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Seronegative Autoimmune Encephalitis in a 6-Year-Old Child: Expanding the Paradigm of Autoimmune Neurology

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KEYWORDS

Autoimmune Encephalitis, Autoimmune Neurology

ABSTRACT:

Autoimmune encephalitis (AIE) refers to a neuroinflammatory condition [1] characterised by formation of autoantibodies against extracellular, intraneural or synaptic antigens. Its manifestation is diverse and variable ranging from behavioral changes to intractable seizures, sometimes proving fatal. First recognised in 2007 with anti NMDA encephalitis[2], the field has since made many strides with the discovery of many more such antibodies like MOG[3], LGI1[4], mGluR5 [5]. However, seronegative autoimmune encephalitis being a diagnosis of exclusion remains to be one of the pitfalls of therapeutic management.

Introduction:

Autoimmune encephalitis (AIE) refers to a neuroinflammatory condition [1] characterised by formation of autoantibodies against extracellular, intraneural or synaptic antigens. Its manifestation is diverse and variable ranging from behavioral changes to intractable seizures, sometimes proving fatal. First recognised in 2007 with anti NMDA encephalitis[2], the field has since made many strides with the discovery of many more such antibodies like MOG[3], LGI1[4], mGluR5 [5]. However, seronegative autoimmune encephalitis being a diagnosis of exclusion remains to be one of the pitfalls of therapeutic management.

Case Report:

A 5 years and 11 month old boy presented with complaints of fever, lasting over two weeks, cough for one week and one episode of generalised tonic clonic seizure. The fever was intermittent in nature, relieved by acetaminophen oral suspension. Patient informant also relayed that there were two episodes of vomiting prior to the child being brought to hospital, both of which were projectile and non bilious in nature. The seizure itself followed the first episode of vomiting, with reports of uprolling of eyes as well as loss of consciousness and involved movement of both upper and lower limbs extending for more than 15 minutes. Post this episode, the patient had altered sensorium. Clinical examination showed meningeal signs - Kernig's and Brudzinki's - as positive with no evidence of focal neurological deficits.The reliability of the patient informant- the mother was confirmed to be good and hence, elicitation of history and investigations began.

Patient History:

Patient had no previous history of febrile seizures. He was born via emergency LSCS in hospital and was admitted in the NICU for the first few days after birth for treatment of neonatal jaundice. Antenatally history was unremarkable. Due to poor lactation, the child was started on formula feeds.

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Recently, the patient had an exanthematous illness, likely chicken pox which was treated at home about a year ago. There was a history of recent travel one month previous to onset of symptoms.

Upon eliciting family history, it was uncovered that father had seizures in the past, approximately 10 years ago, for which he took anti-epileptic drugs for 3 years. Paternal grandmother, also, had an established seizure disorder for which she was not taking any medications.

Clinical Findings:

Child was conscious and irritable, displaying erratic behavior and screaming inappropriate words. It is to be recognised that such behavior is uncharacteristic to the child, as mentioned by parents. Pupils were bilaterally symmetrical and reacting to light with a size of about 3mm.

Meningeal signs i.e. Kernig's and Brudzinki's sign were found to be positive. 48 hours after admission, upon repeat examination for meningeal irritation, it was found to be negative..

All other CNS examinations yielded normal results including reflexes, cranial nerve function and cerebellar signs.

Investigations:

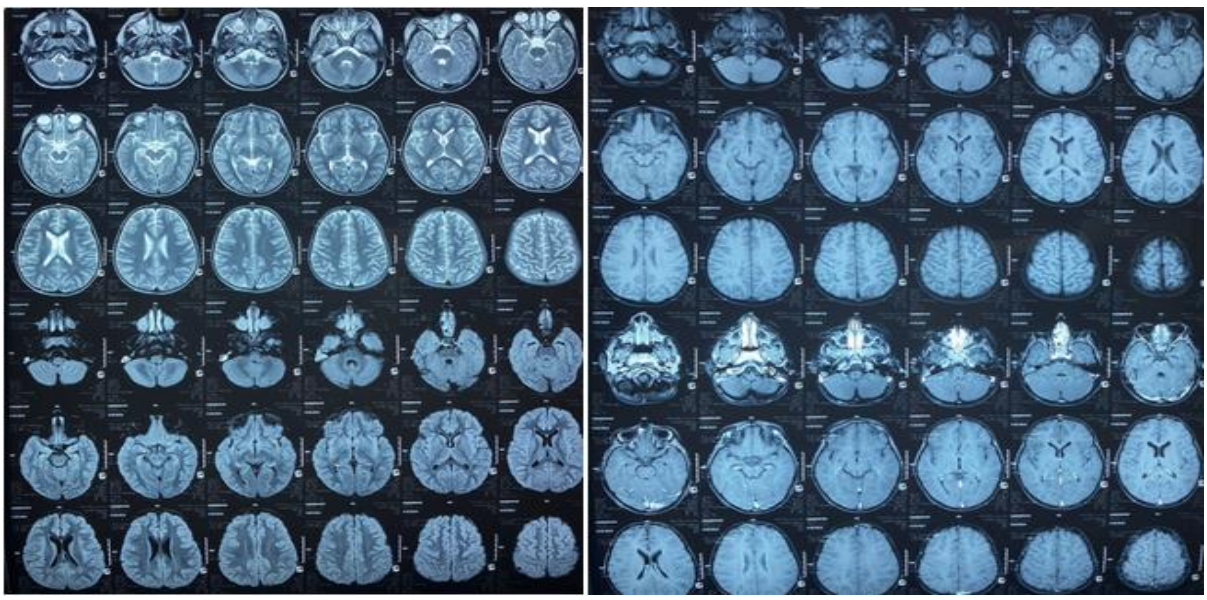
Blood work-

Routine blood work revealed a hemoglobin concentration of 12.8g/dl, WBC count of 14,200 and a platelet count of 2.5, initially. Remarkably the peripheral smear depicted a DLC of 61/34/04/01 on day 1 of admission. On day 8, this would take a turn to give a DLC of 62/33/03/02/00. Furthermore, serum electrolyte studies indicated a sodium imbalance- hyponatremia with values consistently remaining within the range of 125-130 mmol/L on multiple occasions, which was mild but necessitated correction. Potassium, however, was within normal ranges. Mantoux turned out to be negative. CRP was also negative. Conclusively, ESR was 23 pointing towards an inflammatory pathology.

Imaging studies-

On day 1 of admission, CT brain was done and no significant findings were observed.

MRI brain with contrast performed on day 4 of admission showed diffuse leptomeningeal enhancement in the post contrast images, suggesting meningitis. Bilateral mastoiditis was also noticed in the same.



CSF studies-

CSF study, conducted on day 2 of admission, showed about 150 cells leaning towards a lymphocytic predominance, indicating a viral etiology. Additionally, sugar was more than 2/3rds of plasma values. Protein was within normal range, CSF AFB stain was negative and neither microscopy nor culture of CSF yielded any results. CBNAAT of the same gave a negative result

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Autoimmune panel-

CSF for the autoimmune panel was done and showed negative.

DEPARTMENT OF NEUROPATHOLOGY

Autoimmune Laboratory

MRN	**EXT120244665**	**Department**	Neuropathology (Auto Immune Lab)
Name	**MASTER KANISHAKAN**	**Specimen**	Serum
Age / Sex	6 Y/MALE	**Visit Type**	OP
Sample No	AU0310240006	**Collected On**	03/10/2024 10:26
Lab Reference No	XAU-9234	**Received On**	03/10/2024 12:47
Consulting Doctor	DR JAGANATHAN	**Reported On**	04/10/2024 16:15

Test Name	Result	Comments
Autoimmune Encephalitis Mosaic - SERUM (NMDA and VGKC)		
Glutamate receptor, NMDA	**Negative.**	
Glutamate receptor, AMPA1	**Negative.**	
Glutamate receptor, AMPA2	**Negative.**	
CASPR (contactin - associated protein 2/VGKC associated)	**Negative.**	
LGI-1 (Leucine rich glioma inactivated protein 1/ VGKC associated)	**Negative.**	
GABAB receptor (GABABR1,B2)	**Negative.**	

Course of Treatment:

Patient was admitted in the paediatric ICU where he underwent treatment for 10 days. To prevent further seizure activity, the patient was administered a levetiracetam maintenance dose of 10mg/kg/dose, every 12th hourly. 3% NaCl IV fluids were given to the patient to correct the persistent hyponatremia. Furthermore, the patient was administered Tab. Clonazepam 0.125mg twice daily to alleviate erratic behavior and aggressive nature. Despite treatment given, patient displayed waxing and waning symptoms manifesting as erratic behavior. To treat any underlying infections, empirical therapy was promptly initiated with, inj. Ceftriaxone (100 mg/kg) for 7 days, inj. Acyclovir for 7 days, and inj. Vancomycin for 10 days was continued. As per the national guidelines, formulated on the tuberculosis burden in India[7], anti tuberculous therapy was empirically initiated. It was stopped after 7 days due to unremitting CNS irritation symptoms.

