Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

European Journal of Paediatric Neurology 39 (2022) 118–119

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

journal homepage: www.journals.elsevier.com/european-journal-of-paediatric-neurology

Neurologic manifestations in children with COVID-19

We read with great interest the letter by Josef Finsterer, MD, PhD and Daniel Matovu, PhD regarding our paper on neurologic manifestations in children with COVID-19. We thank the authors for their interest in our study. Most of our replies to the questions and comments by the authors of the letter had been already provided in the paper and will be merely a repetition, however we hope it will be helpful for the readers interested in the topic.

The paper includes 15 pediatric patients with COVID-19 who were admitted to the hospital and who had new onset neurological findings, and also a review of the literature which as the authors state, covers the broad spectrum of neurological findings of COVID-19 [1]. Even in our cohort of 15 patients, we observed a broad range of neurological findings across childhood ranging from infancy to adolescence, involving both para- and postinfectious periods, including -but not limited to-febrile/afebrile seizures, status epilepticus, encephalopathy, abnormal eye movements, increased intracranial pressure, posterior reversible leukoencephalopathy and myositis.

The paper includes the cases we followed during a limited time, and do not include all neurological presentations of COVID-19 in childhood as would be expected from a single center series, and this was addressed in detail in the paper, however the cohort still represents diverse neurological findings in childhood [1].

Patients 14 and 15: Cases with viral myositis due to SARS-CoV-2 and other coronavirus types are reported in literature [2,3]. Myositis can be diagnosed with clinical findings and high creatine kinase level in the presence of viral infection, and usually does not necessitate a muscle biopsy. Magnetic resonance imaging (MRI) studies may be used to rule out alternative diagnoses [4].

Patient 2: The patient indeed underwent both head computed tomography and brain MRI study with contrast and findings are summarized in Table 2 [1]. The patient showed no contrast enhancement, abnormal findings are included in the paper. The clinical findings were self-limited and resolved within two days which is an unlikely course for brain stem encephalitis. SARS-CoV-2 infection is regarded as the potential cause of acquired abnormal eye movements in the context of the present outbreak and the relationship between symptoms and positive IgG serology [5].

Patient 5: The patient had a complicated course with prior arterial ischemic stroke thought to be associated with Factor V Leiden mutation and had been maintained on aspirin prophylaxis before admission to our hospital. He was admitted with new onset neurological symptoms and underwent third ventriculostomy for treatment of hydrocephalus [1]. As mentioned in the paper, MRI showed triventricular hydrocephalus associated with aquaductal stenosis and increased leptomeningeal contrast enhancement. This patient had a thick aquaductal band. We consider that there was already a flow-permitting incomplete aquaductal web and it was oblitered due to inflammation. As mentioned in the paper and tables, this patient had normal cerebrospinal fluid (CSF) glucose and protein, negative bacterial culture and negative viral encephalitis PCR panel. Of note, CSF cytocentrifuge and cytopathologic examination revealed activated lymphoid cells, monocytes, ependymal cells, and activated macrophages. As we mentioned in our discussion, presence of increased numbers of lymphocytes and macrophages in CSF samples has been previously reported in literature, suggestive of microglial activation [6,7]. We therefore consider this finding as an evidence supporting increased inflammatory response.

Patient 8: As already mentioned in the paper, the patient had suffered from headache, diplopia on admission [1]. He had 6th nerve palsy, and ophthalmologic examination revealed Grade 4 papilledema. Intracranial hypertension was confirmed based on spinal tap. The cerebrospinal fluid opening pressure was high as presented in Table 1 [1].

Patient 9: As mentioned in the paper, the patient had serial cranial MRI studies including DWIs and SWIs, and MR angiographies (MRA) that revealed infra- and supratentorial multiple microhemorrhages, suggestive of small-vessel vasculitis, bilateral middle cerebral artery stenosis and irregularity consistent with medium-vessel vasculitis and meningioependymal contrast enhancement [1]. The acute phase reactants (sedimentation and C-reactive protein) had an alternating course with high and normal values, ANA and ANCA were not checked. Cerebral computed tomography angiography and a brain biopsy were not performed, as diagnose could be made with the existing results. However, a biopsy can be done on selected cases as an invasive procedure. Previous reports showed cranial vasculitis in COVID-19 patients, most of them were diagnosed by neuroimaging studies, some also had biopsy [8,9]. Inflammatory processes, dysregulated cytokine cascade autoimmunity, possibly had a role in cerebrovascular events in patients with COVID-19 [10]. Hence, the patient was previously healthy, and the neurologic complaints were in close relationship with MIS-C course, along with MRA findings the patient was diagnosed as secondary cerebral vasculitis due to MIS-C.

Regarding encephalopathy, this was diagnosed according to classical definition; depressed or altered level of consciousness, or altered cognition or personality. Encephalopathy is a well-known clinical picture in pediatric neurology practice and was reported as such in other large series in relevant literature [11].

Patient 12: The patient was hospitalized for 48 days. The information regarding this hospital course was already summarized in Table 1 [1]. To overview again, he was intubated, then underwent noninvasive mechanical ventilation, and received oxygen support in the last days of hospitalization. He underwent the following treatments: Intravenous immunoglobulin (IVIg) steroids, immunomodulatory treatment, plasma exchange, prophylactic anticoagulation, antiviral treatment. He experienced weakness more in the lower limbs and muscle atrophy. He was discharged with moderate loss of muscle strength and needed assistance

https://doi.org/10.1016/j.ejpn.2022.06.004

Available online 13 June 2022

for walking. He had steppage gait, impaired vibration sensation in the lower limbs on the last visit. The electromyography (EMG) revealed motor axonal polyneuropathy in lower extremities. Hence the patient was previously healthy, he developed weakness following his long hospital course, along with therapies he received. Therefore, his motor weakness and EMG results were compatible with critical illness neuropathy [12].

Patient 13: The patient was hospitalized due to rash, conjunctival injection, diarrhea, and abdominal pain, and was eventually diagnosed as MIS-C [1]. He underwent following treatments as already outlined in the paper: IVIg, steroids, immunomodulatory treatment, prophylactic anticoagulation, antiviral treatment. On the 15th day of admission, he experienced tingling and pain in the hands and feet with no motor deficit but hyperesthesia. EMG was within normal limits. The clinical features were suggestive of immune-mediated damage which might have caused neuropathic pain in this patient [13].

Regarding the question on exclusion of patients with headache, loss of taste and smell, our cohort included patients who were admitted to the hospital, therefore had moderate/severe disease course [1]. Symptoms such as headache, loss of taste and smell could have been overlooked by physicians, or not well expressed by patients owing to the severity of the disease, level of consciousness or age. On the contrary, there was a risk for exaggerating the number of patients with these symptoms due to secondary headache associated with hypertension or anemia.

Regarding comments on limitations of the study, we discussed the limitations of our study in detail, emphasizing the retrospective nature of our study and patient selection as a tertiary referral center [1]. The final comment, *'Neuro-COVID of the central or peripheral nervous system is not at variance between children and adults why similarities prevail over discrepancies'* is somewhat unclear to us, albeit this has not been the main focus of our paper. Also, classification of the neurological involvement with regards to localization (central, peripheral and both), timing (para-, postinfectious) or age (childhood versus adults) may help better understanding of disease courses such as COVID-19 with novel and unknown aspects.

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