European Journal of Paediatric Neurology 42 (2023) 117–121

Contents lists available at ScienceDirect

European Journal of Paediatric Neurology

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

Pediatric recurrent acute necrotizing encephalomyelitis, RANBP2 genotype and Sars-CoV-2 infection: Diagnosis, pathogenesis and targeted treatments from a case study

Cristina Forest [a,1], Michele Laudisi [b,1], Cristina Malaventura [a], Valeria Tugnoli [c], Giuditta Pellino [a], Elisabetta Marangoni [d], Eleonora Baldi [c], Luca Borgatti [e], Maura Pugliatti [b,c], Agnese Suppiej [a,*]

[a] Department of Medical Sciences-Pediatric Section, University of Ferrara, Ferrara, Italy
[b] Department of Neuroscience and Rehabilitation, University of Ferrara, Italy
[c] S. Anna University Hospital, Department of Neuroscience and Rehabilitation, Ferrara, Italy
[d] Department of Anesthesia and Intensive Care, University of Ferrara, Ferrara, Italy
[e] Pediatric Neuroradiology, S. Anna University Hospital, Ferrara, Italy

ARTICLE INFO

Keywords:
ANE1
Sars-CoV-2
Pediatric
RANBP2
Mitochondrial homeostasis

ABSTRACT

Acute necrotizing encephalopathy (ANE) is a rare disease not yet described in children with Covid-19. RANBP2 gene variations are implicated in recurrences in the genetic form of ANE, the so called ANE1. We report the first case of pediatric ANE1 following Sars-CoV-2 infection. She had a first episode at 2 years of age following influenza type A with full recovery, many other respiratory and non-respiratory febrile viral infections without recurrences and a severe recurrence following Sars-CoV-2 infection, suggesting a potentiation effect on cytokine cascade. Her MRI showed the typical pattern of injury resembling that of mitochondrial disorders, and supported the role of RANBP2 in mitochondrial homeostasis.

This case rises attention on diagnostic challenges and offers several interesting tips for discussion about new perspectives in pathogenesis and targeted treatments.

1. Introduction

In 1995 Mizuguchi [1] firstly described a case of acute necrotizing encephalopathy (ANE) as a sporadic, non-familial, non-recurrent rapidly progressing encephalopathy triggered by viral infections. In 2009, Neilson et al. [2] reported on familial recurrent ANE linked to missense heterozygous mutations in the RANBP2 gene, coding for a ubiquitously expressed nuclear pore protein with a role in regulation of proteostasis, chemokine signaling, intracellular metabolism, and mitochondrial distribution [3]. To date, 96 ANE1 cases (children and adults) triggered by viral infections have been reported in literature [3].

In December 2019, an outbreak of novel coronavirus infection (Sars-CoV-2) started to spread worldwide causing severe acute respiratory syndrome (COVID-19). A number of neurological disorders have been found in association with both Sars-CoV-2 infection and COVID-19 [4], and among these, severe cases of sporadic acute necrotizing encephalopathy (ANE) have been reported [5]. Patients with ANE are otherwise healthy children who develop a cytokine storm primary in the central nervous system in response to (viral) infection, e.g., Influenza [6].

The genetic form of ANE is referred to as ANE1, a rare disease presenting with encephalopathy following a viral febrile illness in carriers of a missense mutation in the gene encoding RAN Binding Protein 2 (RANBP2) [3]. RANBP2 has been implicated in several cellular processes, and ANE1 pathophysiology could be related to RANBP2-promoted cytokines storm or mitochondrial dysfunction [3,7].

We report the first case of pediatric ANE1 following Sars-CoV-2 infection.

