Supplementary data

Supplementary Table 1: Risk of bias assessment.

First author	Year	S1	S2	S3	S4	C1	C2	O1	O2	O3
Aksu Uzunhan	2021	1	1	NA	NA	1	1	NA	1	NA
Chen	2016	1	1	1	NA	1	1	NA	1	1
Fang	2017	1	1	NA	NA	1	1	NA	1	1
Gao	2020	1	1	NA	NA	1	1	NA	1	1
Gürtler	2005	1	1	1	1	1	1	0	0	1
Hoshino	2012	1	1	NA	NA	1	1	NA	0	0
Kasai.	2020	0	1	NA	NA	1	1	NA	0	0
Kashiwagi	2021	1	1	NA	NA	1	1	NA	1	1
Kashiwagi	2015	1	1	0	1	1	0	0	1	0
Kashiwagi	2014	1	1	NA	NA	1	1	0	1	0
Kato	2011	1	1	1	1	1	1	0	0	0
Kawashima	2012	0	1	NA	NA	1	1	0	0	0
Maruyama	2020	1	1	NA	NA	1	1	NA	0	0
Moteki	2021	1	1	NA	NA	1	1	NA	1	1
Ogawa	2020	1	0	NA	NA	1	1	NA	1	1
Qing	2020	1	1	NA	NA	1	1	NA	1	1
Tada	2004	1	1	NA	NA	1	1	NA	1	1
Takanashi	2009	1	1	0	0	0	0	0	1	0
Takanashi	2009	1	1	1	1	1	1	NA	1	0
Toi	2021	1	1	1	1	0	0	1	1	0
Tsubouchi	2018	1	1	1	1	1	1	0	1	0
Xue	2021	1	1	NA	NA	1	1	NA	1	1
Zhang	2020	1	1	NA	NA	1	1	NA	1	1
Zhu	2016	1	1	NA	NA	1	1	NA	1	1
Zhuang	2019	1	1	NA	NA	1	1	NA	1	1

Risk of bias assessment for publications with more than 10 cases. Selection domain: S1: is the case definition adequate; S2: Representativeness of cases; S3: Selection of controls; S4: Definition of controls; Comparability domain: C1: Sex; C2: Age; Outcome domain: O1: Blinded assessors; O2: Follow-up (1 month or resolution); O3: Drop out (reported or > 70%). Ones indicating low risk of bias, zeros indicating high risk of bias.

Abbreviations: NA, not applicable.

Supplementary Table 2: Complete list of entities associated with cytotoxic lesions of the corpus callosum (CLOCC) in adults.

Drug or drug withdrawal or toxins (n=88) (27%)	Antiepileptic drug (unspecified, n=24) Carbamazepine (n=8) Dietary supplement (n=6) Metronidazole (n=6) 5-fluorouracile (n=5) Lithium (n=3) Levetiracetam (n=2) Neuroleptic unspecified (n=2) Neuroleptic malignant syndrome (n=2) Olanzapine (n=2) Phenytoin (n=2) Valproate (n=2) Acute toxic encelopathy unspecified (n=1) Amanita phalloides (n=1) Aripiprazole (n=1) Benzhexol (n=1) Cabergoline (n=1) Capecitabine (n=1) Chemotherapy (n=1) Clozapine (n=1) Corticosteroids (n=1) Dichlormethane (n=1) Diuretic (n=1) Glyophosphat poisoning (n=1) Indomethacine (n=1) Ipilimumab (n=1) IvIg (n=1) Lorazepam (n=1) Mannitol (n=1) Metothrexate (n=1) Oxcarbamazepine (n=1) Risperidone (n=1) Tegafur uracil (n=1) Trihexyphenidyl (n=1) Vigabatrin (n=1)
Viral (n=59) (18%)	COVID 19 (n=15) Influenza virus(n=13) Dengue virus (n=5) Eppstein-barr virus (n=4) Adenovirus (n=2) Hepatitis A virus (n=2) Puumala hanta virus (n=2) Rotavirus (n=2) Viral encephalitis unspecified (n=2) Chikungunya virus (n=1) Cytomegalovirus (n=1) HHV6 (n=1) HIV (n=1) Japanese encephalitis virus (n=1)

