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Case Report

Seronegative Autoimmune Encephalitis: A Challenge for the Neurologist

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Abstract

Autoimmune neurological disorders are diagnosed by antibody testing in serum and cerebrospinal fluid. However, autoimmune encephalitis and refractory autoimmune epilepsies maybe seronegative in 50% cases despite the use of the currently available serological tests. The Antibody Prevalence in Epilepsy and Encephalopathy Score [APE^2] and Response to immunotherapy in epilepsy and encephalopathy scores [RITE^2] enhance the value of early case detection and prevent residual neurological damage in patients with recent cognitive decline or refractory epilepsy. We incorporated these scales to improve efficacy in diagnosing autoimmune-mediated neurological diseases in clinical practice. These parameters hasten the diagnosis of autoimmune spectrum of diseases when used on patients attending busy neurology clinics. The scales enable prognostication and assessment of neurological sequel when applied at follow-up. The improvement of symptoms in the autoimmune spectrum of neurological diseases can be attributed to early case detection and institution of appropriate therapy.

Keywords: Seronegative Autoimmune Encephalitis; Progressive Supranuclear Palsy; Anti-IgLON5 Disease

Introduction

Seronegative autoimmune encephalitis is a term coined for patients who present with the triad of cognitive disturbances, seizures and behavioral abnormalities but continue to evade antibody detection in serum and cerebrospinal fluid. The occurrence of seronegative autoimmune encephalitis is 48% despite the availability of the latest panel of antibody assays.

Case Report

A 75-year-old man presented with progressive impairment of memory, mood swings, irritability and excessive daytime sleepiness of six-weeks duration. As time progressed, he experienced unsteadiness of gait, swallowing difficulty and noisy breathing. His sleep was interrupted by loud snoring, witnessed apneas and rhythmic tapping of feet. He had vocalisation in sleep, dream-enactment

and frequent awakenings suggestive of a complex sleep-disorder. Clinical examination revealed an elderly gentleman with an audible inspiratory stridor and dysexecutive syndrome. His expression was mask-like with bilateral upgaze palsy, bulbar palsy and cogwheel rigidity. There was an autonomic dysfunction with excess sweating, sialorrhea, postural hypotension and resting tachycardia. His resting heart rate was 120/min (Figure 1A), supine blood pressure in the right upper limb was 130/86 mm Hg and standing blood pressure was 100/60 mm Hg with a postural drop of 30/26 mm Hg. Routine blood, urine examination, serum ammonia, thyroid function tests and anti-thyroid antibodies were normal. Cerebrospinal fluid was clear, cells 20 [100% lymphocytes], protein 66.80 mg/dl [normal 20 - 40 mg/dl], sugar 58.00 mg/dl [blood sugar was 110 mg/dl]. Polymerase chain reaction for herpes virus 1 and 2, cytomegalovirus, Epstein Barr virus, varicella zoster, HHV-6 and enteroviruses were negative. Autoimmune, paraneoplastic and anti-IgLON5 antibodies were negative. Prion disorder panel including CSF 14-3-3, neuron specific enolase and tau protein were negative. EEG revealed periodic short interval generalized discharges (Figure 1B), CT of the brain revealed age related cerebral atrophy (Figure 1C), FDG PET - CT of the brain revealed diffuse hypermetabolism in bilateral basal ganglia, mid brain, pons, vermis and cerebellar hemispheres favoring an autoimmune encephalitis (Figure 1D). Sleep studies revealed a severe degree of obstructive sleep apnea (Figure 1E) with periodic limb movement in sleep [PLMS index 80] for which titration with BiPAP was done (Figure 1F). Patient had a poorly structed N3 stage with disruption of the sleep architecture and frequent arousals. He had sleep-related vocalizations, prolonged apneas for 60 seconds and hypoventilation. The Antibody Prevalence in Epilepsy and Encephalopathy [APE^2] and Response to Immunotherapy in Treatment of Epilepsy and Encephalopathy [RITE^2] scores were 4 and 5 each (Table 1A and 1B) before starting therapy. Based on the history, clinical findings, PET-CT report, APE^2, RITE^2 score and a negative IgLON5 antibody assay, a diagnosis of possible anti-IgLON5 disease was made while the differentials excluded were Creutzfeldt-Jakob Disease, Progressive supranuclear palsy, multi-system atrophy, Binswanger Disease and a paraneoplastic limbic encephalitis. Patient received intravenous methyl prednisolone 1 gm daily as an infusion for five days, plasma exchange followed by intravenous immunoglobulin and non-invasive ventilatory support. While in hospital his GCS score was E3M6V4 and he required non-invasive ventilation [AVAPs] for obstructive sleep apnea with hypoventilation and inspiratory stridor. The family wanted domiciliary care, so he was discharged at their insistence and taken home. The assigned home-care nurse reported that he died in his sleep two weeks later following stridor and breathing difficulty.

