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Seronegative Autoimmune Encephalitis: An Easily Missed Case of Suspicion

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ABSTRACT
Autoimmune encephalitis is an acute inflammatory condition of the brain resulting from an autoimmune process, which manifests clinically as seizures, cognitive decline, and neuropsychiatric symptoms. A subset of this condition, referred to as seronegative autoimmune encephalitis, is suspected to have an immunological etiology, although some pathogenic autoantibodies have been identified, many of which still remain unidentified.

I. INTRODUCTION

Autoimmune Encephalitis (AIE) is commonly classified based on either the affected anatomical region or the underlying etiology. The predominant etiologies comprise paraneoplastic and autoimmune conditions, characterised by the production of antibodies against tumour cells and the formation of antibodies targeting extracellular or intracellular channels, ions, or proteins, respectively. Infrequently, Seronegative AIE is detected, denoting a dearth of detectable antibodies.

In this report, we present the case of a 76-year-old male with the aforementioned clinical presentations. We provide a detailed account of the diagnostic challenges encountered in arriving at the diagnosis, the management approach adopted, and the measures to be considered for early identification and treatment.

II. CASE PRESENTATION

76 year old male patient presented to the emergency department with a history of abnormal body movements in the form of twitching of limbs an drooling of saliva for 2 weeks. The patient also complained of episodes of unconsciousness which lasted for a few minutes with confusion and abnormal incoherent speech. Along with the above problems, the patient also had a 3 day history of low appetite and generalised weakness along with drowsiness.

General physical examination revealed diffuse myoclonic jerks but rest of the general physical examination along with the systemic examination was insignificant. Investigations at the time of examination revealed Haemoglobin of 10.6, TLC - 12.6, Platelet Count- 285, serum Albumin 2.8, SGOT - 25, SGPT - 22, Serum Calcium - 8.5, Serum Sodium - 133, Serum Potassium - 4.41.

MRI Brain with Contrast revealed Small Non Enhancing area of blooming seen in the left high frontal paraventricular white matter with no perilesional oedema suggestive of calcified granuloma. EEG was suggestive of severe degree off generalised cerebral dysfunction.

There was a rapid progression I symptoms and suspecting AutoImmune Encephalitis, a PET Scan was ordered along with a Blood and CSF Autoimmune Encephalitis panel along with a CTD profile.

Pet Scan showed no FDG lesions, AutoImmune Encephalitis Panel and CTD Profile were negative.

Still suspecting an AutoImmune pathology, Pulse Steroid therapy was started along with Anti Epileptics and the patient showed improvement after the first day of Methyl Prednisolone and thus the steroids were given for a full course of 5 days. A dose of 110gm (2gm/kg of body weight) of IV Immunoglobulin therapy over 3 days was also started along with the Steroids and the patient showed major improvement in the symptoms vis a vis Improvement in Speech and Consciousness. There was also a significant improvement in Myoclonic Jerks and Appetite of the patient. The patient was thus discharged on Steroids, Anti Epileptics and regular physiotherapy and is in outpatient follow-up without any new complaints with improving symptoms.

III. DISCUSSION

The most prevalent clinical manifestations of Autoimmune Encephalitis (AIE) include seizures, motor weakness, behavioral changes, abnormal movements, psychiatric symptoms, and other symptoms specific to the anatomic localization of the disease process.[2] For instance,

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in our case study, the patient reported recurring episodes of abnormal movements with concomitant loss of consciousness, progressive weakness, memory disturbances and dysarthria , leading to their prompt admission and comprehensive evaluation.

Diagnosing Seronegative Autoimmune Encephalitis is a task that poses considerable difficulty, owing to its indistinct symptoms and negative test outcomes. This challenge mandates a high level of clinical suspicion, as well as the need to exclude various alternative causes, thereby making the diagnosis both a process of exclusion and one of high clinical suspicion requiring prompt action.

Standard diagnostic investigations for Autoimmune encephalitis encompass a suite of baseline tests including complete blood count, liver function tests, renal function tests, and thyroid function tests, alongside targeted antibody panels such as NMDAR, AMPAR, and LGH, among others [3], as well as PET scans and MRI. In our case, in view of the patient's presenting symptoms, a strong suspicion for Autoimmune Encephalitis was held, and the baseline investigations were augmented with antibody panels targeting connective tissue and thyroid disorders. This was done to exclude potential etiologies, such as vasculitis and vascular dementia, and to search for antibodies linked to AIE and other autoimmune disorders. In addition, an MRI of the brain was performed to exclude localized organic causes such as space-occupying lesions or anatomical defects. Recognizing the potential for paraneoplastic etiology, a PET CT scan was conducted to exclude any tumors, which was ultimately ruled out. An EEG was done to rule out epilepsy as well localise site of seizure activity.

