



Laboratory Confirmation of Treatment Effectiveness for NMDA Receptor Encephalitis in Absence of Clinical Findings

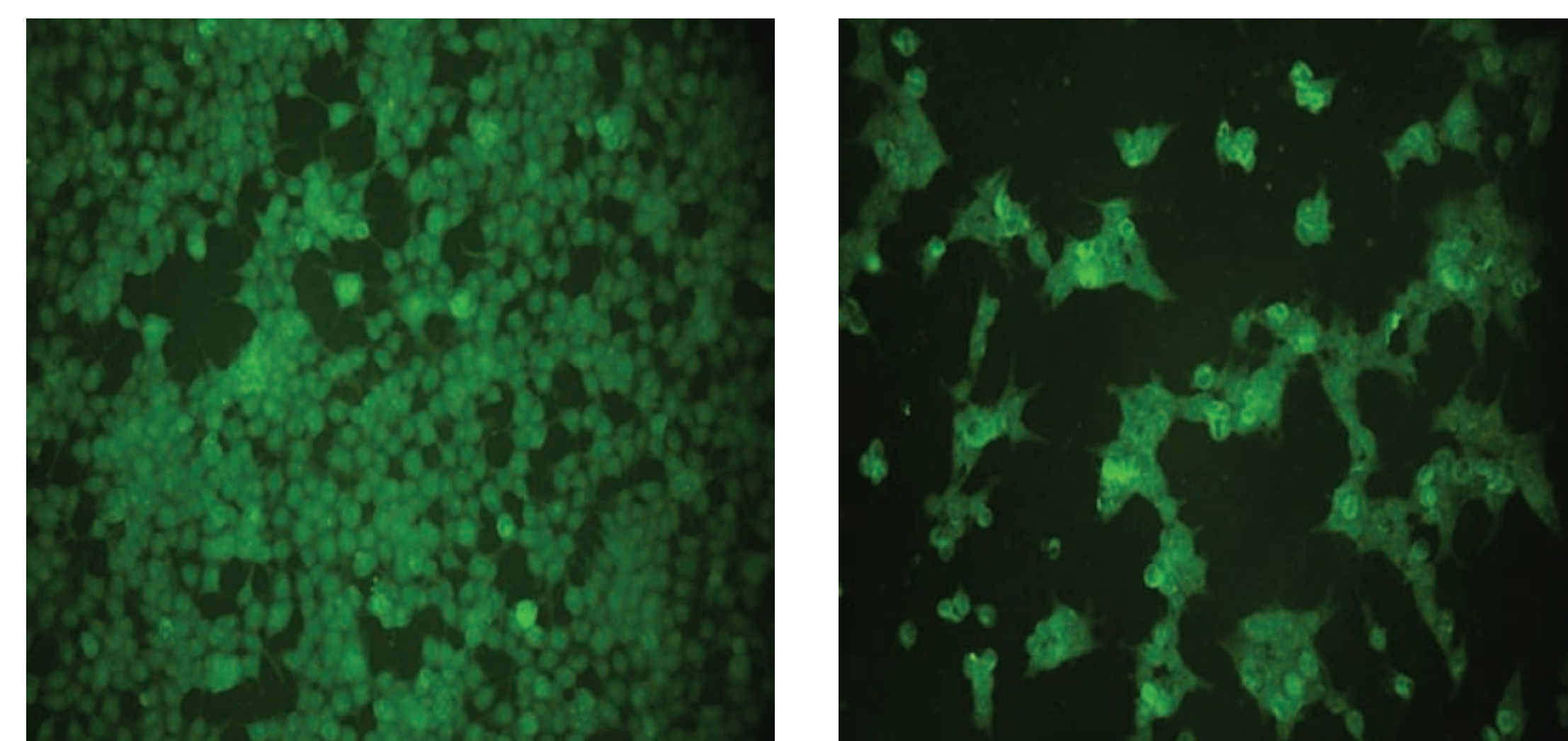
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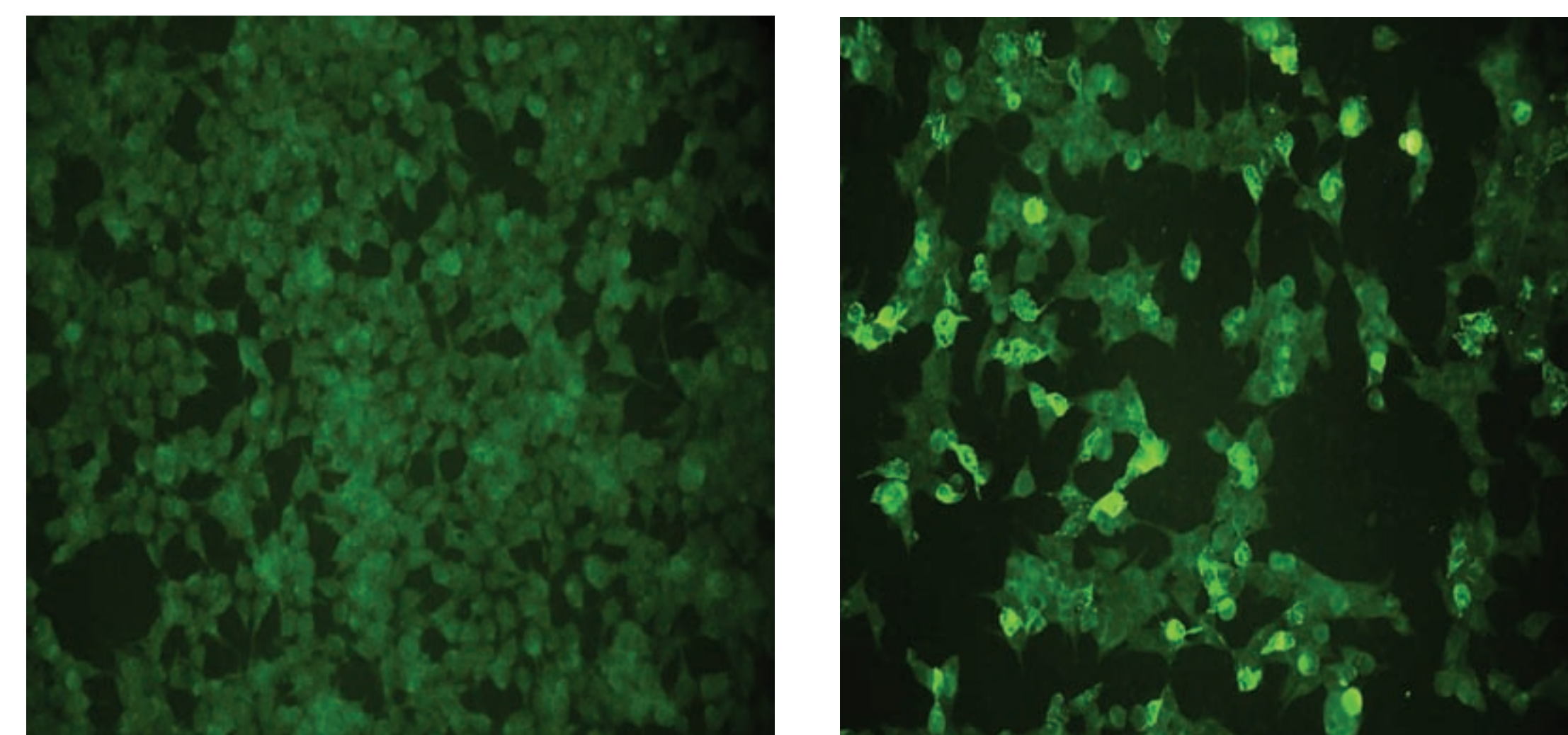
BACKGROUND

