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NORSE Following Viral Infections Like Covid 19

Fiju Chacko, Rohith PS

Baby Memorial Hospital, Kozhikode, Kerala, India. PIN: 673004

Address for Correspondence: Dr. Fiju Chacko, MBBS, MD, DM (Neurology), Professor of Neurology, Jubilee Mission Medical College, Thrissur, Kerala, India. E- mail: drfiju@gmail.com

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New-onset refractory status epilepticus (NORSE) and its subcategory febrile infection-related epilepsy syndrome (FIRES) are rare devastating clinical presentations in those without pre-existing relevant history, often in schoolchildren or young adults, without a clear cause on initial investigations. A cause may later be identified in up to half of them. NORSE can rarely occur as a consequence of COVID-19. NORSE can be defined as refractory status epilepticus in patients without history of seizures and without a clear acute or active structural, toxic or metabolic cause. The most commonly identified cause of NORSE is autoimmune encephalitis. Patients with refractory status epilepticus caused by anti N-methyl-D-aspartate receptor (NMDA) encephalitis without lung involvement have been recently reported in COVID-19 patients such as probable autoimmune encephalitis and encephalomyelitis [1,2]. NMDA encephalitis is one of the most frequent cause of autoimmune encephalitis and it may be triggered by viral infections, particularly Herpes Simplex Virus [3,4]. NMDA encephalitis was reported more than a decade ago, a classical patient usually is a young lady with psychiatric symptoms, refractory seizures, dyskinesia, autonomic instabilities and respond well to immunotherapy IVIG, plasma exchange and rituximab. First Indian case was reported a couple of years later from Kochi - a patient with refractory seizures on ventilator who responded well to immunotherapy [5]. Early initiation of immune therapy (steroids, intravenous immunoglobulins, and plasma exchange) is recommended for autoimmune encephalitis-related NORSE treatment and a delay in treatment often contributes to worse outcome.

A wide variety of neurological manifestations can occur in COVID-19 patients. They may include several syndromes and a suggested autoimmune abnormal response, which may result in encephalitis and NORSE.

Pathogenesis

Upon nasal infection, coronaviruses enter the CNS through the olfactory bulb, causing inflammation and demyelination [6]. A growing number of case reports and series describe a wide array of neurological manifestations in the context of SARS-CoV-2 infection. Encephalitis associated with COVID-19 have been associated with irritability, confusion, drowsiness, and new-onset epilepsy represent one of the main symptoms at onset [2,3].

Evidence suggests a direct neuronal injury, as indicated by increased serum neurofilament light chain (sNfL) levels, in critically ill COVID-19 patients compared to critically ill non-COVID-19 patients [6]. Although the exact pathophysiological mechanisms underlying the development of neurological syndromes are not completely appreciated, some explanatory mechanisms are currently debated, such as [4]:

* Systemic inflammatory response

* Prothrombotic state

* Direct viral invasion

* SARS-CoV-2 infection could trigger autoimmune responses, with a Central Nervous System (CNS) involvement

Differential diagnoses

Metabolic and viral encephalitis, cerebral thrombosis, posterior reversible encephalopathy (PRES), acute disseminated encephalomyelitis (ADEM), and cerebral vasculitis have to be excluded before making the diagnosis of possible autoimmune encephalitis. The time correlation between SARS-CoV-2 infection, neurological symptoms onset, and negative PCR for other viruses on CSF suggests a possible causative role of the SARS-CoV-2 infection in the development of post-acute autoimmune NORSE. The outcome is commonly fatal or burdened by severe neurological sequelae.

Evaluation

Electroencephalography (EEG), routine blood chemistry analyses, and a panel of diagnostic testing, including neuroimaging and biomarkers are needed. Cerebrospinal fluid (CSF) analyses including pressure, cell count, proteins, and glucose. CSF culture and polymerase chain reaction (PCR) for possible organisms, such as bacteria, Mycobacterium tuberculosis, fungi, Herpes viruses, Enteroviruses, Japanese B virus, and Dengue viruses including analysis for SARS-CoV-2. Serum and CSF to be tested for onconeural antibody, such as antiampiphysin, antiCV2, antiMa2/TA, antiRI, antiYo, antiHu, antirecoverin, antiSox1, antititin, antiZic4, antiGAD65/67 (Anti-Glutamate Decarboxylase), antiTr, and antineuronal surface antigens antibodies, as antiNMDAr (N-methyl-D-aspartate receptor), antiVGKC (voltage gated potassium channel), complex LGI1 (leucine-rich glioma inactivated 1) and CASPR2 (Contactin-associated protein-like 2), antiAMPA1r (Anti- α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), antiAMPA2r, antiGABABr (Gamma-aminobutyric acid), antiDPPX (dipeptidyl-peptidase-like protein 6).

A high index of suspicion is essential in diagnosis, especially in those presenting with primarily psychiatric features and is often supported by the development of 'neurological' features, such as dyskinesia and refractory seizures [7]. Quickly recognizing such cases and starting the most appropriate therapy is mandatory as it can be associated with rapid worsening and bad outcomes.

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