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Defining the Clinicoradiologic Syndrome of SARS-CoV-2 Acute Necrotizing Encephalopathy

A Systematic Review and 3 New Pediatric Cases

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Abstract

Background and Objectives

We characterize clinical and neuroimaging features of SARS-CoV-2–related acute necrotizing encephalopathy (ANE).

Methods

Systematic review of English language publications in PubMed and reference lists between January 1, 2020, and June 30, 2023, in accordance with PRISMA guidelines. Patients with SARS-CoV-2 infection who fulfilled diagnostic criteria for sporadic and genetic ANE were included.

Results

From 899 articles, 20 cases (17 single case reports and 3 additional cases) were curated for review (50% female; 8 were children). Associated COVID-19 illnesses were febrile upper respiratory tract infections in children while adults had pneumonia (45.6%) and myocarditis (8.2%). Children had early neurologic deterioration (median day 2 in children vs day 4 in adults), seizures (5 (62.5%) children vs 3 of 9 (33.3%) adults), and motor abnormalities (6 of 7 (85.7%) children vs 3 of 7 (42.9%) adults). Eight of 12 (66.7%) adults and 4 (50.0%) children had high-risk ANE scores. Five (62.5%) children and 12 (66.7%) adults had brain lesions bilaterally and symmetrically in the putamina, external capsules, insula cortex, or medial temporal lobes, in addition to typical thalamic lesions of ANE. Hypotension was only seen in adults (30%). Hematologic derangements were common: lymphopenia (66.7%), coagulopathy (60.0%), or elevated D-dimers (100%), C-reactive protein (91.7%), and ferritin (62.5%). A pathogenic heterozygous c/.1754 C>T variant in *RANBP2* was present in 2 children: one known to have this before SARS-CoV-2 infection, and a patient tested because the SARS-CoV-2 infection was the second encephalopathic illness. Three other children with no prior encephalopathy or family history of encephalopathy were negative for this variant. Fifteen (75%) received immunotherapy (with IV methylprednisolone, immunoglobulins, tocilizumab, or plasma exchange): 6 (40.0%) with monotherapy and 9 (60.0%) had combination therapy. Deaths were in 8 of 17 with data (47.1%): a 2-month-old male infant and 7 adults (87.5%) of median age 56 years (33–70 years), 4 of whom did not receive immunotherapy.

Discussion

Children and adults with SARS-CoV-2 ANE have similar clinical features and neuroimaging characteristics. Mortality is high, predominantly in patients not receiving immunotherapy and at the extremes of age.

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Glossary

ADC = apparent diffusion coefficient; **AFCE** = acute fulminant cerebral edema; **ANE** = acute necrotizing encephalopathy; **ANE-ss** = ANE severity score; **GCS** = Glasgow coma scale; **IVIg** = IV immunoglobulin; **MIS-C** = multisystem inflammatory syndrome in children; **mRS** = modified Rankin score; **PRRs** = pattern recognition receptors; **RISC** = RNA-induced silencing complex.

Introduction

Acute necrotizing encephalopathy (ANE) is a devastating infection-triggered acute encephalopathy syndrome with a distinct clinical presentation and neuroimaging phenotype. Sporadic ANE is more common in infants and school-going children, usually in association with influenza (A and B) virus and human herpesvirus 6/7 infections.[1] These infections trigger a systemic cytokine storm, induce brain microglial activation, and lead to mitochondrial dysfunction that results in neuronal injury mediated through a complex array of immune, excitotoxic, and metabolic mechanisms.[1] In severe ANE, there is rapid neurologic deterioration, multiorgan failure, and extremely poor outcomes, which may be improved with neuroprotective and immunotherapeutic strategies.[2-5] A genetic form of ANE (ANE1) is associated with autosomal dominant loss-of-function variants in *RANBP2*, a gene encoding a component of a nuclear pore (Nup358).[6,7] Outcomes are generally better in ANE1, but there is a 50% risk of recurrence of encephalopathy.[7]

During the COVID-19 pandemic, some patients with SARS-CoV-2 infection with associated neurologic complications were reported to have ANE. We reviewed the clinical presentation and neuroimaging of published cases of children and adults with SARS-CoV-2 ANE alongside 3 additional pediatric cases seen and managed within our group.

Methods

A systematic review of English-language publications curated from PubMed was using the following search terms: "COVID19" OR "SARS-CoV-2" AND "acute necrotizing encephalopathy" OR "acute necrotizing encephalitis" OR "encephalitis" OR "acute hemorrhagic leukoencephalitis" OR "disseminated encephalitis," from January 1, 2020, till June 30, 2023. Reference lists of retrieved articles were screened for additional cases. Figure 1 shows the search, curation, and selection process, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] Inclusion criteria were as follows: pediatric (younger than 18 years) and adult patients (1) with concurrent febrile SARS-CoV-2 infection and (2) fulfilling established diagnostic criteria for either ANE or ANE1 (details in eMethods, links.lww.com/NXI/A952).[2,6,9] Cases of possible ANE with inadequate clinical information and/or incomplete neuroimaging data were excluded. Three additional patients seen by the authors (ARM, PA, HM, KKQ, and TT) were included. Articles were screened by VWML and TT, who then summarized clinical and neuroimaging data. The ANE severity score (ANE-ss) was applied (low risk [score 0–1], medium risk [score 2–4], and high risk [score 5–9]),[10] and outcomes at last follow-up were determined using the modified Rankin score (mRS) (both defined in eMethods).

Descriptive statistics are presented as medians, interquartile range, and range for continuous data and proportions/percentages for categorical/ordinal data. Not all clinical data were available for all patients and are indicated accordingly in the text and tables. Differences between groups were analyzed using the Mann-Whitney *U* test and Fisher exact test for continuous and categorical data, respectively. All tests were 2-tailed, and level of significance was set at $p < 0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

The 3 additional patients were enrolled in institutional studies approved by the Medical Research Ethics Committee, Malaysia (NMRRID-22-01911-GWL) and the SingHealth Centralized Institutional Review Board, Singapore (CIRB2018/2916).

