Case Report

# Fluoro-deoxy glucose positron emission tomography brain as a potent marker for antibody-mediated neurodegeneration in dementia: A case report

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## ABSTRACT

Rapidly progressive dementia (RPD) is a subacute onset progressive disease with cognitive decline which can be associated with vascular, neurodegeneration (prion disease- Creutzfeldt-Jakob disease), inflammatory (immune-mediated or infection), or neoplastic causes. RPD can be fatal with high morbidity and mortality if diagnosis is delayed or misdiagnosed. Our aim is to understand the role and sensitivity of magnetic resonance imaging (MRI) brain versus Fluoro-deoxy glucose positron emission tomography (FDG PET) brain, for the diagnosis of paraneoplastic neurologic syndrome (PNS). We present the case of an 80-year-old female with progressive dementia. MRI brain was suggestive of atrophy in the cerebellum and frontal lobes while FDG PET revealed diffuse hypometabolism in the frontal and temporoparietal region with focal hypermetabolic focus in the left parietal lobe, indicating concomitant neuroinflammation and neurodegeneration. This newer entity named as antibody-mediated neurodegeneration causing dementia can be slowed or reversed to some extent if detected early. However, there is still a lack of consensus on the diagnostic sensitivity of FDG PET Brain in PNS. Our case shows the clinical benefit of FDG PET brain over MRI brain in anti-neuronal antibody-associated dementia to detect neuroinflammatory etiology, a potentially treatable disease.

**Key words:** Autoimmune, Fluoro-deoxy glucose positron emission tomography, Paraneoplastic, Rapidly progressive dementia

The term "rapidly progressive dementia" (RPD) is commonly used to describe a cognitive disorder with fast progression leading to the clinical syndrome of dementia, within a relatively brief time, which is commonly considered to be < either 1 or 2 years. With its varied etiology, clinical manifestations can either be slowly progressive, chronic type (neurodegenerative) or can be an acute-subacute presentation (vascular, infection, metabolic, autoimmune). Precise history, duration of onset of symptoms along with clinical findings can be helpful in the characterization of dementia. RPD due to inflammatory (8–21%) and toxic (1–10%) causes were less common than Alzheimer's disease (16–51%) [1-3].

Diagnostic workup in patients presenting with progressive dementia, therefore, must include routine blood investigations, vasculitis profile, viral markers, cerebrospinal fluid (CSF) analysis (cytology, biochemistry, autoimmune encephalitis (AIE) panel), and neuroimaging which includes magnetic resonance imaging (MRI) brain and fluoro-deoxy glucose positron emission tomography (FDG PET) whole body. This is helpful in differentials of dementia for the reversible and treatable causes. This case report aims to understand the role and sensitivity of MRI brain versus FDG PET brain, for the diagnosis of paraneoplastic neurologic syndrome, associated with neuroinflammation- which is a treatable entity.

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## CASE REPORT

An 88-year-old hypertensive female presented in the emergency department with a sudden fall. She had pre-existing cognitive impairment (memory impairment, reduced word outputs) for over 4 months. She had become dependent for activities of daily living (ADLs) on household help for a month. She lost around 10 kg weight over 3 months. No history of fever, exposure to toxins, abnormal movements, seizure, bladder, or bowel incontinence was reported.

She was hemodynamically (blood pressure, pulse rate, $SpO_2$, temperature) stable. Systemic (respiratory, cardiovascular) examination was unrevealing. Neurologically, the patient was drowsy (Mini-Mental State Examination was not possible due to poor cognition), spontaneously moving all 4 limbs, unable to follow simple commands, poor attention, and meningeal signs were absent. Glasgow Coma scale was E3V2M6.

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Routine blood investigations (hematological and biochemical) were normal. Extensive blood tests (serum antinuclear antibodies, antineutrophil cytoplasmic antibodie, viral markers, thyroid profile, Vitamin B12, Vitamin D, syphilis and Lyme titers, anti-thyroid antibodies, angiotensin-converting enzyme) and CSF analysis (cytology, proteins, 14-3-3, GeneXpert, India ink, cryptococcal), were conducted for infectious, inflammatory, vasculitis and metabolic etiology, which were unremarkable. Tumor markers (carcinoembryonic antigen, cancer antigen [CA] 15–3 CA 15–3, CA 19–9, CA 125) were within the standard range (Table 1). MRI brain was conducted which showed marked bilateral frontal lobe atrophy with mild cerebellar atrophy and few subacute gliotic infarcts sparsely occupying supratentorial and infratentorial regions of the brain in T2/fluid-attenuated inversion recovery sequence (Fig. 1). This could not explain the progressive decline in the cognitive state of the patient and therefore FDG PET whole body was planned which suggested reduced uptake in the cerebrum and a focus on increased uptake in the left parietal lobe in the background of reduced uptake. There was increased uptake in soft tissue nodular lesions in the right breast (Fig. 2). She was started on intravenous-immunoglobulin (IV-IG) (2 g/kg of body weight) for 5 days. Her sensorium gradually became better, she was comprehending and following simple commands.

