



Case Report

Autoimmune Encephalitis versus Creutzfeldt-Jakob disease in a patient with typical Facio-brachial dystonic seizures: A case report with Diagnostic challenges

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ABSTRACT

Background: Diagnosis of rapidly progressive dementia (RPD) is very challenging. There are many conditions that fall into category of RPD ranging from autoimmune causes to neurodegenerative causes. Autoimmune encephalitis should be readily diagnosed and treated because of its response to immunomodulators. However there is no treatment available for conditions like Creutzfeldt-Jakob disease (CJD).

Case presentation: Here we present a case of anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis who presented with only typical facio-brachial dystonic seizures at presentation. On follow up, patient had a rapid cognitive decline with development of myoclonic jerks, akinetic mute state and ultimately death. Neuroimaging showed presence of hyperintensities in two cortical regions namely parietal and occipital on fluid-attenuated inversion recovery (FLAIR) sequence. Electroencephalogram showed diffuse slowing with occasional periodic sharp wave complexes. Thus a diagnosis of probable CJD was made.

Conclusion: Autoimmune encephalitis mimicking CJD or vice versa is not a very commonly encountered phenomenon. This case discusses the clinical overlap of these two conditions and its diagnostic dilemmas. This case presented with typical LGI1 encephalitis and in spite of therapy with immunomodulators had a rapid decline and ultimately turned out to be CJD. This has been rarely described in literature.

1. Introduction

Rapidly progressive dementia remains a challenge in clinical practice. The aetiology ranges from wide spectrum of metabolic, inflammatory and neurodegenerative disorders. Of particular importance is autoimmune encephalitis and other treatable conditions. Patients with anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis have memory disturbances, confusion, and seizures (Irani et al., 2011).

Memory and cognitive deficits may be preceded by facio-brachial dystonic seizures (FBDS) in most of the cases. It is often poorly responsive to antiseizure drugs and is considered a pathognomonic manifestation of LGI1 encephalitis. Creutzfeldt-Jakob disease (CJD) is a clinically heterogeneous disorder, a common feature of which is a rapid cognitive decline with death occurring within a year of diagnosis (Haywood, 1997). The clinical presentation is varied and ranges from dementia, behavioural symptoms, myoclonus, cerebellar signs, extrapyramidal

signs, corticospinal tract involvement and higher cortical functions deficits like apraxia.

Here we present a case who was diagnosed as having LGI1 encephalitis responsive to immunomodulators and subsequently developed a rapid cognitive decline and ultimately died within six months with a diagnosis of probable CJD.

2. Case report

A 45 year old man without any co-morbidities presented with complaints of paroxysmal, stereotyped, involuntary movements involving face and dystonic posturing of right upper arm that lasted for three to five seconds. These facio-brachial dystonic movements (FBDS) occurred in multiple episodes around twenty to thirty times per day. There was no tongue bite, incontinence or impaired awareness associated with it. On examination patient was conscious and oriented to time, place and

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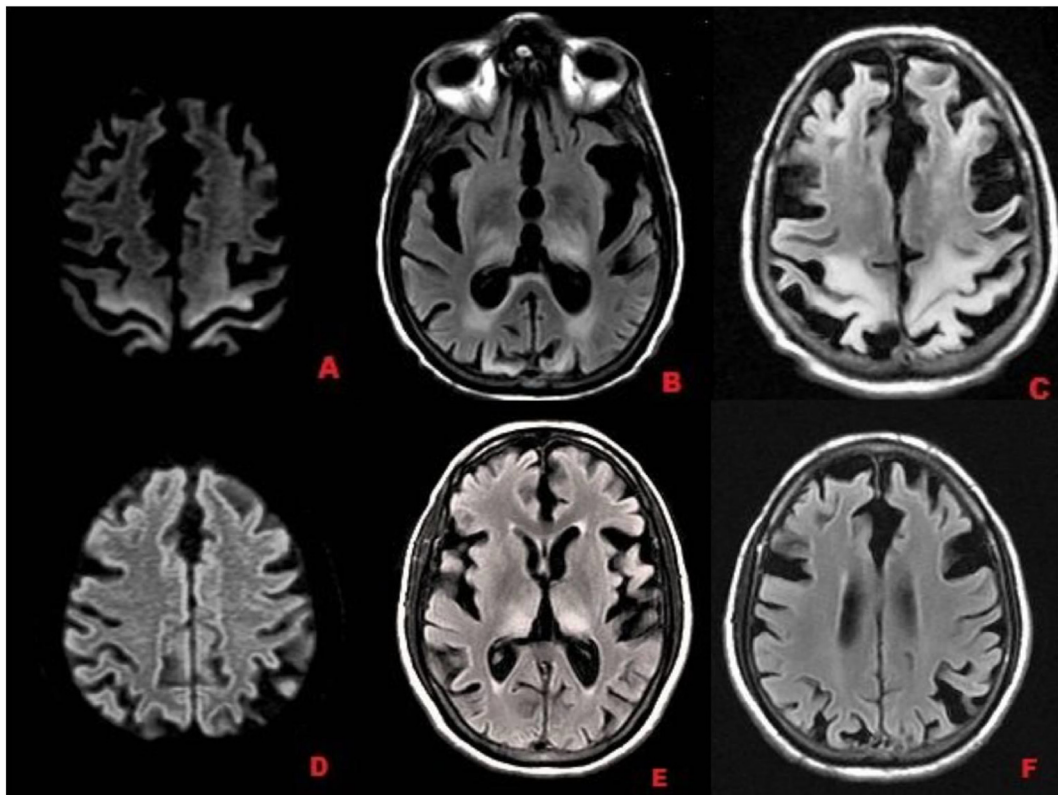