2. Case presentation

A 10-year-old girl accessed the Ferrara University Hospital Pediatric

* Corresponding author. Department of Medical Science, Pediatric Section Arcispedale Sant'Anna, via Aldo Moro n.8, 44124, Italy.
E-mail address: sppgns@unife.it (A. Suppiej).
[1] these authors equally contributed to the manuscript.

https://doi.org/10.1016/j.ejpn.2022.12.010
Received 9 September 2022; Received in revised form 18 December 2022; Accepted 29 December 2022
Available online 4 January 2023

Emergency Department with acute onset of decreased level of consciousness (Glasgow Coma Scale:8 E2, V2, M4) and fever. Her vital signs were stable, in particular she had no signs of shock (heart rate 85 bpm, she had normal breathing with oxygen saturation 97% without respiratory support, blood pressure 125/80 mmHg). She had generalized hypotonia with no posture changes. She had no meningeal clinical signs, no rash. Her pupils were miotic and sluggish. The knee and ankle reflexes were reduced, extensor plantar reflex was present bilaterally, without other neurological signs of corticospinal tract dysfunction. She had absence of gag, oculo-cephalic and corneal reflexes. Family history was unremarkable.

Complete blood count revealed leukopenia and lymphopenia, normal platelet count, with normal levels of C-reactive protein and procalcitonin. Basic metabolic panel, including ammonia, lactic acid and arterial blood gas analysis, was normal. Sars-CoV-2 nasopharyngeal (NP) swab tested positive. Cerebrospinal fluid (CSF) analysis showed an increased protein level (95 mg/dl) without pleocytosis, PCR panel for neurotropic pathogens and for Sars-CoV-2 were negative in CSF. In serum, interleukin (IL)-6 level was in the normal range, CNS auto antibodies including anti-MOG and anti-AQP4 were absent. The search for oligoclonal IgG bands on CSF and serum was negative.

In the acute phase brain and spinal cord magnetic resonance imaging (MRI) confirmed extensive areas of cytotoxic edema in the bilateral thalami, brainstem (pons and midbrain), cerebellar cortex, cervical spinal cord (C3–C4, C5–C6), chiasm and optic tracts (Fig. 1). MRI spectroscopy pattern was suggestive for necrosis. An electroencephalogram (EEG) revealed a slow-wave pattern (delta/theta) with minimal and inconsistent reactivity to noxious stimuli.

Based on clinical presentation, neuroimaging, and CSF findings, a diagnosis of ANE associated with Sars-CoV-2 was made. The score ANESS, described in the literature [8] suggested high risk (brain stem lesions, age over 48 months and CSF protein above 60 mg/dl), the prognostic value is not generally agreed [9].

Already in day 1 the patient was admitted to the intensive care unit (ICU), intubated and mechanically ventilated. As soon as she was admitted to the ICU, she started treatment with Remdesivir and Methylprednisolone (1 gr/day) for 5 days. Following the corticosteroids course the clinical presentation did not improve and imaging worsened with deterioration of the existing lesions and occurrence of new lesions in the cervical spinal cord (Fig. 1). She therefore underwent 5 sessions of plasmapheresis and finally IVIG (2 g/kg/day) for 2 days with no further deterioration.

Subsequent MRI examinations (day 9, day 22, and day 35) documented an improvement of the neuro-radiological picture with marked numerical and dimensional reduction of the hyperintensity areas in FLAIR sequences (Fig. 2).

On day 23, her Sars-Cov-2 NP swab test was negative, the patient was transferred to the neurorehabilitation ward still comatose (GCS 7: E1, V1, M5) with spontaneous breathing via tracheostomy. Unfortunately, more standardized outcome measures are not available.

Of note, at age 2 years, the patient was admitted to pediatric intensive care unit (PICU) with fever, flu symptoms and mental confusion. In that occasion, CSF analysis showed only a slight hyperproteinorrachia (60 mg/dl) and brain MRI revealed hyperintensity of external capsules, cerebellar cortex, hypothalamus and pons on fluid attenuated inversion recovery (FLAIR) sequences with restricted diffusion on diffusion-weighted images (DWI) and without contrast enhancement (CE) (Fig. 3, a-f). At that time NP swab tested positive for Influenza A. She was treated with methylprednisolone (20 mg/kg/day) for 3 days and intravenous immunoglobulin (IVIG) (2 g/kg/day) for 2 days with clinical-radiological improvement (Fig. 3, g-j). She was then discharged home on day 30 after admission with mild dysarthria and walking impairment and diagnosis of atypical acute disseminated encephalomyelitis (ADEM). After 8 months from admission the neurological examination was reported to be normal. Since then she has had other febrile upper respiratory tract viral infections, without neurological symptoms. Her development was reported to be normal. The patient never underwent anti-Sars-CoV-2 vaccination because her parents feared possible ADEM relapses.