Anti-neuronal antibodies and AIE panel showed anti-Yo antibody positivity. A sample from ultrasound -guided biopsy for the right breast was sent for histopathology which reported non-invasive ductal carcinoma of the right breast. Human endothelial receptor 2 (HER-2) was positive (immunohistochemistry 2+).

On discharge, she was conscious, comprehending, and interacting with 15–20/min of word output. Her motor and balance deficits persisted and were dependent on ADLs. She was on follow-up with medical oncology for further treatment. She was further followed up in medical oncology for the treatment of carcinoma of the right breast.

**Table 1: Investigations of the patient**

| Investigations | Result |
|---|---|
| Hemogram | Normal |
| Vasculitis panel | Negative |
| Viral markers | Negative |
| CSF (cells, proteins) | Normal |
| CSF (GeneXpert, biofire, culture panel) | Negative |
| Tumor markers (CEA, CA 15–3, CA 19–9, CA 125) | Negative |
| VDRL | Negative |
| Lymes antibodies | Negative |

**CSF: Cerebrospinal fluid, CEA: Carcinoembryonic antigen, VDRL: Venereal disease research laboratory**

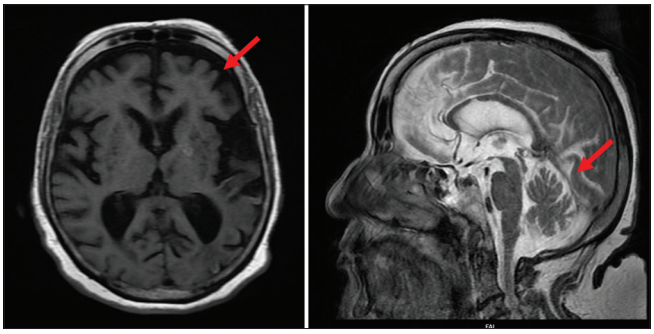

**Figure 1: Magnetic resonance imaging brain is suggestive of diffuse cerebellar atrophy with marked frontal lobe atrophy**

## DISCUSSION

In view of cerebellar atrophy and absence of motor incoordination associated with cerebellar involvement, the closest differential to the presentation was cerebellar cognitive affected syndrome (CCAS). The core features of CCAS consist of executive, spatial, linguistic, and affective changes and this differentiates it from non-specific confusional states or accepted notions of dementia. Arousal, alertness, remote episodic, and semantic memory are preserved [3].

Among the many treatable causes of dementia is immune-mediated dementia which is classically defined as: Subacute onset with a rapidly progressive course, symptoms fluctuation, presence of tremor/myoclonus, coexisting organ-specific autoimmunity, inflammatory CSF, presence of MRI changes suggestive of an inflammatory process, risk factors or recent history of tumor [4].

Antibodies, against cell surface and intracellular proteins, have the potential to induce neurodegeneration with permanent cognitive and brain structural changes by complement activation leading to neuroinflammation and oligodendrocyte dysfunction causing neuronal damage leading to irreversible neurodegeneration. This spectrum consists of dementia, movement disorders, which can mimic Parkinson's disease, progressive supranuclear palsy, cortico-basal syndrome, or multisystem atrophy which are irreversible [5].

The diagnostic criteria of possible AIE include neurological deficits, presence of antibodies, CSF pleocytosis, presence of oligoclonal bands (IG), brain MRI (T2 hyperintensity in one or both medial temporal lobes or multifocal hyperintensities appearing consistent with inflammation/demyelination in the white matter, gray matter, or both), electroencephalogram (EEG). However, as the disease evolves the alterations in these parameters might not be consistent with the clinical findings. This makes the diagnosis and further the management difficult, to pursue immunomodulation apt for AIE. Management has drastically evolved with the advent of novel markers (interleukin-21, neurofilaments, and total tau) and techniques. Sensitivity of neuronal markers being challenged with newer tools and methods (cell-based assays), has made the diagnosis less challenging. The qualitative assessment, in the form of various neuropsychological tests, has always been an asset in a low economic country.

