

# THE LANCET

## Child & Adolescent Health

### Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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## Supplementary appendix:

### **NEUROLOGICAL MANIFESTATIONS OF COVID-19 INFECTION IN UK HOSPITALISED CHILDREN AND ADOLESCENTS: A PROSPECTIVE NATIONAL COHORT STUDY**

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#### **Appendix 1:**

#### **Clinical vignettes of four children with COVID-19 associated neurological or psychiatric disorders.**

##### **a) Acute Disseminated Encephalomyelitis; Myelin Oligodendrocyte Glycoprotein antibody positive (case 4 Supplementary table 1; figure 2, imaging series 1)**

A 2 year-old White girl with a history of neonatal Group B Streptococcal meningitis (full recovery) presented with fever, encephalopathy, ataxia and shock. She was initially treated with intravenous ceftriaxone. Admission PCR of the respiratory secretions was positive for SARS-CoV-2; antibodies for SARS CoV2 PCR were not performed. CSF analysis revealed a mild pleocytosis: WCC 7; biochemistry normal; viral PCR including SARS-COV-2 RNA negative; oligoclonal bands negative. Serum MOG antibody was positive. The MRI brain scan revealed extensive white matter abnormalities in keeping with ADEM (figure 2). She received high dose IV methylprednisolone (30mg/kg/od) for 72 hours followed by an oral tapering course of prednisolone (initial dose 2mg/kg/day) over 4 weeks. By two weeks she had made an apparent full recovery.

##### **b) Paediatric Multisystem Inflammatory Syndrome Temporally associated with COVID-19 with Mild Encephalopathy with Reversible Splenial sign (case 48 Supplementary table 1; figure 2 imaging series 2)**

An 11 year-old Asian boy presented with a 5 day history of fever, headache and 12 hours of progressive encephalopathy. Two months prior, he had an episode of clinically suspected COVID-19 (his mother was SARS-COV-2 PCR positive; he was not tested). On admission he fulfilled the criteria for PIMS-TS and was treated with IV fluid boluses, ceftriaxone and aciclovir. Serum SARS-CoV-2 IgG antibodies were positive. The CSF was acellular; biochemistry was normal. The MRI brain scan revealed characteristic signal change in the splenium of the corpus callosum in keeping with MERS (figure 2). He required PICU support; additional treatment included IVIG (2g/kg) and three days of IV methylprednisolone (1g daily) followed by an oral tapering course of prednisolone. He improved rapidly over 5 days and made an apparent full recovery.

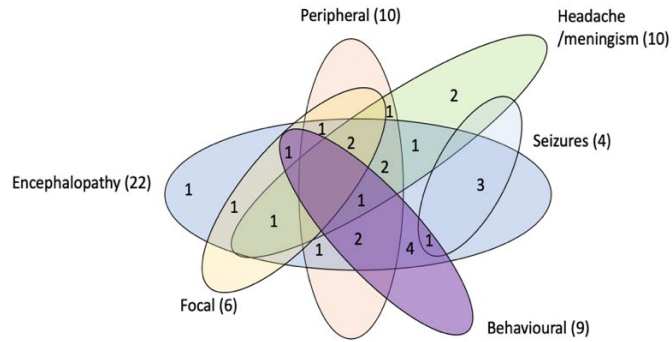
**c) Guillain Barré Syndrome** (case 8 Supplementary table 1; figure 2, imaging series 3)

A 16 month-old Asian boy presented with one-week history of fever, cough and coryza then developed progressive weakness; becoming flaccid in all four limbs and areflexic. Admission PCR of respiratory secretions was negative including for SARS-CoV-2. The CSF was acellular; protein was elevated (1762mg/L). He was admitted to the Paediatric Intensive Care Unit (PICU) and given five days of IVIG; total dose 2g/kg. Admission SARS CoV-2 antibodies (IgG) were positive. The MRI spine demonstrated gadolinium enhancement of the cervical, thoracic and lumbar roots, with florid enhancement of the cauda equina (figure 2). Nerve conduction studies recorded a severe, acute, generalized, sensory and motor peripheral neuropathy, supporting a diagnosis of GBS. Post IVIG mobility and strength improved rapidly and with two weeks of physiotherapy he made an apparent full recovery.