NMDA receptor encephalitis is a rare, debilitating disease that requires a high index of suspicion for diagnosis, but specific testing is available. Typically associated with paraneoplastic syndromes, this disease has been described in absence of neoplasm; a condition that often yields a more challenging treatment course. Treatment can sometimes require trials with numerous agents before clinical improvement is seen. Furthermore, there is often a delay from the start of a treatment regimen until symptom improvement is realized. We present a means of monitoring treatment effectiveness through serial measurements of antibody titers in the CSF. This report demonstrates that improvement in laboratory sampling may precede improvements in clinical symptoms and serve as a guide for treatment effectiveness.

Figure 1: HEK cell line transfected with NR1 subunit and tested with serum at 1:10 starting dilution with subsequent two-fold dilutions



Negative Serum



Positive Serum

CASE REPORT

A 7-year previously healthy boy presented to the ED with acute onset of left hand shaking, lip-smacking, and chewing noises. Father observed excessive motor activity during sleep. He complained of headache 3 days prior to admission and generalized head pain before going to sleep. The next day, he presented to the hospital with continuous orofacial dyskinesias and left arm non-rhythmic, choreo-athetoid movements, dystonic-like posturing of the left arm and hand, and left face grimacing. On admission, CT and MRI of the brain were performed and normal. A 24 h EEG demonstrated persistent 2 to 3 Hz high amplitude slow waves with focus in the right central parietal region spreading over the entire right hemisphere, but no clear epileptiform discharges. These findings were associated with intermittent rhythmic twitching of the left upper extremity and thought to suggest partial-onset seizure arising from the right central parietal region. A 24 hour video EEG was performed which yielded similar findings except that there were also occasional right frontal sharps during sleep with no clinical association. It was noted that during sleep despite persistent right hemisphere slowing, the abnormal movements mostly stopped. Treatment with valproic acid, fosphenytoin and clonazepam for partial onset seizures was initiated. Due to a borderline positive ASO titer (200 IU.mL), Sydenham's chorea was considered and treated with amoxicillin. His movements did seem to modestly improve and he was discharged home with close neurology follow up.