Clinical Features	Score
New-onset, rapidly progressive mental status changes emotional lability	+ 1
Autonomic dysfunction (presenting as labile blood pressure, labile heart rate, persistent tachycardia, postural hypotension)	+ 1
Viral prodrome (runny nose, sore throat, low-grade fever), only to be scored in the absence of underlying malignancy	0
Facial dyskinesias or faciobrachial dystonic movements	0
Seizure refractory to at least 2 antiseizure medications	0
CSF findings consistent with inflammation (elevated CSF protein level >50 mg/dL and/or lymphocytic pleocytosis > 5 cells/dL, if the total number of CSF RBCs is <1000 cells/dL).	+ 2
Brain MRI showing signal changes consistent with limbic encephalitis (medial temporal T2/FLAIR signal changes)	0
Presence of underlying malignancy (excluding cutaneous squamous cell or basal cell carcinomas)	0
Total	4

Table 1A: Antibody prevalence in epilepsy and encephalopathy score [APE^2].

Clinical Features	Score
New onset, rapidly progressive mental status changes that developed over 1-6 weeks or new onset seizure activity (within one year of evaluation).	+1
Neuropsychiatric changes; agitation, aggressiveness, emotional lability.	+1
Autonomic dysfunction [sustained atrial tachycardia or bradycardia, orthostatic hypotension [≥ 20mmHg fall in systolic pressure or≥10mmHg fall in diastolic pressure within three minutes of quiet standing], hyperhidrosis, persistently labile blood pressure, ventricular tachycardia, cardiac asystole or gastrointestinal dysmotility.	+1
Viral prodrome [rhinorrhea, sore throat, low grade fever] to be scored in the absence of underlying systemic malignancy within 5 years of neurological symptom onset.	0
Faciobrachial dystonic seizures.	0
Facial dyskinesias, to be scored in the absence of faciobrachial dystonic seizures.	0
Seizure refractory to at least to two anti-seizure medications.	0
CSF findings consistent with inflammation [elevated CSF protein > 50 mg/dL and/or lymphocytic pleocytosis > 5 cells/mcL, if the total number of CSF RBC is < 1000 cells/mcL].	+2
Brain MRI suggesting encephalitis [T2/FLAIR hyperintensity restricted to one or both medial temporal lobes, or multifocal in grey matter, white matter, or both compatible with demyelination or inflammation].	0
Systemic cancer diagnosed within 5 years of neurological symptom onset. [excluding cutaneous squamous cell carcinoma, basal cell carcinoma, brain tumor, cancer with brain metastasis].	0
Immunotherapy initiated within 6 months of symptom onset.	0
Neural plasma membrane autoantibody detected [NMDAR, GABAAR, GABABR, AMPAR, DPPX, mGluR1, mGluR2, mGluR5, LGI1, IgLON5, CASPR2 or MOG].	0
Total	5

Table 1B: Response to Immunotherapy in epilepsy and encephalopathy score [RITE[2]].