Data Availability

All study data are summarized in eTable 1 (links.lww.com/NXI/A953).

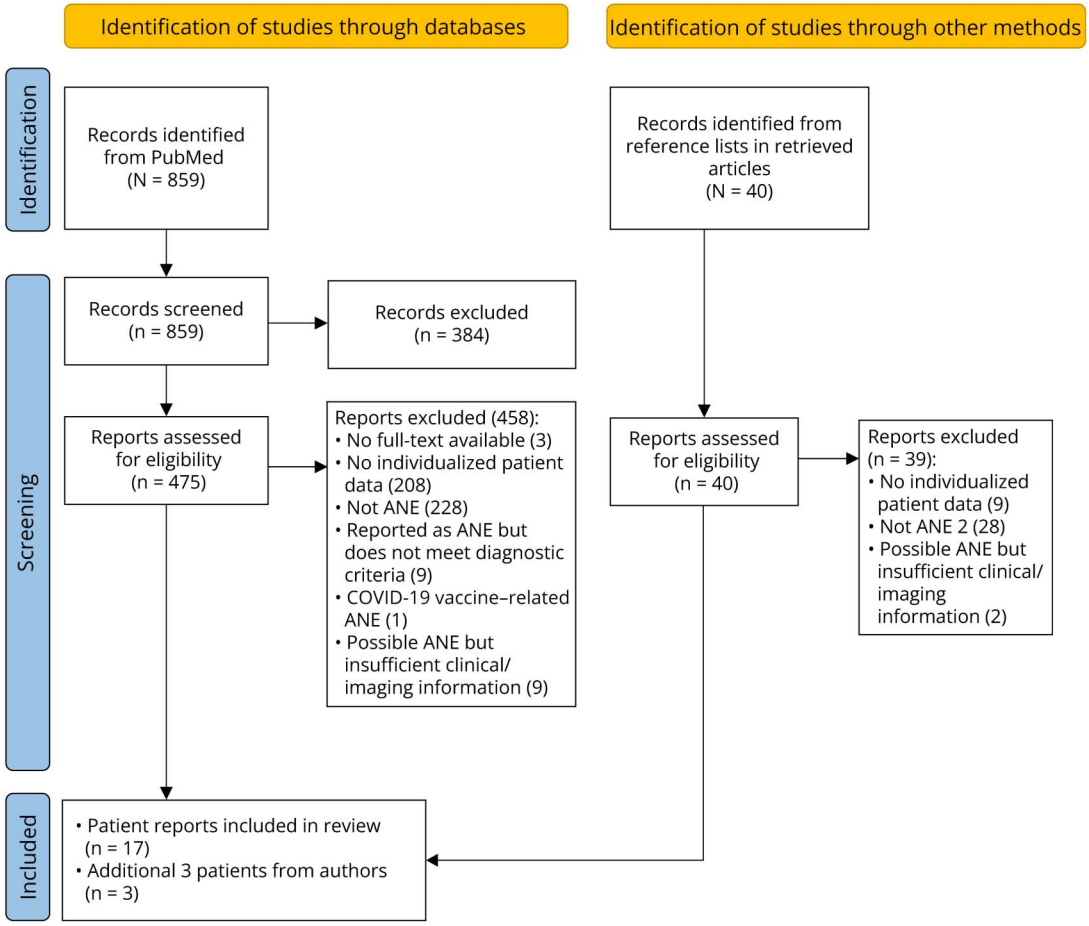
Results

A total of 899 articles were identified (859 from primary search and 40 from reference lists), and 515 relevant articles were screened for eligibility (Figure 1). Individualized patient data of 17 cases (16 single case reports and 1 from a series) fulfilled inclusion criteria (Table 1).[11-27] Reports of adult patients with SARS-CoV-2 ANE were published in the years 2020–2022 while the pediatric reports were from 2022 to 2023, reflecting the changing age-specific predilection of patients with SARS-CoV-2 variants throughout the pandemic.[28] The full patient dataset (8 children, 12 adults; male: female ratio 1:1) is listed in eTable 1 (links.lww.com/NXI/A953). The following are summaries of the 3 additional patients:

Case 1

A 7.2-year old ethnic Malay boy presented in July 2022 with fever (40°C) and cough for a day, followed by 2 short generalized tonic-clonic seizures. Positive nasopharyngeal SARS-CoV-2 PCR with a low cycle threshold confirmed the diagnosis of acute COVID-19 infection. He was unvaccinated

Figure 1 PRISMA Flow Diagram for Literature Review



against COVID-19. Four months earlier, he had a first febrile COVID-19 infection.

At the emergency department, heart rate (160–180/min) and blood pressure (100/50 mm Hg) were stable, but he was encephalopathic (Glasgow coma scale [GCS] E4V1M5). Neck was supple with normal tone and tendon reflexes and equivocal plantar responses. A brain CT scan was normal, and IV levetiracetam (30 mg/kg loading dose, maintenance dose of 500 mg BD) was given for seizures. GCS soon worsened (score 6–7), and he was electively intubated and ventilated.

On day of admission, serum ferritin (7,141 μg/L), lactate dehydrogenase (1382 U/L), D-dimers (>32.00 mg/L), procalcitonin (39.33 μg/L), and C-reactive protein (9.7 mg/L) were elevated with coagulopathy, lymphopenia (lowest 680/mm^3), and thrombocytopenia (77,000/mm^3). Although serum troponin-I levels were raised (258 ng/L), cardiac function and blood pressure remained normal, and there were no mucocutaneous lesions or gastrointestinal symptoms. On day 2, there was transaminitis (alanine aminotransferase 3809 U/L, aspartate aminotransferase >4000 U/L and elevated serum creatinine (117 mmol/L).