Fig. 1. Panel A,B, C was taken in patient's third visit. Panel A shows cortical ribboning in parietal region while T2 FLAIR hyperintensities are seen in thalamus (panel B) and in Bilateral parietal region (panel C) The same Sequences in patient's second Visit do not show any cortical ribboning (panel D) or T2 FLAIR hyperintensities in parietal Lobe (panel F) However there are T2 hyperintensities in Bilateral thalamus as shown in Panel E.

person. There were no cognitive deficit, extrapyramidal and cerebellar features.

Routine biochemical and haematological investigations including electrolytes, hepatic and renal functions were normal. Cerebrospinal fluid (CSF) analysis was within normal limits. Neuroimaging studies revealed diffuse cortical atrophy. A 24 hour electroencephalogram (EEG) monitoring didn't reveal any epileptiform discharges. Antibody against LGI1 was positive in serum. A diagnosis of LGI1 encephalitis was made and patient was initiated on intravenous immunoglobulin and intravenous methylprednisolone. He responded dramatically with complete resolution of FBDS after three days and he was discharged on oral steroids. He remained well for two months into follow up without any FBDS, behavioural abnormality or cognitive impairment.

In the third month of his follow up patient presented with a two weeks history of stiffness of all four limbs, difficulty in walking, reduced verbal output with cognitive decline. On examination patient was conscious, speech was hypophonic. His MMSE (Mini Mental State Examination) was 19/30 with impairment in delayed recall, naming, visuospatial function, verbal comprehension, reading and writing. Rigidity was present in all four limbs. He had generalised bradykinesia with brisk reflexes. There was Myerson's sign and he had prominent gait and truncal ataxia. Routine investigations revealed no abnormality. CSF study was also normal. A repeat neuroimaging was done which showed hyperintensities involving bilateral thalamus and marked cortical atrophy (Fig. 1). Serum autoimmune and paraneoplastic panel were negative. Antibodies to LGI1 were not detected in serum. Thyroid function tests with anti-thyroid peroxidase antibody was also normal. Fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan was done which revealed diffuse hypermetabolism in basal ganglia, thalamus and bilateral cerebellar hemisphere (Fig. 2). At this point our diagnosis was limbic encephalitis versus probable variant CJD. However in the light of PET findings we wanted to give a trial of rituximab but patient had

urosepsis so it was deferred. Instead patient was given IVIG and methylprednisolone and discharged with a course of antibiotics and oral steroids with a plan to follow up for rituximab infusion.

Three weeks later patient came to us in akinetic mute state and he had infrequent myoclonic jerks. A repeat neuroimaging showed T2 FLAIR hyperintensities involving parieto-occipital cortex and increased cortical atrophy (Fig. 1). Neuron specific enolase was found to be raised in CSF. CSF 14-3-3 could not be done. EEG done at this time showed periodic sharp wave complexes (supplementary file) A repeat FDG PET showed diffuse cortical hypometabolism (Fig. 2). Considering the above findings a diagnosis of probable CJD was made. Patient developed aspiration pneumonia and ultimately succumbed to his illness. Patient's attendant didn't give consent for autopsy.

3. Discussion

The wide spectrum of acquired and degenerative disorders are included in the differential diagnosis of rapidly progressive dementia which remains a poorly understood evolving clinical syndrome. Multiple strokes, viral, autoimmune encephalitis, metabolic causes leading to delirium, brain tumours and other treatable causes meet the definition of RPD. They should be readily identified and investigated at initial assessment. Some degenerative dementias also tend to progress rapidly and needs to be kept in differential diagnosis of RPD. Autoimmune encephalitis syndromes remain the important cause of RPD and are associated with antibodies to neuronal cell surface/synaptic proteins and are highly responsive to immunomodulatory therapies (Dalmau and Graus, 2018).