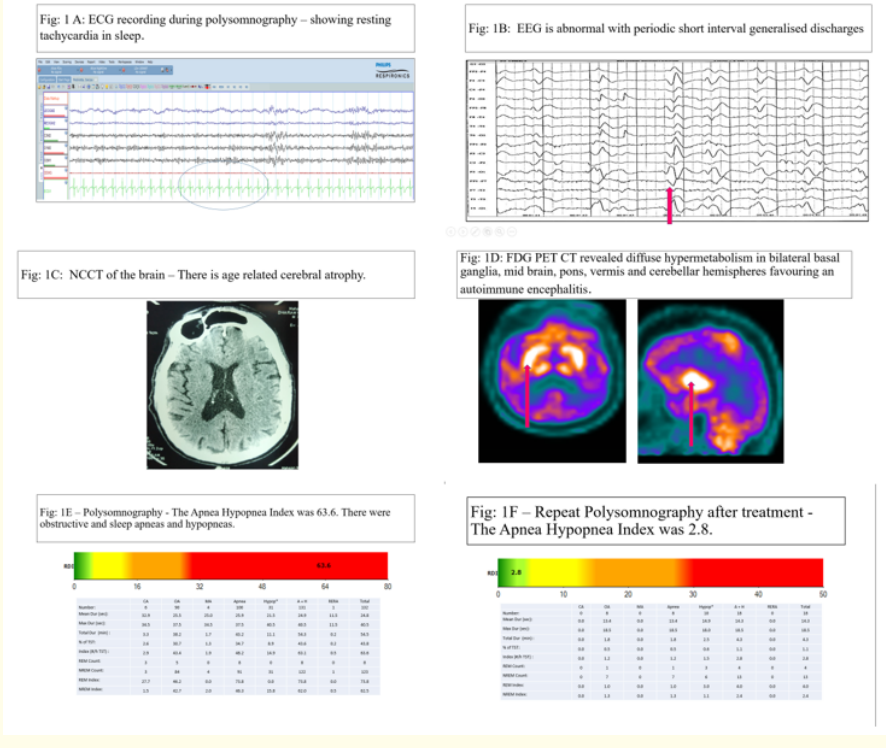

Figure 1

Discussion and Conclusion

Seronegative autoimmune encephalitis presents with altered sensorium, cerebrospinal fluid pleocytosis, typical imaging findings with a negative serology after excluding alternative causes [1,2]. Patients with chronic refractory epilepsy, encephalopathy and cognitive dysfunction require immunotherapy despite routine anti-epileptic medication, if the disease progresses further as in the index case [2,3]. Initiation of treatment in suspected autoantibody negative encephalitis prevents neuronal damage, memory impairment and neurodegeneration [4-6]. Early therapy averts sequel like hippocampal sclerosis, verbal and visual memory decline and brainstem dysfunction in clinically suspected patients [4,5].

The Antibody Prevalence in epilepsy and encephalopathy score [APE^2] is an invaluable bedside clinical scoring system to estimate the probability of an autoimmune etiology in antibody negative patients [4,5]. (Table 1A) An APE score of 4 or more indicates the necessity for antibody testing [4]. The Response to immunotherapy in epilepsy and encephalopathy score [RITE^2] score was derived from the analysis of retrospective studies to identify patients of autoimmune etiology who respond to immunotherapy [5] (Table 1B). A score less than 7 is associated with refractoriness to immunotherapy [5]. The combined use of both these scales enables clinicians to apply an efficient evidence based approach for the diagnosis of autoimmune neurological diseases that require further evaluation and treatment [5]. Cognitive improvement following early immunotherapy cannot be overemphasized thus enhancing the value of these parameters in patients who present to busy hospitals where rapid screening, case detection and early treatment are necessary [5]. Elderly people have a challenging time with autoimmune encephalitis due to the occurrence of age-related comorbidities that affect cognition and memory [7]. Older people with autoimmune encephalitis have a higher chance of being antibody negative on routine testing and in 58.3% of antibody negative limbic encephalitis, a neoplastic process can be identified on follow-up visits [7]. In children, rapid cognitive decline, impairment of memory, refractory seizures and dyskinesias are suggestive of an autoimmune etiology despite negative antibody assays [8]. The APE^2 and RITE^2 scales are invaluable to enhance the yield of diagnosis in patients suspected of autoimmune encephalopathy or epilepsy irrespective of age [8]. Young children and the elderly are the vulnerable members of our society who are susceptible to antibody mediated illnesses and the neurocognitive outcome depends on the speed of instituting immunotherapy and disease modifying agents [8]. These clinical rating scales are of immense importance to improve functional outcome and to achieve complete remission in patients affected with autoimmune neurological diseases [9].

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