On day 1, he was given 30 mg/kg of IV methylprednisolone and 1g/kg of IV immunoglobulins (IVIgs) (presuming multisystem inflammatory syndrome in children [MIS-C]). Brain MRI on day 1 showed lesions in bilateral thalami, caudate nuclei, putamina, external capsules, medial temporal lobes, cerebral/cerebellar white matter, and pons, consistent with ANE (Figure 2). Because ANE-ss was high (score of 6), therapeutic hypothermia (35–36°C, for 72 hours) was initiated and IV tocilizumab (single 8 mg/kg dose) was given. He received a second dose of IVIg (1g/kg, on day 2), 5 days of IV methylprednisolone (30 mg/kg), and antimicrobials (IV ceftriaxone 100 mg/kg q24h for 7 days, IV ciprofloxacin 10 mg/kg q8h and IV acyclovir 20 mg/kg q8h for 2 days, and IV remdesivir 5 mg/kg, single dose). CSF analysis (day 2) showed no pleocytosis but elevated protein (0.90 g/L) and was negative for pathogens including SARS-CoV-2. The serum SARS-CoV-2 IgG (RBD) antibody was positive (6269 AU/mL), but serum N-protein antibody was negative. Genetic testing for *RANBP2* was negative.

He gradually improved and was extubated on day 6. Subsequent hospital stay was notable for a brief focal seizure (day 18). At discharge (day 30), he was ambulant with mild truncal ataxia and had language difficulties (modified Rankin

Table 1 Cases of SARS-CoV-2–Related Acute Necrotizing Encephalopathy (ANE) Included for Review (20 in Total)

No	Author	Country	Year reported	Pediatric or adult patients	Type of report	Full text and images available	Number of cases
1	Lee (this report)	Singapore, Malaysia	2023	Pediatric	Case series	Yes	3
2	Khan et al[11]	United States	2022	Pediatric	Case report	Yes	1
3	Mierzewska-Schmidt et al[12]	Poland	2022	Pediatric	Case report	Yes	1
4	Wang et al[13]	Taiwan	2022	Pediatric	Case report	Yes	1
5	Ho et al[14]	Singapore	2023	Pediatric	Case report	Yes	1
6	Forest et al[15]	Italy	2023	Pediatric	Case report	Yes	1
7	Breit et al[16]	United States	2021	Adult	Case report	Yes	1
8	Ong et al[17]	Malaysia	2022	Adult	Case report	Yes	1
9	Elkady and Rabinstein[18]	Egypt	2020	Adult	Case report	Yes	1
10	Gadani and Cohen[19]	United States	2022	Adult	Case report	Yes	1
11	Kremer et al[20]	France	2020	Adult	Case report	Yes	1
12	Virhammar et al[21]	Sweden	2020	Adult	Case report	Yes	1
13	Diallo et al[22]	France	2022	Adult	Case report	Yes	1
14	Morvan and Kerambrun[23]	France	2021	Adult	Case report	Yes	1
15	Poyiadji et al[24]	United States	2020	Adult	Case report	Yes	1
16	Dixon et al[25]	United Kingdom	2020	Adult	Case report	Yes	1
17	Paterson et al[26]	United Kingdom	2020	Adult	1 case in a series	Yes	1
18	Ziemele et al[27]	Latvia	2021	Adult	Case report	Yes	1

scale, mRS = 3). He was prescribed oral prednisolone (for 6 weeks) and levetiracetam. At home, there were behavioral outbursts, impulse control issues, and language perseveration. At 6 months, the ataxia, behavioral symptoms, and language difficulties had completely resolved, and levetiracetam was discontinued. He had returned to school (at age level) and remains independent in all activities of daily living (mRS 1).

Case 2

A 3.2-year-old Malay boy, with underlying scoliosis and expressive speech delay, was admitted in February 2022 following 2 days of high fever (41.9°C), poor feeding, diarrhea, and 2 generalized seizures. Recurrent seizures and encephalopathy (GCS 6 [E1V1M4]) at the emergency department prompted intubation and treatment for status epilepticus with IV phenytoin (20 mg/kg loading dose) and midazolam infusion. Nasopharyngeal aspirate PCR for SARS-CoV-2 was positive. Physical examination revealed hyperreflexia while CT brain showed hypodensities in bilateral thalami and pons, suggestive of ANE. MRI brain (day 4) showed additional lesions in the frontal and medial temporal lobes, putamina, and caudate nuclei (Figure 3). His ANE-ss was 6 (high risk), and IV methylprednisolone (30 mg/kg/d for 5 days) was promptly administered (day 1) followed by IV tocilizumab (single 12 mg/kg dose) and antimicrobials (IV meropenem, 40 mg/kg q8h for 10 days; IV acyclovir, 20 mg/kg q8h; and IV azithromycin, 15 mg/kg stat/and then 5 mg/kg q24h, both for 5 days).