Due to recurrent episodes of infection-related encephalopathy

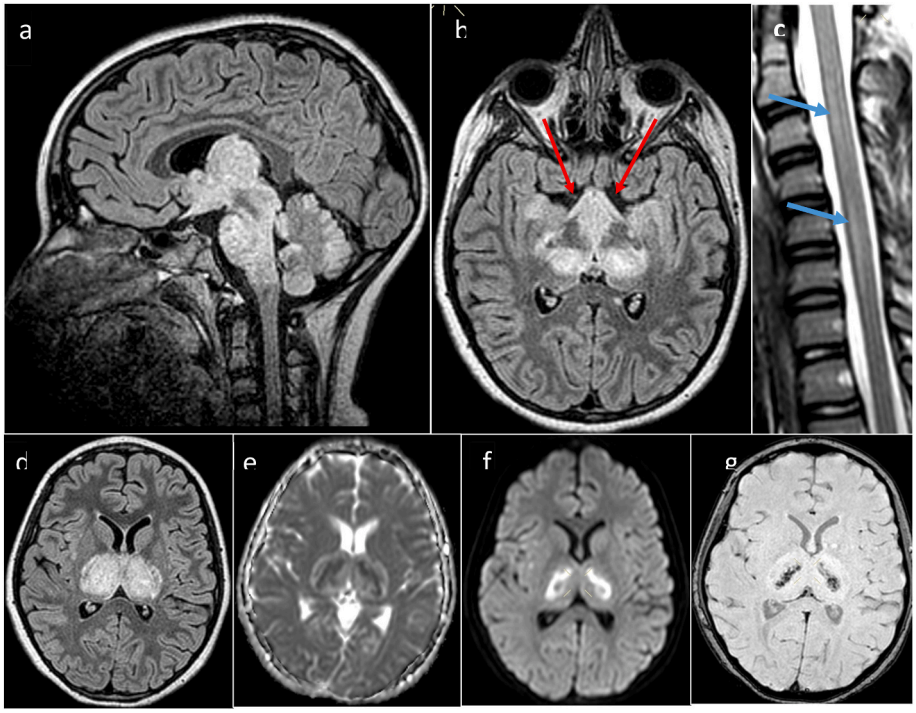

Fig. 1. FLAIR hyperintense areas (a, b, d) in the thalami, pons, midbrain, cerebellar cortex, chiasm and optic tracts (red arrows). T2 hyperintense lesions in the cervical spinal cord (c, blue arrows). Bilateral thalamic involvement with central necrosis and hemosiderin deposit (FLAIR, d; ADC, e; DWI, f; SWI, g). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

