

### Diagnosing SARS-CoV-2 related NMDAR-positive immune encephalitis requires documentation of a time-linked COVID-infection

We read with interest the article by Luizaga et al. about a two years old, previously healthy male who developed abnormal movements, falls, and recurrent unilateral facial weakness.<sup>1</sup> Hospital work-up 48 hours after onset did not disclose an explainable cause, why he was discharged again after 24 hours.<sup>1</sup> Because manifestations progressed over the next days, and because he additionally had developed dysphagia, he was hospitalised a second time 14 days after onset of symptoms.<sup>1</sup> The second work-up revealed quadraparesis, choreo-athetosis, dystonia, aphasia, episodes of crying, irritability, and dysphagia.<sup>1</sup> Upon positive oligoclonal bands, diffuse delta-activity on electroencephalography (EEG), and elevated antibodies against the N-methyl-d-aspartate receptor (NMDAR) in the serum and cerebrospinal fluid (CSF), the patient was diagnosed with autoimmune encephalitis.<sup>1</sup> Because IgG and IgM antibodies against SARS-CoV-2 were positive in the serum, autoimmune encephalitis was interpreted as driven by a previous SARS-CoV-2 infection.<sup>1</sup> Partial recovery could be achieved after 18 days of hospitalisation upon steroids, intravenous immunoglobulins (IVIGs), physiotherapy, speech therapy, and occupational therapy.<sup>1</sup> The study is promising but raises concerns that should be discussed.


We disagree that there is a causal relation between SARS-CoV-2 and NMDAR positive immune encephalitis. IgG antibodies against SARS-CoV-2 can persist up to 7 months after the infection<sup>2</sup> and IgM antibodies against SARS-CoV-2 have been reported to persist up to 8 months after the acute infection.<sup>3</sup> Assuming that these antibodies in the serum of the index patient were produced already several months earlier, a causal relation between SARS-CoV-2 and immune encephalitis is rather unlikely. Only, if we assume a SARS-CoV-2 infection shortly prior to onset of immune-encephalitis, a causal relation would be conceivable. However, there were no clinical indications for a symptomatic SARS-CoV-2 infection shortly before onset of immune encephalitis.

Furthermore, it is not understandable why the comprehensive diagnostic work-up did not start earlier than two weeks after onset of the progressive manifestations. We should know why

diagnostic work-up during the first hospitalisation was limited to blood tests and imaging and why no forced work-up was pursued. It is also not mentioned which type of tomography was carried out at the initial visit to the hospital 48 hours after onset of the neurological abnormalities.<sup>1</sup> It is also not indicated if contrast medium was applied or not. We should be informed if the patient had undergone a cerebral magnetic resonance imaging (MRI) or a cerebral computed tomography (CCT) scan and if contrast medium was applied or not. In a previously healthy child who experienced falls, intermittent facial weakness, and abnormal movements, it is justified to make every conceivable effort to clarify the cause of such abnormalities.

There is a discrepancy between the first and the second evaluation.<sup>1</sup> Initially, the patient was described with “abnormal movements.” Since the patient was diagnosed with acute ataxia in the first hospital, we assume that the abnormal movements were interpreted as ataxia. However, during the second hospitalisation the patient was diagnosed with chore-athetosis. This discrepancy should be solved. Particularly, we should know if there was a change in the clinical presentation or if “abnormal movements” were initially misinterpreted as ataxia. It is also unclear, which type of dystonia was diagnosed in the index patient.

Overall, the interesting study has limitations that call the results and their interpretation into question. Clarifying these weaknesses would strengthen the conclusions and could improve the study. In a child with progressive cerebral abnormalities it is crucial that every effort is made to clarify the cause of these abnormalities as soon as possible.

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### *In answer*

### **Possibility of a temporal relationship between SARS-CoV-2 infection and the development of immune-mediated encephalitis**

*Mr. Editor:*

We thank J. Finsterer for his comments regarding our article.<sup>1</sup> We appreciate your feedback on our article and would like to encourage discussion as from your input. We will address the points raised by the author in the same order in which they were listed.


Although the literature establishes that SARS-CoV-2 antibodies may remain detectable in blood for several months, if we consider that the first case of Covid-19 in Argentina was confirmed on March 3<sup>rd</sup>, 2020<sup>2</sup> and that in our patient the serological test to detect antibodies was performed on July 2<sup>nd</sup>, 2020, it is reasonable to suspect that the infection preceded the development of encephalitis by a short period of time. Looking at the incidence of infections during this period, it is more likely that the infection was at some time closer to July than to March.<sup>2,3</sup>


Clinical research has shown that postviral autoimmune encephalitis is an established mechanism of disease. The production of virus-induced antibodies might be a generalized mechanism not limited to the herpes simplex virus and to the anti-N-methyl-D-aspartate receptor (NMDAR) antibodies.<sup>4</sup>

The absence of clinical manifestations suggestive of acute SARS-CoV-2 infection does not rule it out. In our country, 21% of confirmed pediatric cases have been described as asymptomatic,<sup>3</sup> and an even higher prevalence is suspected among asymptomatic pediatric patients

in whom screening was not performed. Therefore, ignoring the possible temporal association between the past infection and the current clinical features could be an error on our side.

Regarding failure to perform extensive ancillary tests at the onset of clinical signs and symptoms, it is worth pointing out that the patient's initial care was provided at another facility. Last but not least, early clinical manifestations were described on the basis of the information provided by the patient's parents. We understand that there is no disagreement, since we are not describing a clinical evaluation preceding ours. The report detailed the topography of dystonia regarded as secondary to encephalitis.

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