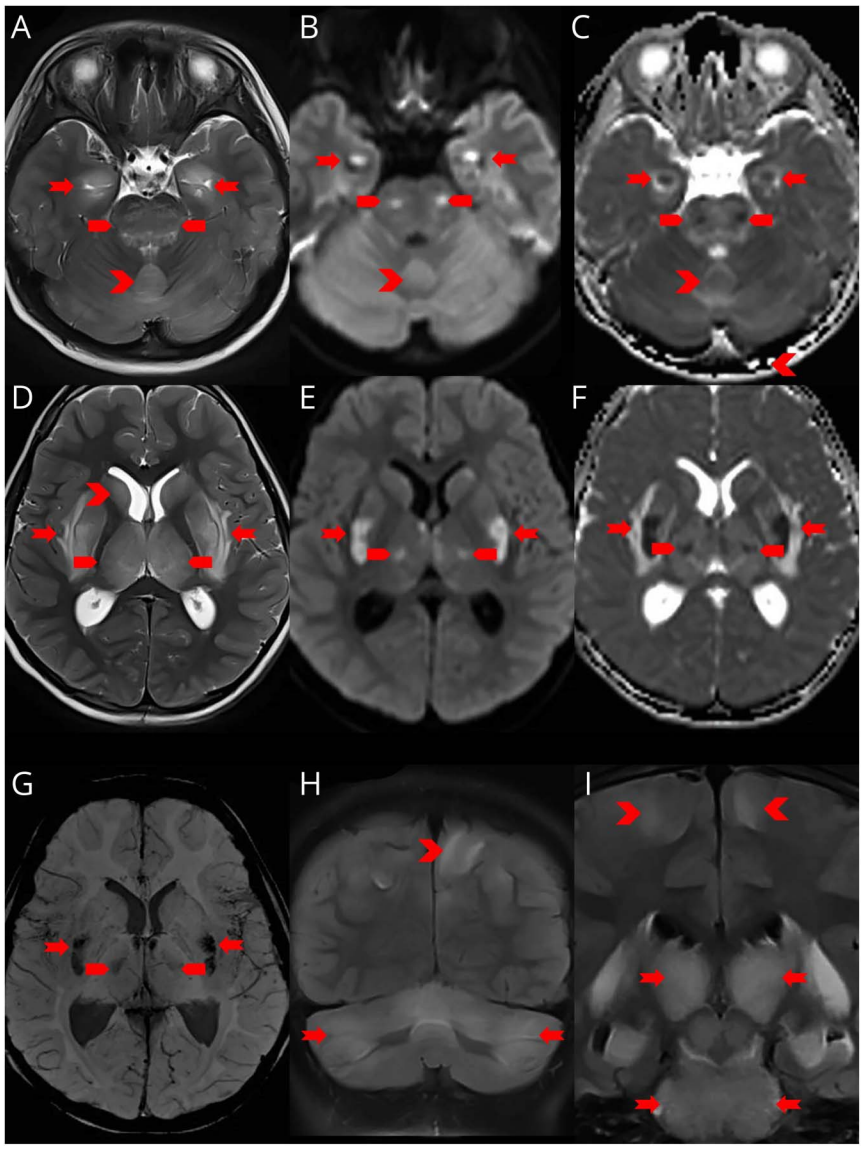
He had multisystem involvement: hepatic transaminitis (alanine aminotransferase 2625 U/L, aspartate aminotransferase 6,582 U/L), elevated lactate dehydrogenase >3,325 U/L, and coagulopathy on day 1 and raised acute phase reactants (elevated serum ferritin [10,134 μg/L], D-dimers [14.48 mg/L]) when first sampled on day 2. CSF analysis (day 3) showed no cells, raised protein (0.72 g/L), and was negative for pathogens including SARS-CoV-2.

He was extubated on day 5. At discharge (day 25), he required maximal assistance for transfers, feeding, and self-care (mRS 5), At 10 months, he spoke in short phrases and required mild assistance for walking and self-care (mRS 3).

Case 3 (Known Patient With ANE1)

This case is an 8.9-year-old Malay girl with mild learning and behavioral difficulties as sequelae from a febrile encephalopathy at age 2 years and was known to have genetic ANE (c/.1754 C>T variant in *RANBP2*; index case was an older brother). This current illness in March 2022 was a SARS-CoV-2–positive febrile encephalopathy with seizures

Figure 2 Brain MRI for Case 1 on Day 1 of Encephalopathy, Highlighting the Neuroimaging Pattern in Early ANE



Axial T2-weighted (A), diffusion weighted (B) and apparent diffusion coefficient, ADC (C) images: Bilateral lesions with T2 signal prolongation (hyperintensity) and restricted diffusion (cytotoxic edema) in the medial temporal (red arrows) and pons (red hexagons). There are also lesions with T2 signal prolongation (hyperintensity) and facilitated diffusion (vasogenic edema) in the cerebellar vermis (red chevrons) and cerebellar gray matter. Axial T2-weighted (D), DW (F), ADC (G), and susceptibility-weighted (H) images: Bilateral lesions with T2 signal prolongation and restricted diffusion in the bilateral external capsules, putamina (both next to red arrows), and thalami (red hexagons) and lesions with T2 prolongation in the bilateral caudate nuclei (red chevron). The lesions in the putamina and thalamus show susceptibility artefact (image H, red arrows and hexagons, respectively). Coronal T2 fluid-attenuated inversion recovery, FLAIR (E and F) images: Hyperintense lesions in cerebral gray (red chevrons) and bilateral cerebellar gray (H, red arrows), thalami (I, upper red arrows), and pons (I, red yellow arrows).

requiring mechanical ventilation and ICU admission for 12 days. MRI brain revealed new hemorrhagic lesions in bilateral thalami and pons in addition to bilateral putaminal and medial temporal lobe encephalomalacia from the earlier episode (Figure 4). She had thrombocytopenia and elevated liver enzymes but without elevation of acute phase reactants, hypotension, or cardiac involvement. She was given IV methylprednisolone (30 mg/kg/d) and IVIg (1g/kg/d) for 5 and 2 days, respectively.

