Journal of Neuroimmunology 328 (2019) 76–77

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Association of typhoid fever with anti-NMDAR encephalitis in a young child

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1. Introduction

Anti-*N*-methyl D-aspartate receptor (NMDAR) encephalitis is an autoimmune disorder characterized by production of autoantibodies against the NR1 subunit of NMDAR (Dalmau et al., 2011). The clinical course of the disease passes through five distinct phases described by Iizuka et al. (2008): prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery. Since its first description in 2005 where association was found in young women with ovarian teratomas, it has been increasingly identified in all age groups, particularly children. With improving clinical experience and diagnostic techniques, it has fundamentally changed the approach to neuropsychiatric and encephalitic disorders. We describe a pediatric patient with anti-NMDAR encephalitis who had concomitant Salmonella bacteremia and a good response to first line immunosuppression.

2. Case summary

A previously healthy, 4-year-old girl presented with one month history of low to moderate grade, intermittent fever. There were no localizing symptoms. Parents gave symptomatic treatment for fever and used alternative medicine therapies. Blood investigations done during the second week of fever showed normal blood counts and a positive Widal test (both O and H antigen titer of 1:240), suggestive of typhoid fever. She did not receive any antibiotics. Around 15 days after the fever onset, she started exhibiting behavioral changes. The child became increasingly irritable, restless, agitated, started biting her parents and had episodes of encopresis and enuresis. Sleep wake pattern was altered with increased drowsiness during the day and insomnia at night. At presentation to our hospital, she had low grade fever and stable vital signs but was alternately drowsy and irritable. She did not respond to verbal commands but could localize pain. She appeared restless and would intermittently hit or bite caretakers. There was no focal deficit. Eye examination was normal. There were no meningeal signs, cerebellar signs or cranial nerve palsies. Tone and reflexes were normal. On direct questioning, mother recalled one episode of visual hallucination which had happened 4 days prior.

With this background of febrile encephalopathy with neuropsychiatric manifestations and behavioral abnormalities, a possibility of infectious or autoimmune encephalitis was considered. The patient was started on IV antibiotics, acyclovir and supportive measures. Blood counts, liver and renal function tests, malarial antigen, dengue serology and basic metabolic tests were normal. Cerebrospinal fluid (CSF) showed normal cytology and biochemistry. Gram stain and culture did not show any bacterial growth. MRI Brain with contrast was also normal. Electroencephalography (EEG) showed generalized slowing of background activity with high amplitude delta waves but no epileptiform activity (Fig. 1). On the second day of hospital stay, she developed features of shock and required inotropic support. She started having fluctuations in heart rate and blood pressure which were managed symptomatically.

Blood culture sent at the time of admission grew *Salmonella typhi* which was multi-drug sensitive. CSF viral testing was negative, but CSF anti-NMDAR antibody was positive. Plasma antibody testing was not done at this time. She was started on pulse IV Methylprednisolone for autoimmune encephalitis and IV antibiotics were continued. Within 3 days of starting steroids, child showed significant improvement with resolution of autonomic disturbances, return of normal sensorium, cessation of aggressive behavior and return of normal bowel and bladder habit. Ultrasonography of abdomen did not reveal a tumor. Repeat blood culture was sterile. She was continued on pulse steroids and discharged home on oral steroids after 10 days of hospital stay. Steroids were slowly tapered off over 2.5 months. On 3.5 months of follow up, child is symptom free and back to her pre-illness level of functioning. Plasma anti-NMDAR testing done on follow-up is negative.

3. Discussion

The link between autoimmune CNS disorders and infections is multifaceted. While autoimmune encephalitis is thought to be triggered by infections in many cases, autoimmune mechanisms are postulated to be involved in the pathogenesis of infectious encephalitides. The strongest link comes from the proven association between Herpes simplex encephalitis (HSE) and anti-NMDAR antibodies. Relapse in some patients with HSE has been shown to be linked to the presence of anti-NMDAR antibodies (Prüss et al., 2012). HS virus is also presumed

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https://doi.org/10.1016/j.jneuroim.2018.12.006
Received 2 November 2018; Received in revised form 18 December 2018; Accepted 18 December 2018