It is essential to keep in mind that psychiatric or behavioral disorders may also present as differentials for Autoimmune encephalitis. In our case, a detailed psychiatric evaluation was conducted to exclude this possibility.[4]

In addition to these investigations, Graus et al have outlined specific diagnostic criteria for probable autoimmune encephalitis in the absence of detectable autoantibodies, which can facilitate prompt diagnosis and treatment.[5]

Derived from – [5] .A clinical approach to diagnosis of autoimmune encephalitis. Graus F, Titulaer MJ, Balu R, et al. Lancet Neurol. 2016;15:391–404.

Criteria for autoantibody-negative but probable autoimmune encephalitis

Diagnosis can be made when all four of the following criteria have been met:

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well defined syndromes of autoimmune encephalitis (eg, typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well characterised autoantibodies in serum and CSF, and at least two of the following criteria:
   - MRI abnormalities suggestive of autoimmune encephalitis*
   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both*
   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (eg, tumour)
4. Reasonable exclusion of alternative causes

Immunosuppressive therapy, representing the conventional therapeutic modality for Autoimmune Encephalitis, is contingent upon the patient's response to the treatment and is considered as the yardstick for prognostic outcomes. However, the timely commencement of immunotherapy is recommended for optimized prognostic implications. The initial approach typically involves the use of steroids (IV methylprednisolone 1g/day for 3-7 days), which is supplemented by intravenous immunoglobulin (IVIG) therapy(2g/day over 3-5days). [6][7][8][9] In the current instance, our patient manifested a swift response to the therapeutic regimen that

incorporated steroids and IVIG. This was evidenced by a rapid and continuous improvement of the weakness and dysarthria, followed by a notable improvement in the occurrences of aberrant movements, culminating in an improvement in memory function.

In cases that are refractory to the conventional therapeutic interventions, plasma exchange and Rituximab may be considered. Despite the efficacy of various immunosuppressive therapies, convalescence from Autoimmune encephalitis can be prolonged, and relapses are known to occur frequently. [6][7][8][9]

Thus, this condition could be deemed a diagnosis of exclusion and of high suspicion. This is due to the absence of supportive evidence and positive findings on diagnostic investigations, which necessitates the exclusion of various other disorders. Nevertheless, it is imperative to maintain a high degree of clinical suspicion and promptly initiate appropriate measures for a favorable prognosis. Waiting for laboratory results that could take days to weeks is inadvisable, as this could exacerbate the patient's condition. [10]

The identification of seronegative autoimmune encephalitis (AIE) presents a unique and multifaceted obstacle. Firstly, the condition's clinical manifestation varies significantly, secondly, there is an absence of autoimmune antibodies that may be responsible for it, making it arduous to establish the underlying etiology. [1]

Firstly, it should be noted that receiving the results of antibody testing can often take several days to return from the laboratory. Furthermore, it is crucial to recognize that an affirmative outcome does not necessarily constitute a conclusive diagnosis, while a negative result does not entirely exclude it. [11]

There are diverse determinants of seronegative AIE, including the inadequate precision of laboratory tests, antigen depletion, immunosuppressive therapy, immunodeficiencies, and immunosenescence. Thus, diagnosing seronegative AIE is usually based on clinical features and other available evaluations such as histopathological and radiological diagnostic tests.[12].

Several factors may lead to seronegativity in AIE, such as the assay's type, sensitivity, and specificity employed to detect specific autoantibodies associated with a specific autoimmune disease (AID). Furthermore, unknown antibodies may also contribute to AIE.

Another crucial factor is the actual antibody concentration in the blood, which varies depending on its production kinetics, diffusion, and removal or adsorption rate. The absence of an autoantibody in the blood may occur due to its absorption mediated by cells and tissues, rather than non-production. [12]

All of these factors pose a peculiar challenge in clinical practice, which may lead to false or delayed diagnoses, resulting in poor prognosis and making it primarily a diagnosis of exclusion, requiring high clinical suspicion for prompt treatment.

IV. CONCLUSIONS

In summary, there are numerous causes for seronegativity in Autoimmune encephalitis and several challenges in identifying the condition, making it crucial to maintain a heightened sense of suspicion for seronegative Autoimmune encephalitis in cases with similar presentations, even in the absence of positive test results. Delayed treatment has been linked to a decline in prognosis; thus, it is imperative to bear in mind the diagnostic criteria and promptly initiate treatment in cases where there is a high likelihood of the disease, leading to a better prognosis.

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