FBDS movements as presented in our patient are highly stereotyped, predominantly affect the arm and ipsilateral face, and are slower than myoclonus and are pathognomonic manifestations of anti-leucine rich inactivated glioma 1 encephalitis (Irani et al., 2011).

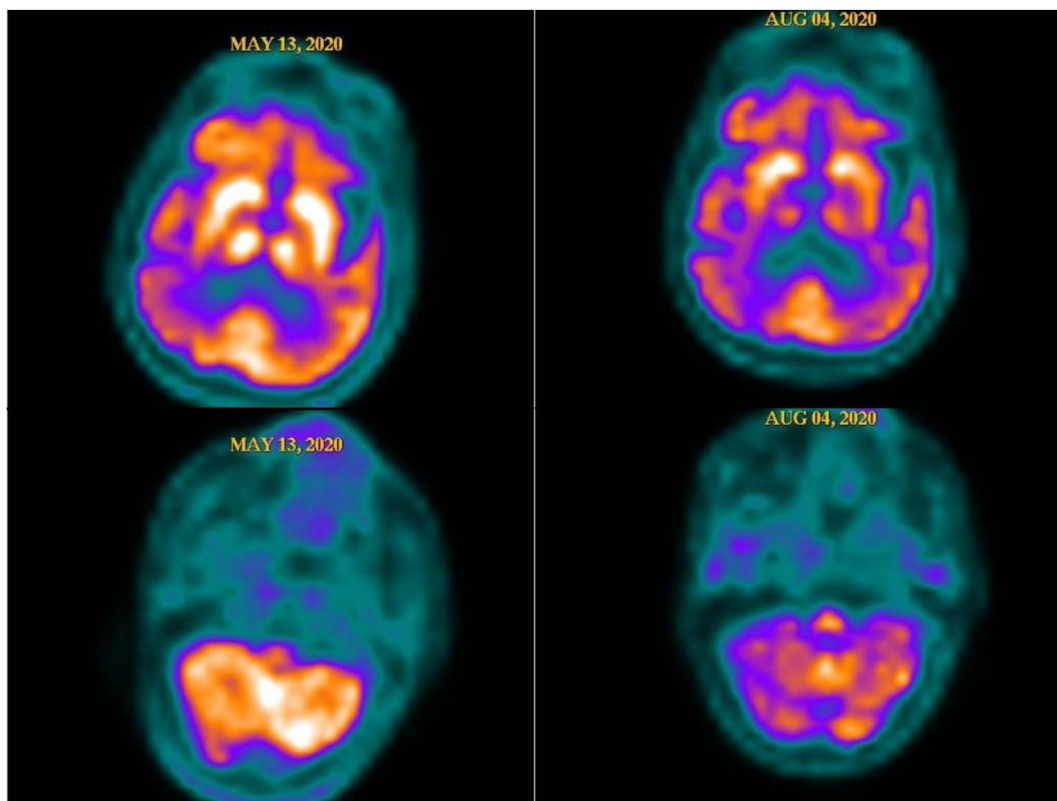


Fig. 2. Diffuse cortical atrophy with dilated ventricles and basal cisterns with few ill defined hypometabolic hypodensities involving the bilateral parieto-occipital, peri-ventricular and bilateral thalamo-ganglio-capsular regions with few areas of focal uptake in bilateral caudate regions with global cortical hypometabolism with mild to moderate hypometabolism in bilateral thalami. As compared to the previous PET CT scan dated May 13, 2020; there is increase in the degree of cortical atrophy. The bilateral basal ganglia, brainstem and bilateral cerebral hemispheres shows resolution of the previously noted increased glucose metabolism. The bilateral thalami show reduction in glucose metabolism.

At presentation the patient was not having any cognitive or behavioural impairment. It is pertinent to treat the patient in initial stages to prevent the further progression of the disease into encephalopathy, cognitive impairment and refractory seizures. The LGI1 antibodies were positive in serum. Our patient responded to methylprednisolone and intravenous immunoglobulins. FBDS improved completely in one week and he remained stable on oral steroids for two months.

Further, the patient progressed to have prominent limbs and truncal rigidity along with impairment in cognitive function primarily in memory and executive functions. He deteriorated and became completely mute and bed bound within next two months. With such a rapidly progressive dementia and prominent EPS features the possibility of CJD was considered.

The presentation of prion disease is highly heterogeneous with distinct causes, clinical features and durations (Collinge, 2011). It readily mimics a wide range of potentially reversible or treatable disorders. Our patient was fulfilling the probable criteria for sCJD as proposed by the Centres for Disease Control and Prevention (CDC) (<https://www.cdc.gov/prion,2018>).

Autoimmune encephalitis with antibodies against neuronal surface antigens (NSA-abs) and Creutzfeldt-Jakob disease (CJD) may present with similar clinical features making the diagnosis a challenge as in our patient.