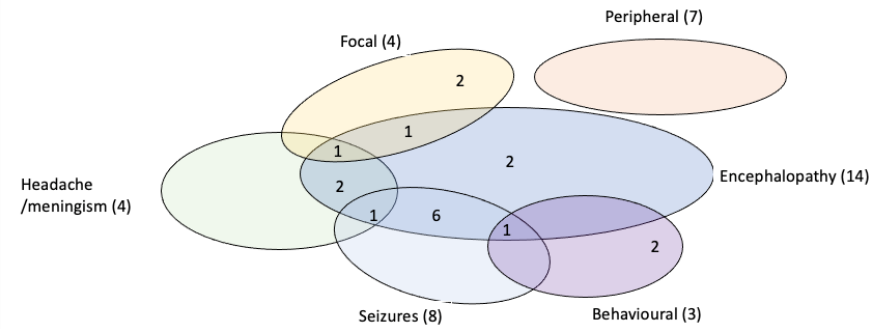
**d) Acute Psychosis** (case 23 Supplementary table 1)

A 10 year-old Black girl presented with explosive onset of aggressive behaviour and self-harm with auditory and visual hallucinations preceded two weeks earlier by coryza and cough. Six months earlier, she had an episode where she became withdrawn following a phase of poor appetite. At admission, nasal secretions were SARS-CoV-2 PCR positive. Neurological examination was normal. Extensive organic investigations were negative: MRI brain and EEG were normal, the CSF was acellular; biochemistry was normal, viral and bacterial PCR was negative and CSF neurotransmitters were normal, an immunology work up was unremarkable. Serum SARS-CoV-2 IgG antibodies were positive on day five of admission. Her psychotic manifestations persisted throughout the admission and the consulting paediatric psychiatrist concluded that COVID-19 could be a cause for her severe psychotic illness. She was discharged after one month taking oral olanzapine with intensive psychiatric team support.

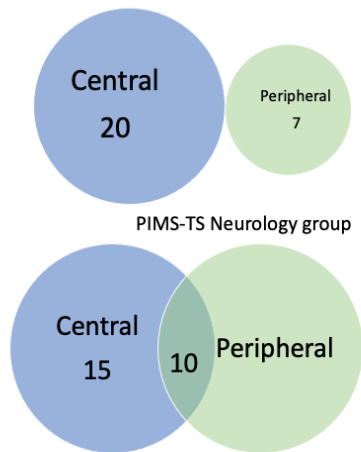
a) PIMS-TS Neurology group n=25



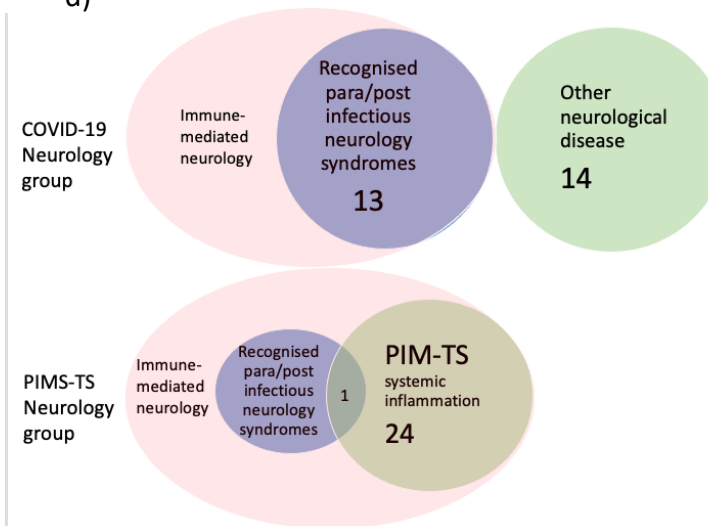
b) COVID-19 Neurology group n=27



c) COVID-19 Neurology group



d) COVID-19 Neurology group



Appendix 2; Figure 1: Venn diagrams

(a,b) Comparison of the overlapping neurological features in the PIMS-TS neurology (a) and COVID-19 neurology groups (b)

c) Central and peripheral nervous system disorders showing an overlap in 10 PIMS-TS neurology cases and none in the COVID-19 neurology group

d) The interplay between those with recognised neuro-immune disorders and the probable underlying immune mediated disease in both the COVID-19 and PIMS-TS neurology groups

### **Appendix 3:**

#### **Cases excluded due to inadequate neurological manifestations:**

1. 9 year old boy. PIMS-TS. Moderate headache and meningism only, normal CSF analysis, no neuroimaging, no PICU admission, full recovery.
2. 10 year old boy. PIMS-TS. Moderate headache only, no lumbar puncture or neuroimaging, no PICU admission, full recovery.
3. 13 year old girl. PIMS-TS. Very brief mild encephalopathy; no neuroimaging, lumbar puncture, one day on PICU, full recovery.
4. 14 year old girl. PIMS-TS. Brief encephalopathy considered to be due to post PICU sedation; no lumbar puncture or neuroimaging, full recovery.
5. 6 month old female with congenital heart disease; intermittent mild encephalopathy, treated with remdesivir, no lumbar puncture, evidence of established microhaemorrhages on MRI brain, recovered quickly from COVID-19 but on PICU for 100 days due to cardiac disease and died before surgery.
6. 4 year old boy, worsening of known tics and obsessive compulsive features two weeks after resolution of his COVID-19 infection. The panel felt the change in child's routine due to the pandemic could be significant and the natural history of neuropsychiatric disorders is one of fluctuation.