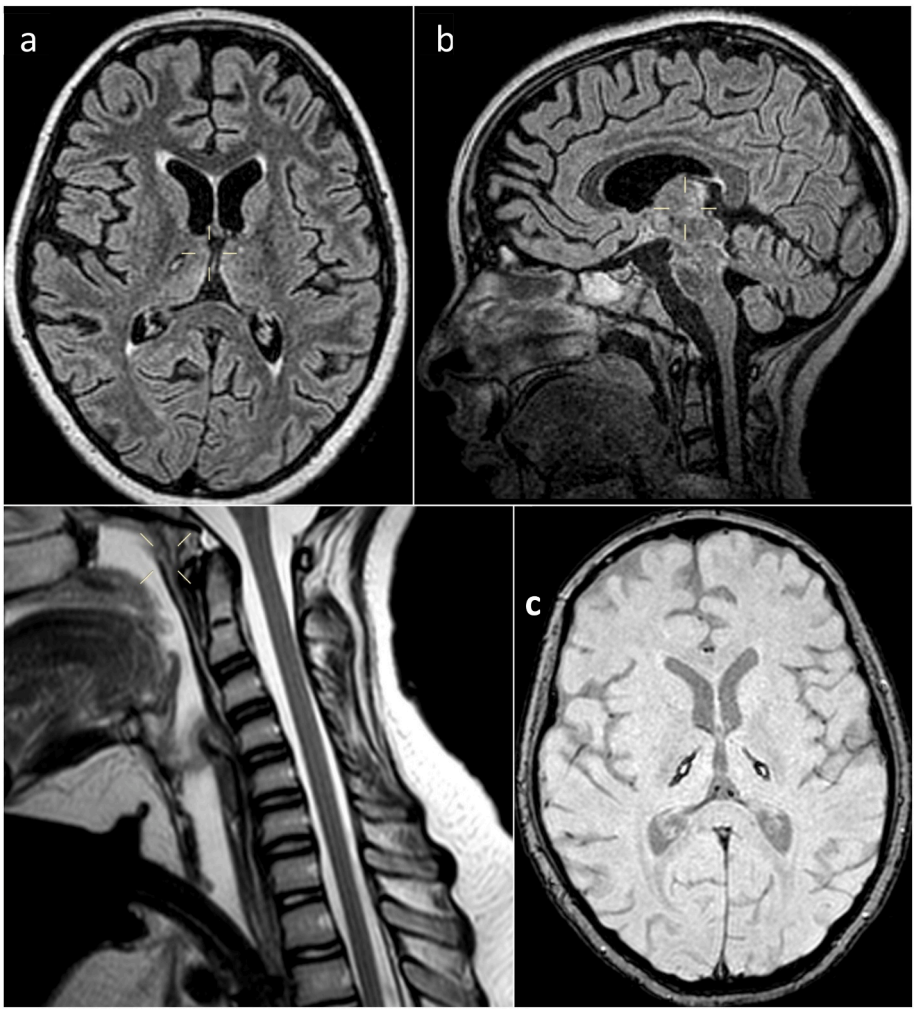

Fig. 2. MRI at day 35 after symptoms onset. Sharp reduction of FLAIR hyperintensities in the brain stem, thalami and cerebellar cortex (a, b); disappearance of cervical spinal cord lesion (c); residual hemosiderin deposition in necrotic areas in both thalami (d).

