CT might show areas of hypo attenuation, CTA and MRA might show focal or multifocal segmental small and medium sized blood vessel narrowing. MRI might show areas of infarction, with various stages of healing [8].

T2 and FLAIR might show high-intensity lesions in the white matter, which is completely non-specific findings. Meningeal enhancement and intracranial haemorrhage can also be seen. Normal MRI exclude the diagnosis, but histopathology remains the gold standard [8–10].

Treatment of primary angiitis is mainly based on high dose steroids and cytotoxic drugs.

Case presentation

A 30-year-old male was first diagnosed with Hodgkin lymphoma Stage IIA in 2009 with relapses in the head and mediastinal regions in 2013 and 2017, for which he was treated by chemotherapy and radiation therapy (2009, 2013 and 2017) along with autologous stem cell transplantation (2017).

Since then, he has been in remission until December 2020 when he presented for a follow-up visit and reported B symptoms for the last two months. He was then admitted for further investigation and evaluation with a provisional diagnosis of a relapse. Six days following his admission, a whole body ^{18}FDG PET/CT revealed multiple FDG-avid lymph nodes of the neck with no evidence of FDG-avid lymphadenopathy in the mediastinum or elsewhere in the study. In addition, his blood work-up showed pancytopenia with blast cells in the peripheral blood. Later on, a biopsy result from a lymph node of the neck has proved the relapse.

Two weeks following the admission, he started developing new CNS manifestations such as headache, forgetfulness, facial numbness, nystagmus, dysarthria, dysphagia, ataxia along with an impaired cerebellar examination, for which he was further evaluated by an MRI of the brain revealing

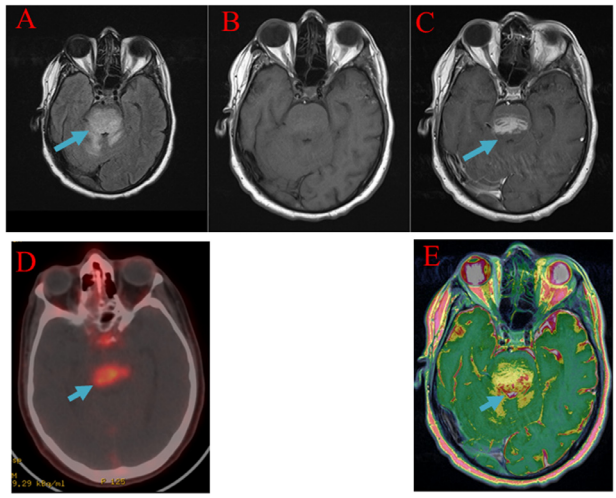

Fig. 1 – Axial images at the level of pons: Flair (A), T1 WI MR pre (B), and post contrast (C), fused ^{18}F Choline PET/CT (D) and fused ^{18}F Choline MR (E) are showing hyperintensity lesion blue arrows in (A) with contrast enhancement and choline activities.

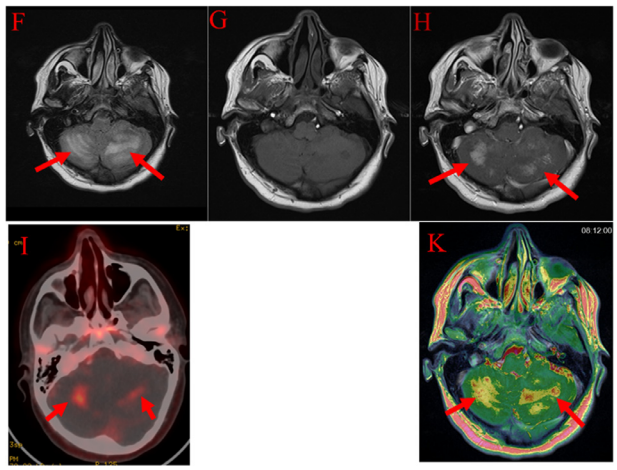

Fig. 2 – Axial images at the level of cerebellum: Flair (F), T1 WI MR pre (G), and post contrast (H), fused ^{18}F Choline PET/CT (I) and fused ^{18}F Choline MR (K) are showing hyperintensity lesion red arrows in (F) with contrast enhancement and choline activities.

abnormal leptomeningeal enhancement involving the posterior fossa structures in addition to T1WMR post contrast hyperdensities involving the midbrain/pons and the cerebellum (Fig. 1 and Fig. 2). Due to an elevated level of lymphocytes in a CSF sample, the primary differential diagnoses were secondary CNS lymphomas, tuberculous meningitis or vasculitis.