	Measles (n=1) Mumps (n=1) Severe fever with thrombomozytopenia virus (n=1) Tick-borne encephalitis (n=1) Varicella zoster virus (n=1) Viral meningitis unspecified (n=1) Viral respiratory tract infection (n=1)
Vascular (n=60) (18%)	Subarachnoidal hemorrhage (n=49) Cerebral venous thrombosis (n=2) Ischemic stroke (n=2) Fat embolism in sickle cell disease (n=1) Pulmonary embolism (n=1) Reversible cerebral vasoconstriction syndrome (n=1) Segmental artery mediolysis (n=1) Subdural empyema (n=1) Subdural hematoma surgery (n=1) Thrombotic thrombocytopenic purpura (n=1)
Bacterial and plasmodia (n=34) (10%)	Plasmodium falciparum (n=8) Mycoplasma pneumoniae (n=7) Staphlyococcus aureus (n=4) Legionella (n=3) Salmonella typhii (n=2) Bortadella pertussis (n=1) Chlamydia pneumoniae (n=1) Enterococcus faecalis (n=1) Escheria coli (n=1) Klebsiella pneumoniae (n=1) Meningococcus (n=1) Mycobacterium tuberculosis (n=1) Orientia tsutsugamushi (n=1) Staphylococcus aureus (n=1) Streptococcus pneumoniae (n=1)
Seizure and epilepsy (n=20) (6%)	Epilepsy (n=17) Seizure (n=2) Status epilepticus (n=1)
Metabolic (n=10) (3%)	Hypoglycemia (n=7) Acyl-CoA dehydrogenase deficiency (n=1) Diabetes (n=1) Hyperglycemia (n=1)
Pregnancy-associated (n=8) (2%)	Eclampsia (n=1) Eclampsia-associated PRES (n=1) Postpartum (n=1) Postpartum cerebral angiopathy (n=1) Postpartum encelopathy (n=1) Postpartum preeclampsia (n=1) Postpartum psychosis (n=1) Pregnancy (n=1)

Autoimmune (n=6) (1.8%)	GFAP antibodies (n=2) Anti-VGKC antibodies (n=1) Anti-yo rhombencephalitis (n=1) NMDA encephalitis (n=1) SLE (n=1)
Trauma (n=4) (1.2%)	Traumatic brain injury (n=4)
Neoplasia (n=4) (1.2%)	Insulinoma (n=1) Leucemia (n=1) Mantle cell lymphoma (n=1) Melanocytoma (n=1)
Other (38) (12%)	Demyelination disease (n=3) Hyponatremia (n=3) Marchiafava-Bignami Disease (n=3) Csf pressure drop (n=2) Acute intermittent porphyria (n=1) Acute onset psychosis (n=1) Acute urinary retention (n=1) Acyl-CoA dehydrogenase deficiency (n=1) Alcoholism (n=1) Aseptic meningomyelitis (n=1) Atypical HUS (n=1) Blood transfusion (n=1) Cesareansection (n=1) COVID vaccine (n=1) Deep brain stimulation (n=1) Delirious mania (n=1) ECMO (n=1) Fanconi syndrome (n=1) Gastric bypass (n=1) Graves disease (n=1) HaNDL (n=1) Hemicrania continua (n=1) High altitude sickness (n=1) Hyperthyroidism (n=1) Hypernatremia (n=1) Hypoxia (n=1) Meningitis retention syndrome (n=1) Migraine (n=1) Parkinsonism (n=1) Rabies vaccine (n=1) Thyroid storm (n=1)

In 330 patients an associated disease was identified, in 86 patients, no associated disease could be identified (number of subjects per associated disease is reported in brackets).

Abbreviations: CSF, cerebrospinal fluid; ECMO, extracorporeal membrane oxygenation; GFAP, Glial fibrillary acidic protein; HaNDL, headache accompanied with transient neurologic deficits and cerebrospinal fluid lymphocytosis; HHV-6, human herpes virus 6; HIV, human immunodeficiency virus; HUS, Hemolytic-uremic syndrome; IVIg, intravenous immunoglobulins; NMDA, N-methyl-D-

aspartate; PRES, Posterior Reversible Encephalopathy Syndrome; SLE, systemic lupus erythematosus; VGKC, voltage-gated potassium channel.

Supplementary table 3: Complete list of entities associated with cytotoxic lesions of the corpus callosum (CLOCC) in children.