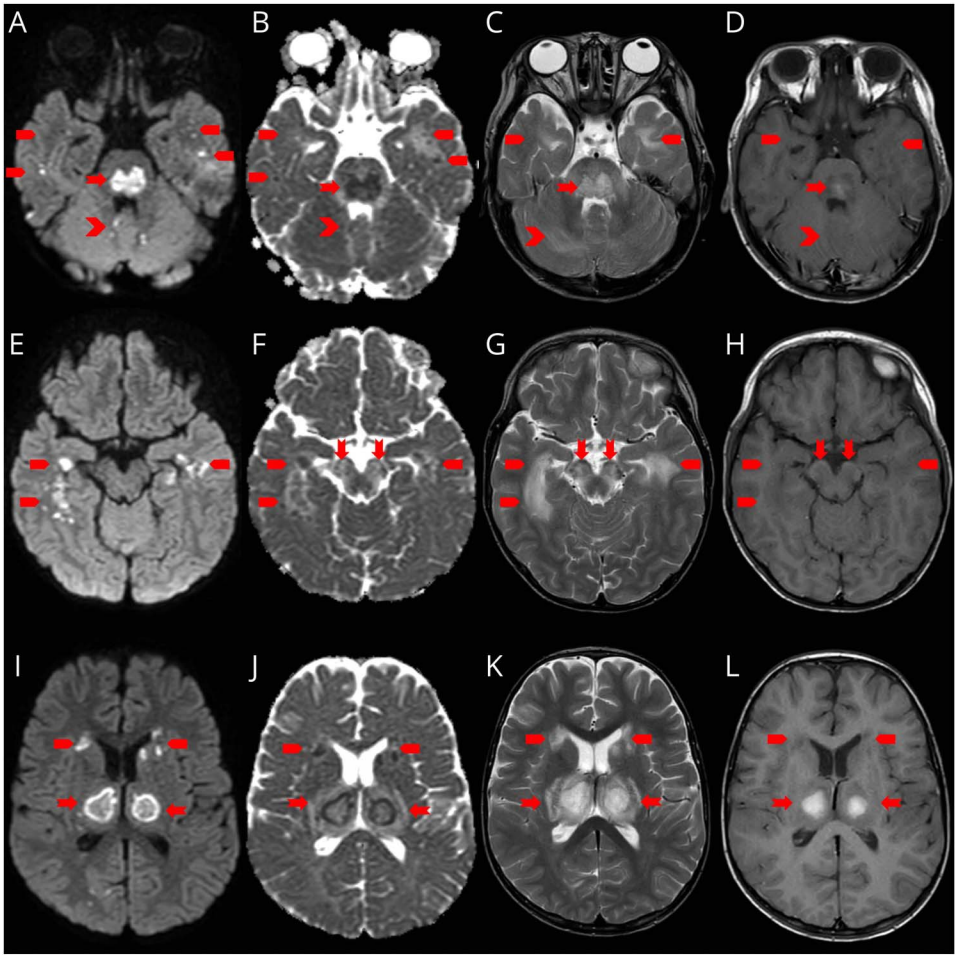
At discharge (1 month), she had generalized weakness, swallowing impairment, and aphasia. She continued to improve and at 6 months postillness was back to her previous level of functioning: able to walk unaided, dress and feed herself with minimal assistance, and simple language and understanding (mRS 3). There were no further seizures.

Summary of All 20 Cases

Table 2 compares SARS-CoV-2 ANE between pediatric and adult patients. There were no major differences in neurologic features, organ system involvement, laboratory features, and neuroimaging characteristics between the groups.

Associated COVID-19 infections were mild febrile upper respiratory tract infections in all children (by National Institute of Health COVID-19 guidelines[29]) while pneumonia (5 in 11 adults [45.6%]) and myocarditis (2, 18.2%) were present in adults. In children, neurologic deterioration occurred earlier in the course of the febrile illness (median day 2 vs day 4 in adults) while seizures (5 [62.5%] children vs 3 of 9 [33.3%] adults) and motor abnormalities (6 of 7 [85.7%] children vs 3 of 7 [42.9%] adults) were common. High-risk ANE severity scores were present in 8 of 12 (66.7%) adults and in 4 (50.0%) children.

Figure 3 Brain MRI for Case 2 on Day 4 of Encephalopathy—the Characteristic Trilaminar Pattern of Thalamic Lesions has Been Established but Clear Evidence of Necrotic Change Is Already Present in the Thalamus and Pons



Axial diffusion-weighted, DWI (A), apparent diffusion coefficient, ADC (B), T2-weighted (C), and T1-weighted (D) images: lesions with a mixture of restricted diffusion (cytotoxic edema) and facilitated diffusion (vasogenic edema) in the bilateral medial temporal lobes (red hexagons), cerebellar white matter regions, and cerebellar vermis (red chevrons). These areas show T2 signal prolongation (hyperintensity) and T1 signal prolongation (hypointensity). In the pons (red arrows), there is a confluent area of restricted diffusion with T2 prolongation. However, some areas show T1 signal shortening (hyperintensity) indicating necrosis (red arrow). Axial diffusion-weighted (E), apparent diffusion coefficient, ADC (F), T2-weighted (G), and T1-weighted (H) images: lesions with a mixture of restricted and facilitated diffusion in the bilateral medial temporal (red hexagons), with T2 signal prolongation (hyperintensity) and T1 signal prolongation (hypointensity). In the midbrain and cerebral peduncles (red arrows), there is facilitated diffusion alone. Axial diffusion weighted (I), apparent diffusion coefficient (J), T2-weighted (K), and T1-weighted (L) images: lesions with a mixture of restricted and facilitated diffusion in the bilateral caudate nuclei, anterior putamen, and periventricular frontal white matter (red hexagons), with T2 and T1 signal prolongation. The thalamic lesions have a trilaminar pattern with an outermost ring of facilitated diffusion (hyperintensity/high ADC values, with T2 prolongation) from vasogenic edema, a middle ring of restricted diffusion (high signal on DWI and hypointensity/low ADC values) from cytotoxic edema, and a central region with necrosis (best appreciated on T1 with signal shortening (hyperintensity) (red arrows).

Figures 2 and 3 illustrate typical brain lesions observed in patients with SARS-CoV-2 ANE. Lesions in the putamina, external capsules, insula cortex, or medial temporal lobes were seen in 5 (62.5%) of children and 8 (66.7%) of adults. Hypotension was seen in adults (3 of 10, 30%) but in none of the children. However, children were more likely to have elevated liver enzymes (5 children [62.5%] vs 1 of 8 adults [12.5%], $p = 0.026$). Hematologic derangements were common to both adults and children, notably lymphopenia (8 of 12, 66.7%), coagulopathy (6 of 10, 60.0%), and elevated acute phase reactants: D-dimers (9 of 9, 100%), c-reactive protein (11 of 12, 91.7%) and ferritin (5 of 8, 62.5%).