Neuroimaging, particularly, FDG PET is a better and more sensitive modality compared to MRI brain in immune-mediated encephalitis and can also help in treatment strategies and prognosis. There are reports of FDG PET being an early marker as compared to existing and conventional neurological diagnostic tools, such as EEG and MRI. Patterns of metabolism do not vary between seronegative and seropositive patients, which mean the diagnosis

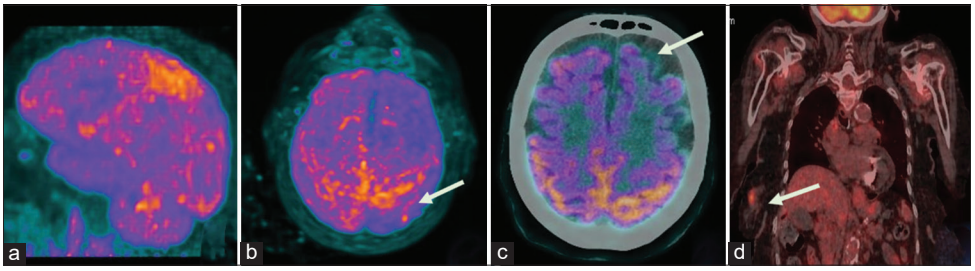


**Figure 2: 18F-FDG PET/CT (a and b) showing Maximum intensity projection PET images, (c) showing fused axial PET/CT images, d showing coronal section. (a) Reduced FDG uptake in temporoparietal and frontal region with preserved FDG uptake in sensorimotor cortex; (b) Foci of increased FDG uptake in left parietal region in background of suppressed FDG uptake in left parietal region; (c) Asymmetrical atrophy of bilateral frontal lobes with reduced FDG uptake; (d) Soft tissue nodular lesion in right breast parenchyma with increased FDG uptake. 18F-FDG PET/CT: 18F Fluoro-deoxy glucose positron emission tomography computed tomography**

is more precise with PET. In due course of time, the patterns in FDG PET were defined and correlated with autoantibodies. Mesial temporal lobe hypermetabolism has been described in both NMDAR and anti-leucine-rich-glioma-inactivated-1 (LGI1) AIE. Hypometabolism in the cingulate, medial and mid-frontal, and parietotemporal cortices in LGI1 AIE and hypermetabolism in the basal ganglia, cerebellum, and brain stem, areas are hypothesized to be associated with the Facio brachial dystonic movements associated with LGI1 AIE. The treatment responsiveness seen in our patient to IVIG is due to autoimmune dementia which has a good outcome with IGs. Although a series of comparative studies of neuroimaging have reported FDG PET as an early and sensitive diagnostic marker than MRI brain [6-9].

In our patient, FDG PET was planned which suggested atrophic changes predominantly in frontal lobes with diffuse hypometabolism in bilateral frontal, temporoparietal regions and a focus on increased uptake in the left parietal lobe in the background of hypometabolism. These are suggestive of an inflammatory process along with neurodegeneration being simultaneously present, which could possibly be the reason for reversible dementia after immunomodulation. Anti-Yo antibodies do not respond well to immunomodulators, (IV-IG or plasma exchange), corticosteroids, or rituximab. The efficacy of immunosuppression therapies (cyclophosphamide) and trastuzumab (in HER-2 positive) is also not proven [10].

## CONCLUSION

RPD has been difficult to diagnose for clinicians due to atypical presentation. The varied pathological implications associated with its etiology, many being still unknown, can lead to the misdiagnosis of irreversible dementia. However, there are caveats to be filled with undiscovered antibodies, sensitive investigation techniques, and specific biomarkers to reduce the global burden of the disease. This lacuna can be filled with the addition of FDG PET as a tool for introducing immunomodulation in an early phase of the disease and further guiding for continuation. Our patient showed a positive response to IVIG treatment, which contrasts with what is typically reported in the literature. We emphasize the importance of PET and propose to be introduced in diagnostic criteria of immune-mediated encephalitis as an early diagnostic, prognostic marker, as well as, for strategizing the treatment. However, for better understanding, larger studies are needed to correlate the findings of PET with associated antibodies.

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