Inj. methylprednisolone 30mg/kg/day was commenced on day 10 of admission, in view of autoimmune encephalitis as a diagnosis of exclusion, and was continued for 6 days. Patient symptoms were noticeably relieved. It was then switched to an oral steroid therapy-prednisolone 1mg/kg/day which was to be continued for at least 3 to 6 months during which regular follow up is mandatory.

Interestingly, throughout the course of stay, blood pressure remained within physiological limits with no signs or symptoms of increased intracranial pressure.

At discharge, it was advised that patient undergo regular follow-up for the CNS symptoms and growth monitoring.

Outcome and Follow Up:

Following pulse steroid therapy 2mg/kg/day, the patient showed significant improvement with resolution of nearly all complaints. Patient is symptomatically better and clinically stable with all clinical parameters within normal range. Additionally, Serum NMO with MOG antibody profile turned out to be negative. However, the patient displayed features of Cushingoid status prompting an adjustment in the dose of oral steroids to 10 mg OD as well as increasing the frequency of follow up appointments to closely monitor for further signs of steroid toxicity. Following these changes, the severity of the features has significantly decreased.

Discussion:

Seronegative autoimmune encephalitis poses several challenges in its diagnosis and management. Being a diagnosis of exclusion, all other diagnoses must be eliminated to make a conclusive diagnosis which is quite challenging. And due to the specificity and sensitivity issues of the test for autoimmune panel, it is likely that a large number of cases go unreported.

It is postulated that there is a multifactorial process involved in the onset of the disease including but not limited to tumors[9] and infections [10].

Due to the increase in the number of cases diagnosed as Acute Encephalitis Syndrome (AES), an ambiguous diagnosis that covers a wide etiology, empirical therapy for any patient present with symptoms that fit the picture is necessitated. [8]

Recent studies have indicated higher risk of development of epilepsy post treatment of autoimmune encephalitis, as well as impairment of verbal comprehension index, working memory index and most concerningly, executive function [10]. Therefore, developmental history and scholastic performance are regularly evaluated.

Conclusion:

This case highlights the diagnostic challenges and therapeutic success in treating seronegative autoimmune encephalitis in a pediatric patient. It emphasizes the importance of clinical vigilance, even when serological tests are negative, and the potential for a positive response to immunotherapy. Further research is needed

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to improve diagnostic strategies and understanding of this rare, but potentially devastating condition.

Table 4 Proposed classification criteria for possible, definite antibody-positive and probable antibody-negative pediatric AE

		Diagnostic categories		
Categorical features of AE	**Specific diagnostic features**	Possible AE	Probable antibody-negative AE	Definite antibody-positive AE
1. Evidence of acute or subacute symptom onset	Onset of neurologic and/or psychiatric symptoms over ≤3 mo in a previously healthy child	Yes	Yes	Yes
2. Clinical evidence of neurologic dysfunction	Features include:	≥2 features present	≥2 features present	≥2 features present
	Altered mental status/level of consciousness or EEG with slowing or epileptiform activity (focal or generalized)			
	Focal neurologic deficits			
	Cognitive difficulties[a]			
	Acute developmental regression			
	Movement disorder (except tics)			
	Psychiatric symptoms			
	Seizures not explained by a previously known seizure disorder or other condition			
3. Paraclinical evidence of neuroinflammation	Features include:	Not available	≥1 features present	≥1[b] features present
	CSF inflammatory changes (leukocytosis >5 cells/mm^3 and/or oligoclonal banding)			
	MRI features of encephalitis			
	Brain biopsy showing inflammatory infiltrates and excluding other disorders			
4. AE serology	Presence in serum and/or CSF of well-characterized autoantibodies associated with AE	Not available	No	Yes
5. Exclusion of other etiologies	Reasonable exclusion of alternative causes, including other causes of CNS inflammation	Yes	Yes	Yes

Abbreviation: AE = autoimmune encephalitis.
[a] Severe cognitive dysfunction that is not attributable to a primary psychiatric syndrome as documented by a qualified clinician (e.g., neurologist, psychiatrist, and neuropsychologist) or a significant drop in IQ (>20 points).
[b] When antibodies against NMDA receptor, gamma-aminobutyric acid A receptor, or glutamic acid decarboxylase 65 are present in CSF, further paraclinical markers of neuroinflammation are not required to diagnose definite AE. When only serum antibodies are present, one or more paraclinical marker(s) of neuroinflammation is required.

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