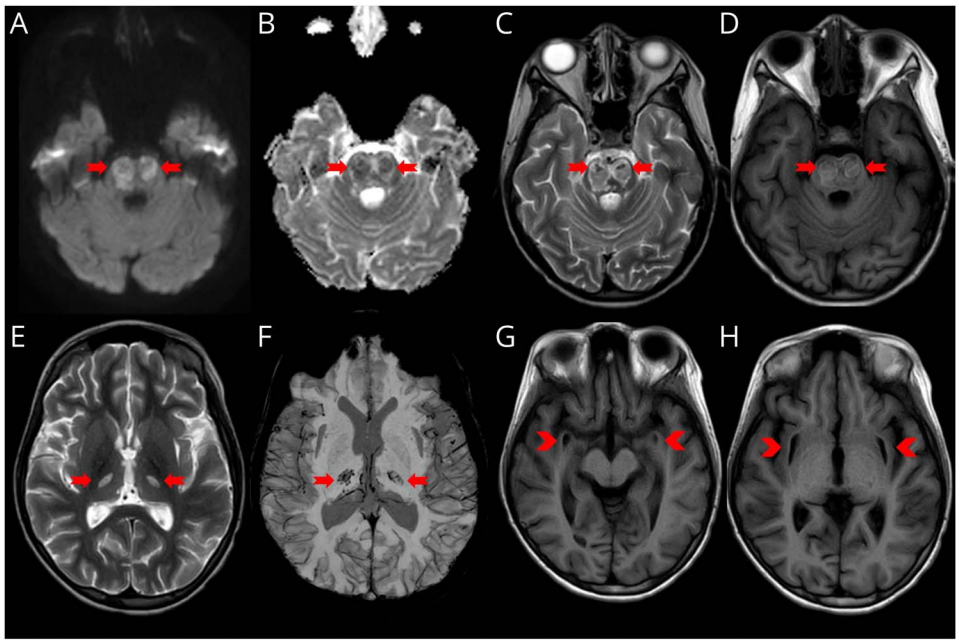
Data on treatment are available for all but 1 patient (94%). Fifteen (78.9%) received immunotherapy: 6 (40.0%) with monotherapy (3 IV methylprednisolone [MP], 2 IV dexamethasone, 1 IV immunoglobulins [IVIg]) and 9 (60.0%) receiving combination therapy (5 children had MP, IVIg, and IV tocilizumab [TCZ], 1 child was given MP and TCZ, and 1 child had MP, IVIg, and plasma exchange while 2 adults had plasma exchange with either MP or IVIG, respectively).

Deaths (47.1%, in 8 of 17 with data) were at the extremes of age: a 2-month-old male infant and 7 adults (87.5%) of median age 56 (33–70 years) and included 4 patients (3 adults and 1 child) not receiving immunotherapy. Although mortality was lower in children, 4 patients (50.0%) had moderate to severe disability at discharge. Case 3 was known to already have a pathogenic variant in *RANBP2*, whilst case 6 had a history of demyelination and tested positive for a pathogenic variant in *RANBP2*. RANBP2 testing was also performed in 3 other children, all of whom had no prior encephalopathy and had no family history of encephalopathy, and were negative for pathogenic variants in this gene. None of the adult patients were tested for *RANBP2* variants, and none were reported to have had a history of encephalopathy.

Discussion

ANE is an uncommon neurologic syndrome associated with SARS-CoV-2 infection in adults and children because only 20 published patient reports (and 10 possible others, Figure 1)

Figure 4 Brain MRI for Case 3 on Day 6 of Encephalopathy With New and Old Lesions



Axial diffusion weighted(A), Apparent diffusion coefficient, ADC (B), T2-weighted (C), and T1-weighted (D) images: A new lesion in the pons with restricted diffusion and T2 signal prolongation (hyperintensity) but T1 signal shortening (hyperintensity) indicates the presence of necrosis (red arrows). Axial T2-weighted (E) and susceptibility (F) images: T2 prolongation (swelling) and susceptibility artefacts (hemorrhage) in new thalamic lesions bilaterally (red arrows). Axial T1-weighted (E, F) images: Old lesions from a previous episode of ANE1 encephalopathy at age 2 years (a typical lesion distribution in ANE1): focal atrophy and encephalomalacia in the bilateral medial temporal regions and external capsules (red chevrons).

were available.[26,30-32] However, nearly 50% in this cohort died, and most survivors had moderate to severe disability.

The clinical features, CSF biochemistry (absence of pleocytosis, elevated protein), and distribution of core brain lesions (thalami, cerebellum, and pons) are essentially similar in SARS-CoV-2, sporadic, and genetic ANE. Thalamic lesions in SARS-CoV-2 ANE also show the characteristic trilaminar appearance on apparent diffusion coefficient (ADC) MRI sequences: an outermost ring of hyperintensity from vasogenic edema, a middle ring of hypointensity from cytotoxic edema, and an inner area of necrosis (hyperintensity in both ADC and T1 MRI sequences) (Figure 3, J–L). Additional brain lesions are by definition not present in sporadic ANE,[2] but common in genetic ANE: caudate nuclei, anterior putamina, medial temporal lobes, insula, and external capsules. In our cohort of SARS-CoV-2 ANE, additional brain lesions in this exact same distribution was present in 72% of patients who were either negative for a pathogenic variant in *RANBP2* or without a history of encephalopathy. Notably, patients with SARS-CoV-2 ANE also have bilateral amygdala lesions (these appear as hypointense circles on MRI ADC images; Figures 2C and 3F).[24]