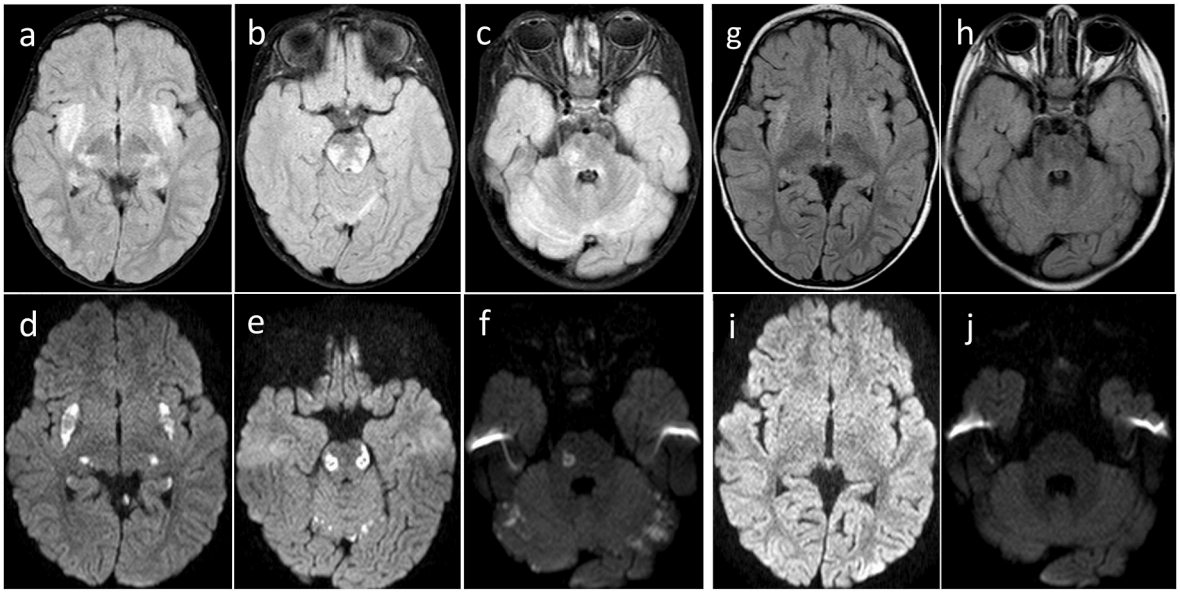

Fig. 3. MRI study at patient's first episode (age 2 years). FLAIR-STIR areas (a,b,c) of hyperintensity involving external capsules, cerebellar cortex and pons with restricted diffusion on DWI (d,e,f); MRI hyperintensity reduction in FLAIR-STIR (g, h), without restricted diffusion on DWI (i,j) at day 22 after symptoms onset.

suggestive of ANE, a whole-exome sequencing of patient and parent DNA targeted on ANE1 phenotype was performed, which revealed c.1754C > T p.(Thr585Met) de novo mutation in heterozygous state on RANBP2 gene, already known in literature as pathogenic.

3. Discussion

We report on the first case of genetically confirmed ANE1 after infection with Sars-CoV-2 in a child.

The diagnosis in ANE and ANE1 is suggested by MRI typically showing symmetric and diffusion restricted hyperintense T2 signal prolongation in the thalami, brainstem and cerebellum, sometimes associated with lesions in the cervical spinal cord, medial temporal lobes or insular cortex, and in other subcortical regions including mammillary bodies, hippocampus, amygdala, claustrum, and external capsule [6,10]. The differential diagnosis between ADEM and ANE needs implementation of standard MRI sequences with apparent diffusion coefficient calculation and susceptibility weighted imaging, in order to distinguish cytotoxic from vasogenic edema and to detect microhaemorrages, as demonstrated by the reported case. Moreover, differently from isolated ANE, patients with ANE1 could present involvement of additional CNS structures, including the external capsule and claustrum, medial temporal lobes and limbic structures including amygdalae, hippocampi and spinal cord. It is noteworthy to mention that, during the episode occurring at the age of two years, our patient presented MRI lesions typically involving the external capsules and at that time ANE1 could be suspected [11]. Interestingly, our case also featured an involvement of the optic chiasm and the optic tract bilaterally, which, to the best of our knowledge has never been reported in literature before. This peculiar radiological feature could depict an even rarer variant of ANE1 overlapping with other CNS leucoencephalopathies such as neuromyelitis optica spectrum disorders (NMOSD). However, in our patient anti-AQP4 antibodies were absent.

Due to the inflammatory pathogenesis of ANE, immunotherapy with corticosteroids and intravenous immunoglobulins is usually the first line therapy [6]. Sometimes plasma exchange or interleukin-6 receptor blockage could be employed. Considering the severity of ANE, plasmapheresis was preferentially performed. Since IL-6 level was normal we did not treat the patient with IL-6 receptor blockage, considering also that treatment used already stabilized the clinical and neuroradiological progression. However, the treatment with Tocilizumab, a recombinant humanized monoclonal blocking the IL-6 receptor should be considered since it has been successfully used in some cases even in the absence of raised IL-6 levels [12].

There is still lack of consensus on the best second line therapeutic strategy, particularly in ANE1 [6]. In these patients, immunoprophylactic treatment to prevent ANE recurrences is suggested [6].