Viral (n=409) (75.5%)	Influenza virus (A or B) (n=187) Rotavirus (n=140) Adenovirus (n=10) Human herpes virus 6 (n=16) COVID 19 (n=10) Mumps (n=8) Respiratory-syncytial virus (n=6) Eppstein-barr-virus (n=4) Viral gastroenteritis unspecified (n=4) Coxsackie Virus (n=3) Cytomegalovirus (n=3) Echovirus (n=3) Herpes-simplex virus (n=3) Viral encelopathy, unspecified (n=2) Viral respiratory infection, unspecified (n=2) Parvovirus B19 (n=2) Varizella-zoster virus (n=2) Dengue virus (n=1) Hand-foot-mouth disease (n=1) Parainfluenza virus (n=1) Rhinovirus (n=1)
Bacterial (40) (7.4%)	Mycoplasma pneumoniae (n=15) Enterococcus faecalis (n=5) Escheria coli (n=4) Streptococcus pneumoniae (n=3) Listeria monocytogenes (n=2) Salmonella (n=2) Bacterial encelopathy (n=1) Bacterial menigitis (n=1) Cryptococcus (n=1) Group B streptococcus (n=1) Klebsiella pneumoniae (n=1) Legionella (n=1) Meningococcemia (n=1) Neisseria meningitidis (n=1) Rickettsia rickettsii (n=1)
Seizure or epilepsy (n=19) (3.5%)	Epilepsy (n=10) Seizure (n=7) Benign infantile epilepsy (n=2)
Electrolyte disbalance (n=18) (3.3%)	Hyponatremia (n=18)
Vascular (n=13) (2.4%)	Kawasaki Disease (n=13)
Drug, toxine and vaccination (12) (2.2%)	Mumps vaccination (n=6) Antiepileptica (n=1) Carbon monoxide (n=1)

	Electronic-cigarette or vaping product use-associated lung injury EVALI (n=1) Steroids (n=1) Sulfonylurea Intoxikation (n=1) Tetracycline (n=1)
Trauma (n=10) (1.8%)	DAI (n=9) Brain injury (n=1)
Autoimmune (n=4) (0.7%)	Anti GFAP astrocytopathy (n=2) SLE (n=2)
Other (17) (3.1%)	Acute encelopathy in congenital adrenal hyperplasia (n=3) Thyroid crisis (n=2) Acute toxic encelopathy unspecified cause (n=1) Adrenocortical insufficiency (n=1) Apparent-life threatening event in infancy (n=1) acute lymphoblastic leukemia (n=1) Argininosuccinic adicuria (n=1) Hyperglycemia (n=1) Hypothermia (n=1) Hypoglycemia (n=1) Mitochondrial disease (n=1) Saposin B deficiency (n=1) Status migrainosus (n=1) Stool amoeba cysts (n=1)

In 542 patients an associated disease was identified, in 395 patients the cause remained unknown (number of subjects per associated disease is reported in brackets).

Abbreviations: *DAI, diffuse axonal injury; GFAP, glial fibrillary acidic protein; SLE, systemic lupus erythematosus.*

Supplementary table 4: Complete list of entities, sex, and age associated with lesions other than splenium.

Location involving	Male sex (%)	Disease entity	Age
Genu (n=15)	77%	Mycoplasma pneumoniae (n=3) Benign partial epilepsy in infancy (n=2) Influenza A (n=2) Influenza unspecified (n=1) Adenovirus (n=1) Non alcoholic partially reversible Marchiafava-Bignami Disease (n=1) Respiratory syncytial virus (n=1) Kawasaki Disease (n=1) Rotavirus enterocolitis (n=1) Unknown (n=2)	13 children (median age 8.5 years) 2 adults (median age 52 years)
Corpus (n=2)	(50%)	Non alcoholic partially reversible Marchiafava-Bignami Disease (n=1) Influenza A (n=1)	1 adult (78 years) 1 child (10 years)
Entire (n=6)	(50%)	Parainfluenza (n=1) Adenovirus (n=1) Salmonella enteritis (n=1) Influenza A (n=1) e. coli pyelonephritis (n=1) Unknown (n=1)	6 children (median age 8 years)

Search string

(Cytotoxic lesion* of the corpus callosum) OR (cloccs) OR (transient lesion* of the splenium of the corpus callosum) OR (transient focal lesion* in the splenium of the corpus callosum) OR (transient splenial lesion*) OR (mild encephalitis with a reversible isolated SCC lesion) OR (mild encephalopathy with a reversible isolated SCC lesion) OR (mild encephalopathy with reversible splenial lesions) OR (reversible splenial lesion*) OR ("reversible splenial lesion syndrome") OR (RESLES) OR (clinically silent lesion* in the splenium of the corpus callosum)

List of publications included in the systematic review (in alphabetical order)

1. Abenhaim Halpern, L., et al., Mild encephalopathy with splenial lesion and parainfluenza virus infection. Pediatr Neurol, 2013. 48(3): p. 252-4.
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