Although genetic testing for *RANBP2* was not available for many patients in our cohort, the presence of multisystem organ involvement (uncharacteristic of genetic ANE) render the possibility of an undiagnosed *RANBP2* disorder less likely. Systemic or multiorgan involvement is common in sporadic ANE, but not the combination of lymphopenia, thrombocytopenia, and elevated acute phase reactants, as seen in patients with SARS-CoV-2 ANE. This pattern of hematologic abnormalities is also typical of SARS-CoV-2 MIS-C syndrome,[33,34] an important differential diagnosis. Patients with SARS-CoV-2 ANE with shock, cardiac, or hematologic involvement will readily fulfill the case definition for MIS-C (≥2 systems involvement), such as the patient described in case 1. However, brain lesions in ANE have a defined neuroimaging phenotype[2] and is different to lesions confined to cerebral vascular territories or from hypoperfusion injury that is commonly reported in MIS-C.[34]

Lymphopenia and elevated acute phase reactants are reported in all forms of severe COVID-19 infection,[35] including critically ill adult and pediatric COVID-19 patients with stroke and other encephalopathy syndromes.[26,30,31] This includes acute fulminant cerebral edema (AFCE), a severe and frequently fatal infection-triggered encephalopathy syndrome primarily seen in infants.[36,37] The neurologic deterioration occurs earlier and more rapidly in AFCE than in ANE because of widespread cerebral edema developing precipitously over 12–24 hours.[36,37] In case 1, hematologic derangements were an early feature (day 1) preceding the development of brain lesions on cranial CT imaging. Hence, the presence of lymphopenia and elevated acute phase reactants in a patient with a SARS-CoV-2 febrile encephalopathy with unremarkable early neuroimaging should alert the clinician to the potential development of an evolving severe neurologic syndrome such as ANE or AFCE. These biomarkers are a useful indicator of severe ANE disease because the incidence of hypotension and thrombocytopenia, key components of the ANE severity score,[10] was low in patients with SARS-CoV-2 ANE.

The similarities in the pattern of brain lesions in patients with genetic and SARS-CoV-2 ANE raises important questions on the role of nuclear pore biology in SARS-CoV-2 virus

Table 2 Patient Characteristics

Item	Children n = 8 unless stated otherwise	Adults n = 12 unless stated otherwise	Total n = 20 unless stated otherwise	*p* Value
Median age (quartiles, range), y	5.1 (0.85, 9.72; 0.1–11)	55.5 (33.0, 58.8; 19.0–70)	32.0 (7.47, 56.0; 0.1–70.0)	—
Male sex, n (%)	4 (50.0)	6 (50.0)	10 (50.0)	0.999
Encephalopathy, median, day of illness (quartiles, range), y	2.0 (2.0, 3.0; 1–7)	4.0 (1.0, 7.0; 1–10)	3.0 (1.5, 6.5; 1–7)	0.342
Severe encephalopathy, (GCS ≤8) at nadir, n (%)	7 (87.5)	7 of 8 (87.5)	14 of 16 (87.5)	—
Seizures	5 (62.5)	3 of 9 (33.3)	8 of 17 (47.1)	0.347
Pyramidal and/or extrapyramidal signs	6 of 7 (85.7)	3 of 7 (42.9)	9 of 14 (64.3)	0.266
Cranial nerve deficits	3 of 6 (50.0)	4 of 7 (57.1)	7 of 13 (53.8)	0.999
Hypotension	0 (0.0)	3 of 10 (30.0)	3 of 16 (18.8)	—
Elevated liver enzymes	5 (62.5)	1 of 8 (12.5)	6 of 16 (37.5)	0.119
Platelet count <100,000/mm^3	2 (25.0)	2 of 7 (28.6)	4 of 15 (26.7)	0.999
Lymphopenia <1,000/mm^3	5 (62.5)	3 of 4 (75.0)	8 of 12 (66.7)	0.999
Coagulopathy	3 of 7 (42.9)	3 of 3 (100.0)	6 of 10 (60.0)	—
Elevated D-dimers/DIVC (>0.5 microg/mL)	4 of 4 (100.0)	5 of 5 (100.0)	9 of 9 (100.0)	—
Elevated ferritin >1,000 mcg/mL	3 of 4 (75.0)	2 of 4 (50.0)	5 of 8 (62.5)	0.999
Elevated CRP (>5.0 mg/L)	6 of 7 (85.7)	5 of 5 (100.0)	11 of 12 (91.7)	—
Elevated procalcitonin (>2 μg/L)	2 of 4 (50.0)	0 of 1 (0.0)	2 of 5 (40.0)	—
AKI (urea or creatinine increase)	3 of 7 (42.9)	2 of 4 (50.0)	5 of 11 (45.5)	0.999
Elevated CK > 1,000 IU/L	2 of 5 (40.0)	1 of 4 (25.0)	3 of 9 (33.3)	0.999
MRI brain lesions				
Bilateral thalamus	8 (100.0)	12 (100.0)	20 (100.0)	—
Pons	7 (87.5)	12 (100.0)	19 (95.0)	—
Cerebellum	4 (50.0)	5 (41.7)	9 (45.0)	0.999
Cerebral white matter	3 (37.5)	3 (25.0)	6 (30.0)	0.642
External capsule/insula	5 (62.5)	7 (58.3)	12 (60.0)	0.999
Medial temporal/amygdala/hippocampus	5 (62.5)	8 (66.7)	13 (65.0)	0.999
Other areas, e.g., Midbrain, gray matter, caudate/putamen	5 (62.5)	7 (58.3)	12 (60.0)	0.999
ANE Severity Score				
0–1 (mild)	1 (12.5)	0 (0.0)	1 (5.0)	—
2–4 (moderate)	3 (37.5)	4 (33.3)	7 (35.0)	0.999
5–9 (severe)	4 (50.0)	8 (66.7)	12 (60.0)	0.650
Treatment	n = 8	n = 11	n = 19	
Steroids	7 (87.5)	6 (54.5)	13 (68.4)	0.177
IVIg	6 (75.0)	2 (18.9)	8 (42.1)	0.024*
Tocilizumab	5 (62.5)	0 (0.0)	5 (26.3)	—
Plasma exchange	1 (12.5)	2 (18.9)	3 (15.8)	0.999
Hypothermia	2 (25.0)	0 (0.0)	2 (10.5)	—