A recently published study demonstrated presence of neuronal surface antigens in patients CSF with rapid neurological deterioration (Grau-Rivera et al., 2014). CJD is also considered as the mimicker of VGKC encephalitis, fifteen cases of VGKC mimicking CJD has been described by Geschwind et al. 2008 (Geschwind et al., 2008).

MRI Brain showed severe generalised cortical atrophy. The initial PET shows area of hypermetabolism in bilateral basal ganglia, brainstem and bilateral cerebral hemispheres consistent with encephalitis (Fig. 2). The

hypermetabolism suggests autoimmune process (Baumgartner et al., 2013). The repeat imaging shows resolution of the hypermetabolism and the areas of hypometabolism in both the parietal and occipital lobe. Bilateral thalamo-ganglio-capsular regions also showed hypometabolism. The bilateral thalami showed reduction in glucose metabolism. This neuroimaging findings are consistent with CJD (Fig. 2). The patients with sCJD show decreased glucose metabolism in bilateral parietal, frontal, and occipital cortices (Kim et al., 2011).

FDG-PET has an important role to play in the differential diagnosis between AIE and prion diseases. Different brain metabolic patterns differentiate sCJD from AIE, though none of the pattern is specific. Patients with a prion disease exhibit a hypometabolic pattern affecting subcortical and extensive cortical areas (Prieto et al., 2015).

There is evidence of clinical and neuroimaging shift from autoimmune encephalitis progressing to CJD. This case describes possible clinical overlap of autoimmune encephalopathies and prion diseases. Grau-Rivera et al. in their study have demonstrated low, but clinically relevant, number of patients with suspected CJD having NSA-antibodies-associated neurologic disorders that are potentially responsive to immunotherapy.

Clinical response was good in our patient up to two months follow up. It has been postulated in a case report by Heather Angus-Leppan et al. that the rapid destruction of cerebral tissue by prion disease releases neuronal antigens, leading to development of the antibodies as secondary events (Angus-Leppan et al., 2013). The majority of degenerative diseases, however, result from an improper restoration of immune tolerance to specific self-antigens (de Haan et al., 2017).

But in this case we had positive antibody to the neuronal antigen and then the progression of disease to CJD which makes us wonder whether the autoimmunity triggered the neurodegenerative process. This possibility and hypothesis need to be further explored and investigated. There

Table 1
Illustrating various studies on autoimmune encephalitis and CJD overlap.

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|-----------------------------|------|---|--|--|
| Zuhorn et al. | 2014 | Rapid progressive cognitive impairment. | CASPR-2 | Died. Post mortem diagnosis of CJD made |
| Christopher R. Newey et al. | 2013 | 17 month history of gait instability and confusion | VGKC | Received IVIG but died. Post mortem diagnosis of CJD |
| Wietse A. Wiels et al. | 2018 | Schizophrenia spectrum disorder | Glycine receptor antibody | Received IVIG and other immunomodulatory therapy but died. Post mortem diagnosis of CJD was made (VV1 subtype) |
| Yudan Lv et al. | 2015 | Rapid cognitive impairment. Hyponatremia, atypical fbds | Antibody negative | MRI and EEG suggestive of CJD |
| John C. Probasco et al. | 2014 | Rapid Cognitive impairment. | VGKC (Voltage gated potassium channel) | MRI suggestive of CJD but Patient was finally diagnosed to have Autoimmune encephalitis |
| Michael D. Geschwind et al. | 2008 | Cohort of 15 patients with Suspected CJD | VGKC | Most of the patients improved with immunomodulatory therapy |

has been various case reports and series describing cases of CJD ultimately turning out to be autoimmune encephalitis or vice versa as summarised in the table (Table 1). As described in the (Table 1) Yudan Lv et al. described a case similar to ours but had atypical FBDS and was antibody negative.

Our case is unique in various aspects. Firstly our patient presented with only typical FBDS in the beginning. Available case reports in literature as mentioned in Table 1 had rapidly progressive cognitive impairment as the presenting feature which is not seen in this case. Secondly after responding well to immunomodulatory therapy patient had a rapid deterioration which manifested both clinically as well as on imaging. It leads us to a possibility that it was an autoimmune mediated accelerated neurodegeneration. The limitation to study is non availability of CSF 14 3 3, CSF RT-QuIC (Real time quaking induced conversion) and a post mortem tissue diagnosis in our institution. But these limitations do not change the diagnosis of Probable sCJD which is seen in our patient.

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Author statement

All authors have contributed to manuscript preparation and case workup as mentioned below.

VS, SK and PMP were involved in acquisition of data, case report conception, draft preparation and critical revision of manuscript.

PB and KR were involved in critical revision of manuscript.

RV was involved in analysis of images and draft preparation.

Declaration of competing interest

The authors declare that there is no conflict of interest. All authors have agreed upon the final manuscript before submission.

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