Therefore, the patient was then started on anti-tuberculous mediations; however, without subsequent clinical or radiological improvement. A right occipital brain biopsy was then performed showing evidence of small vessel vasculitis likely secondary to Hodgkin's lymphoma; lymphohistiocytic type without evidence of brain lymphoma or

infection. Finally, the patient has been substantially improved clinically and radiologically after being commenced on immunosuppressive therapy for his biopsy-proven vasculitis of the brain: cyclophosphamide and methylprednisolone. F18-Choline brain PET/CT was performed before starting the aforementioned immunosuppressive medications, which revealed abnormal choline activities seen corresponding to the MRI-described abnormal signal intensities at the pons and cerebellum.

He is currently taking Brentuximab for his lymphoma relapse in addition to steroids and cyclophosphamide which has steadily improved his neurological manifestations, but with residual dysarthria, dysphagia and ataxia for which he is following up with the swallow and speech therapy, and the rehabilitation therapy.

Discussion

The hallmark of Cerebral vasculitis is the inflammatory process of blood vessel walls that typically involves small-medium sized arteries and veins particularly those located in leptomeninges and subcortical areas. T-lymphocytes and activated macrophages infiltrates vessels walls and the adventitia with subsequent intimal proliferation and fibrosis leading to vascular occlusion. Such changes are the most frequent and called the granulomatous pattern, unlike some other specimens that disclose the so-called atypical CNS angiitis patterns consisting in predominantly lymphocytic infiltrates (lymphocytic pattern), necrotizing vasculitis with fibrinous necrosis (necrotizing pattern) or mixed patterns [11].

Imaging signs of cerebral vasculitis may be direct (eg, vessel wall thickening and contrast material enhancement) or indirect (eg, cerebral perfusion deficits, ischemic brain lesions, intracerebral or subarachnoid haemorrhage, and vascular stenosis) [12].

Molecular imaging particularly with the hybrid imaging technique that combines positron emission tomography and CT/MRI is playing evolving and growing rules in oncological imaging and some of the inflammatory conditions. The forefront and the most widely used radiotracer for PET imaging is FDG. It reflects intracellular glucose metabolism which is usually increased in malignant tissue, known as Warburg effect [12].

For example; positron emission tomography (PET)/CT helps confirm the presence of large vessel vasculitis when clinical findings and other imaging findings are nonspecific and it can help in monitoring these patients to detect disease activity [13–16].

FDG PET CT evaluation of the brain inflammatory condition might be hampered by the physiological tracer distribution within the cerebral cortex; therefore, its sensitivity might be limited with that regard.

Choline is a precursor of phospholipids, such as sphingomyelin and phosphatidylcholine (lecithin), which is essential for cell membrane synthesis during the cell proliferation process, the event that is augmented in malignant tissues [17]

Furthermore; It is known that choline is also accumulating in inflammatory diseases like sarcoidosis [18]. Wyss et al [19] have shown by autoradiography study in animal models with experimental bacterial infections of soft tissue that flourocholin is avidly accumulated in inflammatory infiltrates in particular granulocyte and macrophages due to upregulation of choline kinase in these cells. An important enzyme needed for the phosphorylation of choline which is in a further step it is metabolized to phosphatidylcholine and incorporated into the cell membrane.

In a step further; Beppu *et al*. [20] reported a marked elevation of Choline in case of central nervous system vasculitis as measured by MRI spectroscopy.

Our patient pathology specimen revealed lymphohistiocyte infiltration involving the superficial parenchyma of the small vessel that well could explain both the enhancement on MRI post contrast administration and the increased choline activity noted in PET/CT scan.

In conclusion; Our patient is the first reported case with biopsy proved cerebral vasculitis with corresponding abnormal choline activity at the site of the biopsy proved pathology matching the enhancement pattern on MRI. Such preliminary findings should encourage a prospective trial to evaluate the role of choline PET/CT imaging in patients with newly diagnosed cerebral vasculitis and during the course of immunosuppressive therapy to monitor the response to therapy.

Patient consent

Authors are confirming that the presented study is under an approved project by the research ethical committee and research advisor board at the institutions. Furthermore, no patient's identification been presented in this manuscript. Yet original consent and permission was signed by the patient for any future need.

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