One other issue raised by our case is the role of vaccination in general. Our patient had completed the standard vaccination schedule without complications, but she had not been vaccinated for Sars-CoV-2. Despite controversial reports, some vaccines, such as the flu vaccine, appear to be safe in ANE1 and can even prevent disease recurrence triggered by viral infections [7]. What consequences the Sars-CoV-2 vaccine may lead to in patients with RANBP2 gene mutation remains to be elucidated.

More caution is needed in these children, since occasional case reports suggest that vaccine against COVID could allow to an aberrant immune response mechanisms and ANE [13,14]. However, the disastrous course of disease in our patient suggest that vaccination should not be discouraged. An issue for future research should be the possible protective role of drugs supporting the mitochondrial function in the para-vaccination period. There are several neurotrophic viruses that had been reported to trigger ANE and ANE1 in the literature such as influenza A, dengue, rotavirus, syncytial respiratory virus and many others. In our patient the recurrence of ANE1 only after specific viral infections (eg., influenza A and Sars-CoV-2), besides having had many other respiratory and non-respiratory febrile viral infections is intriguing. Moreover, she showed increased severity of recurrence following Sars-CoV-2 infection. These findings suggest the possibility of potentiation of different mechanisms, in line with recent studies showing that ORF6, a Sars-CoV-2 protein downregulates the expression of RANBP2, by acting on the nucleus-cytoplasmic transport of cytokine mRNA, possibly leading to potentiation of the cytokine storm during COVID-19 [15]. Moreover, RANBP2 shows in vitro anti-retroviral activity [16] and its loss of function seems to be related also to susceptibility to infection itself [6].

In our patient, MRI patterns of lesions shared similarities with those of metabolic and/or mitochondrial disorders such as Leigh syndrome, supporting the role of RANBP2 in mitochondrial homeostasis and opening future directions for ANE1 therapy.

Genetic tests are recommended in recurrent ANE, and also for therapeutic implications. ANE1 treatment should include prophylaxis of severe recurrences (eg., with adequate energy support and antioxidants during intercurrent viral infections).

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Declaration of competing interest

The authors of the Manuscript **"Pediatric recurrent acute necrotizing encephalomyelitis, RANBP2 genotype and Sars-CoV-2 infection: diagnosis, pathogenesis and targeted treatments from a case study"** have no conflicts of interest to disclose.

References

[1] M. Mizuguchi, J. Abe, K. Mikkaichi, et al., Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions, J. Neurol. Neurosurg. Psychiatry 58 (5) (1995) 555–561, https://doi.org/10.1136/jnnp.58.5.555.

[2] D.E. Neilson, M.D. Adams, C.M. Orr, et al., Infection-triggered familial or recurrent cases of acute necrotizing encephalopathy caused by mutations in a component of the nuclear pore, RANBP2. Am J Hum Genet. 84 (1) (2009) 44–51, https://doi.org/10.1016/j.ajhg.2008.12.009.

[3] J. Jiang, Y.E. Wang, A.F. Palazzo, Q. Shen, Roles of nucleoporin RanBP2/nup358 in acute necrotizing encephalopathy type 1 (ANE1) and viral infection, Int. J. Mol. Sci. 23 (7) (2022) 3548, https://doi.org/10.3390/ijms23073548. Published 2022 Mar 24.

[4] L. Mao, H. Jin, M. Wang, et al., Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in wuhan, China, JAMA Neurol. 77 (6) (2020) 683–690, https://doi.org/10.1001/jamaneurol.2020.1127.

[5] N. Poyiadji, G. Shahin, D. Noujaim, M. Stone, S. Patel, B. Griffith, COVID-19-associated acute hemorrhagic necrotizing encephalopathy: imaging features, Radiology 296 (2) (2020) E119–E120, https://doi.org/10.1148/radiol.2020201187.