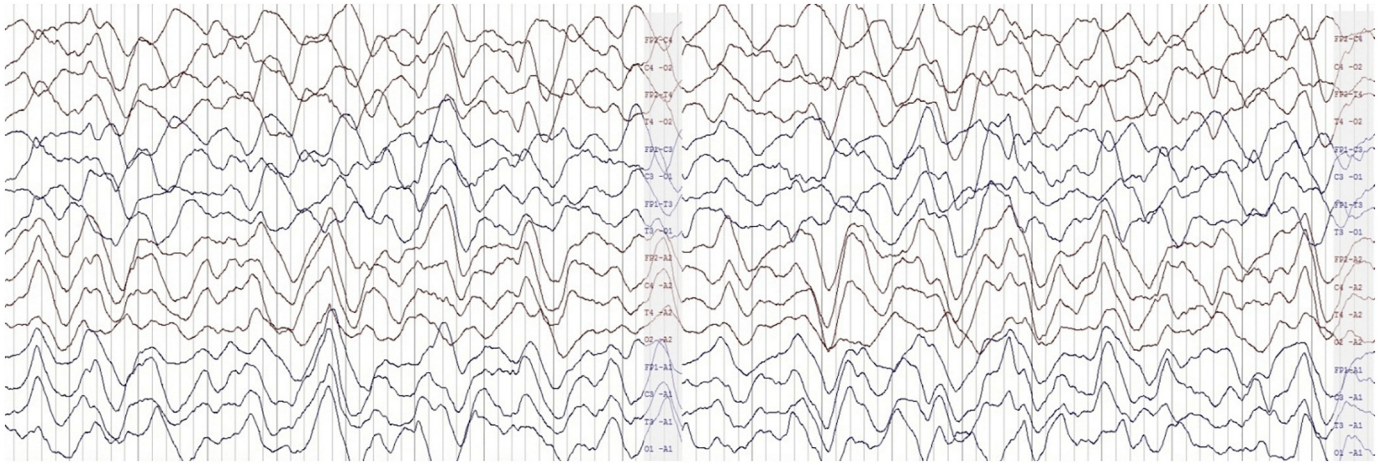

Fig. 1. EEG of the patient showing slow, continuous, high amplitude rhythmic activity in the delta range. No epileptiform discharges were seen.

to be the trigger in many patients with anti-NMDAR encephalitis (Armangue et al., 2014). Overall, around 70% of patients with anti-NMDAR encephalitis show a prodromal phase prior to the onset of CNS symptoms (Dalmau et al., 2011). Many of these patients have a respiratory illness, thus suggesting other viral triggers. The seasonality of anti-NMDAR encephalitis would also suggest the same (Adang et al., 2014). Other infectious agents, including varicella-zoster virus (Schäbitz et al., 2014), Mycoplasma pneumoniae (Gable et al., 2009), H1N1 (Baltagi et al., 2010), HHV6, mumps, enterovirus have also been linked. Vaccinations such as TdaP-IPV, H1N1 and Japanese encephalitis vaccine have also been implicated as triggering factors (Dalmau et al., 2011; Hofmann et al., 2011; Wang, 2017).

Our patient is unique because she was found to have *Salmonella typhi* bacteremia concomitant with CSF anti-NMDAR autoantibodies. We could not find any previous report of *Salmonella* infection or typhoid fever acting as the trigger for autoimmune encephalitis. Typhoid fever is an endemic water-borne infection in many developing countries including India and is itself commonly associated with many neurological manifestations, such as encephalopathy, neuropsychiatric disorders, cerebral edema, cerebellar ataxia, Parkinsonism, acute disseminated encephalomyelitis and brainstem encephalitis. Rare presentations include neuropathy, Guillain-Barre syndrome, transverse myelitis, myositis etc. The frequency of enteric encephalopathy has decreased in recent times owing to better available diagnostic and treatment modalities, but the emergence of drug resistant bacteria has changed the spectrum (Ali et al., 1997; Osuntokun et al., 1972). Neurological manifestations of typhoid fever can appear anytime during the illness and their mechanism is unclear. Endotoxemia and autoimmune mechanisms are considered to be likely pathways. The therapeutic response to steroids further strengthens the likely role of autoimmune pathways (Chisti et al., 2009; Ichikawa et al., 2009). In our patient, the possibility of enteric encephalopathy was considered but the preponderance of behavior and personality changes, lack of neurological signs, autonomic manifestations, normal CSF examination and normal neuroimaging pointed us towards an autoimmune encephalitis.

The possible triggering effect of typhoid fever in anti-NMDAR encephalitis needs to be considered. Given the prevalence and endemicity of typhoid fever in India, it has important diagnostic considerations. Also, in previously reported studies of enteric encephalopathy, autoimmune testing has not been performed. We suggest that a subset of these patients may have had specific autoimmune mechanisms, such as, anti-NMDAR antibodies as the pathway. In paraneoplastic or HSE mediated anti-NMDAR encephalitis, exposure of naïve B cells to NMDAR has been postulated to be the underlying mechanism (Dalmau, 2016). A similar mechanism involving molecular mimicry by *Salmonella typhi* and generation of antigen- experienced memory B cells and CNS plasma cells may be involved in typhoid fever associated autoimmune encephalitis.

However, since this observation has been made in a single patient, it is possible that it might be a circumstantial finding. Nevertheless, a high index of suspicion should be maintained to differentiate possible autoimmune encephalitis from presumed infectious encephalitis. It remains to be seen whether routine testing for autoantibodies in patients with CNS symptoms and enteric fever will confer any advantage in terms of treatment and outcome.

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