Three days following this initial discharge, he returned to the neurology clinic with periods of unresponsiveness to external stimuli, incontinence and inability to ambulate or speak and was subsequently readmitted for further evaluation. Initial CSF sampling revealed an elevated total nucleated cell count (16 cells/hpf) with lymphocytic predominance (96%), low protein (12mg/dL) and normal glucose (63 mg/dL). Laboratory tests failed to reveal any underlying infectious etiology for the encephalitis. Further workup including MRI abdomen, nuclear medicine bone scan, and CT of chest, brain, neck. Abd/pelvis were essentially normal with the exception of some pneumonitis and a left renal cyst. Repeat EEG, now 9 days from his original admission showed continuous generalized 2-3 Hz delta slowing with amplitude of 80-90 microvolts and absence of consistent alpha rhythm suggestive of diffuse cerebral disturbance or encephalopathy. EEG also showed continuous high amplitude and delta slowing of right parieto-occipital region indicating subcortical dysfunction in this area. No epileptiform discharges were seen despite continuous movements of left arm and eyes. Follow-up MRI of the brain progressively showed probable restricted diffusion in both cerebellar hemispheres, and subtle corresponding increased FLAIR signals in the inferior portion of both cerebellar hemispheres and the superior portion of left cerebellar hemisphere, concerning for cerebellitis. The lateral and third ventricles were also very mildly increased in size compared to prior.

Evaluation of his CSF by a cell-based indirect immunofluorescence assay for the presence of N-methyl-D aspartate receptor (NMDAR) antibodies confirmed the diagnosis of NMDAR encephalitis. Later, an initial antibody titer of 1:160 was determined.

Treatment protocols of steroid, IVIg therapy and plasmapheresis failed to reduce symptoms and he had minimal response to anti-seizure medication. His movement disorder progressed and continued to worsen despite ongoing treatment with clonazepam, trihexyphenidyl and fosphenytoin. A gastrostomy tube was placed due to the inability to provide adequate enteral nutrition. Two weeks into his hospitalization, he transferred to the ICU secondary to respiratory failure requiring mechanical ventilation and pharmacologic paralysis as a consequence of his dystonia. A tracheostomy was placed secondary to prolonged respiratory failure.

Treatment with Rituximab was initiated weekly for 1 month with repeat baseline and weekly subsequent CSF samples drawn to monitor the levels of NMDAR antibodies upon discovery of a quantitative result being able to be obtained. Progressive decline in his antibody levels from 1:160 to 1:40 to 1:20 occurred during the following weeks however, daily holidays from paralytic drips revealed little change in his symptoms and were not tolerated for more than a couple of minutes at a time. When NMDAR antibody titers fell to 1:10, he began tolerating the breaks from medical paralysis. Spontaneous breathing trials began shortly after. He was eventually able to tolerate a wheelchair. Although he showed little purposeful movements and minimal ability to respond to communication, his choreoathetosis had considerably improved and was almost nonexistent. He was transferred to a neuro rehabilitation institute for further monitoring and to help facilitate in home training.

DISCUSSION

NMDA receptor encephalitis is a rare, debilitating disease that is most commonly affects young women. Typically associated with paraneoplastic syndromes, most commonly ovarian teratoma, this disease has been described in absence of neoplasm; a condition that often yields a more challenging treatment course. A high level of suspicion is therefore required for diagnosis but specific testing is available. The disease is reversible with 75% of patients fully recover after appropriate treatment (immunotherapy or tumor removal, if required) and 25% left with memory, cognitive, or motor deficits as well as some rare fatalities.

Because the condition is so rare and can present in numerous ways diagnosis is often delayed. Indeed specific antibody testing needs to be sought in order to confirm the diagnosis. Furthermore, treatment of this condition is often difficult and typically undertaken in a step-wise approach. When steroids or IVIg fail to improve symptoms more invasive therapies such as plasmapheresis or direct immune modulation with agents such as Rituximab becomes necessary. To further delay the overall treatment course, often symptom improvement is not seen for a few weeks once responsive treatment is begun.

Once Rituximab therapy was undertaken a decrease in the antibody titer was seen the following week although there was no improvement in the patients clinical situation. Once antibody titers reached a level of 1:10 clinical improvement was observed.

CONCLUSIONS

NMDA receptor encephalitis remains a challenging diagnosis and condition that is difficult to treat. Our observations suggest that serial quantitative measurements of NMDAR antibody levels may indicate effective treatment early following initiation. Therefore, these levels could be used as a surrogate for treatment effectiveness. As this observation is currently made in only one case, further prospective analysis of this hypothesis is warranted.

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