[6] A.F. Palazzo, J. Joseph, M. Lim, K.T. Thakur, Workshop on RanBP2/Nup358 and acute necrotizing encephalopathy, Nucleus 13 (1) (2022 Dec) 154–169, https://doi.org/10.1080/19491034.2022.2069071. PMID: 35485383; PMCID: PMC9067512.

[7] J.M. Levine, N. Ahsan, E. Ho, J.D. Santoro, Genetic acute necrotizing encephalopathy associated with RANBP2: clinical and therapeutic implications in pediatrics, Mult Scler Relat Disord 43 (2020), 102194, https://doi.org/10.1016/j.msard.2020.102194.

[8] H. Yamamoto, A. Okumura, J. Natsume, S. Kojima, M. Mizuguchi, A severity score for acute necrotizing encephalopathy, Brain Dev. 37 (3) (2015 Mar) 322–327, https://doi.org/10.1016/j.braindev.2014.05.007. Epub 2014 Jun 12. PMID: 24931733.

[9] C.K. Chow, C.K.L. Ma, Presentation and outcome of acute necrotizing encephalopathy of childhood: a 10-year single-center retrospective study from Hong Kong, J. Child Neurol. 35 (10) (2020 Sep) 674–680, https://doi.org/10.1177/0883073820927915. Epub 2020 Jun 4. PMID: 32493103.

[10] X. Wu, W. Wu, W. Pan, L. Wu, K. Liu, H.L. Zhang, Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder, Mediat. Inflamm. 2015 (2015), 792578, https://doi.org/10.1155/2015/792578.

[11] R.R. Singh, S. Sedani, M. Lim, E. Wassmer, M. Absoud, RANBP2 mutation and acute necrotizing encephalopathy: 2 cases and a literature review of the expanding clinico-radiological phenotype, Eur. J. Paediatr. Neurol. 19 (2) (2015 Mar) 106–113, https://doi.org/10.1016/j.ejpn.2014.11.010. Epub 2014 Dec 9. PMID: 25522933.

[12] P. Shukla, A. Mandalla, M.J. Elrick, A. Venkatesan, Clinical manifestations and pathogenesis of acute necrotizing encephalopathy: the interface between systemic infection and neurologic injury, Front. Neurol. 12 (2022 Jan 4), 628811, https://doi.org/10.3389/fneur.2021.628811. PMID: 35058867; PMCID: PMC8764155.
[13] M.R. Bensaidane, V. Picher-Martel, F. Émond, G. De Serres, N. Dupré, P. Beauchemin, Case report: acute necrotizing encephalopathy following COVID-19 vaccine, Front. Neurol. 13 (2022 Apr 29), 872734, https://doi.org/10.3389/fneur.2022.872734. PMID: 35572945; PMCID: PMC9099242.
[14] T. Pongpitakmetha, P. Hemachudha, W. Rattanawong, P. Thanapornsangsuth, A. Viswanathan, T. Hemachudha, COVID-19 related acute necrotizing encephalopathy with extremely high interleukin-6 and RANBP2 mutation in a patient with recently immunized inactivated virus vaccine and no pulmonary involvement, BMC Infect. Dis. 22 (1) (2022 Jul 23) 640, https://doi.org/10.1186/s12879-022-07610-0. PMID: 35870896; PMCID: PMC9308110.
[15] J.G. Lee, W. Huang, H. Lee, J. van de Leemput, M.A. Kane, Z. Han, Characterization of SARS-CoV-2 proteins reveals Orf6 pathogenicity, subcellular localization, host interactions and attenuation by Selinexor, Cell Biosci. 11 (1) (2021) 58, https://doi.org/10.1186/s13578-021-00568-7. Published 2021 Mar 25.
[16] J.O. Bock, I. Ortea, Re-analysis of SARS-CoV-2-infected host cell proteomics time-course data by impact pathway analysis and network analysis: a potential link with inflammatory response, Aging (Albany NY) 12 (12) (2020 Jun 23) 11277–11286, https://doi.org/10.18632/aging.103524. Epub 2020 Jun 23. PMID: 32575076; PMCID: PMC7343490.