Continued

Table 2 Patient Characteristics *(continued)*

Item	Children n = 8 unless stated otherwise	Adults n = 12 unless stated otherwise	Total n = 20 unless stated otherwise	*p* Value
Pathogenic RANBP2 variant	2 of 5 (40.0)	Not done	—	—
Family history of acute encephalopathy or ANE	Only in 1 of 2 patients already known to have RANBP2 disease	None	—	—
Outcome	n = 7	n = 10	n = 17	
mRS 0–1	2 (28.6)	1 (10.0)	3 (17.6)	0.537
mRS 2–3	2 (28.6)	0 (0.0)	2 (11.8)	—
mRS 4–5	2 (28.6)	2 (20.0)	4 (23.5)	0.999
mRS 6 (death)	1 (14.3)	7 (70.0)	8 (47.1)	0.049*

Abbreviations: AKI = acute kidney injury; ANE = acute necrotizing encephalopathy; CK = creatine kinase; CRP = C-reactive protein; DIVC = disseminated intravascular coagulation; GCS = Glasgow coma scale; IVIg = IV immunoglobulins; mRS = modified Rankin score; * $p < 0.05$.

infection. RanBP2 is a component of the nuclear pore complex, which regulates the movement of macromolecules between the nucleus and cytosol. During viral infection, the nuclear pore is a central hub used by both the immune system and viruses. Viruses contain pathogen-associated molecular patterns that are recognized by antiviral host cytosolic pattern recognition receptors (PRRs).[38] When activated, PRRs trigger the nuclear import of transcription factors that then turn on proinflammatory genes, whose mRNA products must be exported from the nucleus to the cytoplasm to produce antiviral proteins.[38] To evade these cytosolic sensors, viruses use the nuclear pore to enter the nucleoplasm. Other viruses inhibit the nuclear import of PRR-activated transcription factors or the nuclear export of proinflammatory mRNAs.[38] Indeed, many viruses produce proteins that interact with RanBP2 to promote their nuclear entry and/or inhibit antiviral responses.[39,40] RanBP2 in turn directly regulates the translation of proinflammatory mRNAs such as interleukin-6 and TNF-α mRNAs.[41] This is mainly achieved by stabilizing interactions between the RNA-induced silencing complex (RISC) and proinflammatory mRNAs as these exit the nuclear pore.[41] RanBP2 has been shown to directly bind and posttranslationally modify components of RISC,[41-44] and pathogenic gene variants appear to disrupt its binding to GW182, an RISC component.[44] RanBP2 has an important role in the regulation of neuronal mitochondrial function, and this loss of function contributes to ANE pathobiology.[39,45]

Within the context of SARS-CoV-2, it has been observed that infection leads to decreased RanBP2 protein levels.[46] In addition, SARS-CoV-2 proteins have been shown to interact with various nucleoporins and nuclear transport receptors, which helps the virus evade the host antiviral innate immunity by interfering with the nuclear import of crucial components in innate immune signaling.[38,39,47] In particular, SARS-CoV-2 is known to alter nuclear pore function through the viral protein ORF6, which binds to 2 nuclear pore proteins, Nup98 and RAE1, and inhibits the nuclear import of innate immune signals, such as STAT1, and the nuclear export of mRNAs, likely to inhibit antiviral responses.[48-50]

Early diagnostic neuroimaging, intensive care support, and neuroprotection strategies are important in critically ill patients with ANE.[2-4] Therapeutic hypothermia, or targeted temperature management (normothermia or mild hypothermia at 35–36°C), inhibits microglial activation and proinflammatory cytokine production, a key step in ANE pathobiology leading to neuronal injury.[51] The pediatric patients in our review (Table 2) received early treatment with IV steroids, immunoglobulins, and tocilizumab, a practice more common to pediatric neurologists.[3,52,53] However, evidence for this is based on observational data because it is challenging to conduct randomized controlled trials in a rare condition such as ANE. Serendipitously, the COVID-19 pandemic has provided the opportunity to objectively study anticytokine treatment strategies in COVID-19 disease, which essentially shares a hyperinflammatory pathobiology with infection-triggered encephalopathy syndromes such as ANE and AFCE. In the multicenter REMAP-CAP study, the early use (within 24 hours of ICU admission) of interleukin-6 receptor antagonists tocilizumab and sarilumab in critically ill adults with COVID-19 disease receiving multiorgan support led to improved outcomes, including survival, when compared with nonimmunotherapy controls.[54]

Our review is limited by the retrospective and observational study design, the small number of cases, missing clinical information, and lack of genetic testing. Ten published cases of possible SARS-COV-2 ANE were excluded because of insufficient neuroimaging data. Included articles were single case reports, which likely represents a bias of patients with severe disease.

We have characterized the clinical and neuroimaging features of children and adults with SARS-CoV-2 ANE. Mortality is high, especially in those not receiving immunotherapy and patients at the extremes of age. The neuroimaging phenotype in SARS-CoV-2 ANE, essentially a sporadic form of ANE, exhibiting specific extrathalamic features that were previously only observed in genetic ANE (RANBP2 encephalopathy) reinforces the idea that sporadic and genetic ANE are related conditions. This also raises the possibility of nuclear pore dysfunction in SARS-CoV-2–associated acute neurologic disease and will merit further study. Data from more patients will help develop risk predictors for outcome and validate the utility of ANE-ss in SARS-CoV-2 ANE.

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