### **Appendix 4:**

#### **Cases excluded due to lack of evidence of SARS-CoV-2 infection:**

1. Term born male infant. Neonatal circulatory shock and persistent pulmonary hypertension of the newborn (PPHN) from birth; MRI brain imaging on day 15 after birth revealed multiple small foci of haemorrhage in the parasagittal and periventricular white matter, clustered small haemorrhagic foci within the inferior aspect of both cerebellar hemispheres and small and small foci of dependent haemorrhage within the occipital horns or the lateral ventricles. The mother had a clinical diagnosis of respiratory COVID-19 at approximately 28 weeks gestation. Maternal IgG was negative after the infant's birth. SARS-CoV-2 PCR of the neonate's respiratory secretions on day 2 after birth and subsequent serum IgG were negative.
2. Term born male infant. Perinatal left middle cerebral artery stroke diagnosed day nine after birth on MRI brain. The mother had a clinical diagnosis of respiratory COVID-19 at approximately 28 weeks gestation. Maternal IgG was negative after the infant's birth. SARS-CoV-2 PCR of the neonate's respiratory secretions on day 14 after and subsequent serum IgG were negative.
3. Infant male aged 4 months with Acute Necrotizing Encephalopathy presenting with circulatory shock and seizures; genetic testing for RANBP2 negative. Infant deteriorated and died rapidly; post-mortem was declined. Maternal SARS-CoV-2 PCR of respiratory secretions positive on day 1 (asymptomatic, undertaken for screening), infant's respiratory secretions PCR negative.
4. 16 year old girl with clinically suspected COVID-19 with fever, loss of taste, abdominal pain, fatigue, exacerbation of migraine and new onset anxiety disorder. SARS-CoV-2 PCR of respiratory secretions and serum IgG negative.
5. 14 year old boy with clinically suspected COVID-19 with fever, dyspnoea, loss of smell and taste who developed new anxiety symptoms, sleep disorder and fatigue.

SARS-CoV-2 PCR of respiratory secretions negative, IgG not performed. MRI brain performed at one month follow up was normal.

Case [reference if reported]	Age [years (y) or months (m)], Sex (M/F), Ethnicity/Co-morbidities	Clinical presentation: systemic/ nervous system	SARS-CoV-2 Respiratory PCR/ Serum IgG	Laboratory features: blood/cerebrospinal fluid	EEG/NCS & EMG	CT/MRI brain +/- MRI spine imaging	Diagnoses & neurological or psychiatric syndromes	Days in PICU/ Inotropes (Y/N)	Immune therapy	Outcome Modified Rankin Scale Score
<b>COVID Neurology group (n=27)</b>										
1	10y, F, Asian	Fever, ageusia, vomiting/encephalopathy, headache	PCR +ve/ IgG -ve	CRP 21, WCC 10, MOG Ab +ve/D4 CSF WCC 6075, P 0.53, G 4.8, viral PCR & bacterial PCR -ve (including SARS-CoV-2); D38, WCC 5, P 0.48, G 3, viral & bacterial PCR (including SARS-CoV-2) -ve	N/N	CT N, MRI D6 N; D44 cortical & basal ganglia T2 lesions & subcortical white matter lesions consistent with ADEM	Encephalitis: ADEM	3/N	IVMP*	2, unfavourable outcome: Memory problems
2 [9]	13m, F, Asian	Fever, hypertension/encephalopathy, agitation, dystonic posturing	PCR +ve & adenovirus +ve/ IgG +ve	CRP 12, WCC 6, MOG Ab +ve/CSF WCC 10, P 0.31, G 4.7, viral & bacterial PCR (including SARS-COV-2 RNA) -ve, OCB -ve	Diffuse background slowing/NP	MRI: Diffuse abnormal T2 signal involving all lobes of the brain (bilateral subcortical white matter), thalami, corpus callosum, cerebellar & pons consistent with ADEM	Encephalitis: ADEM	7/N	IVMP*	1, favourable outcome
3	12m, M, White	Fever/encephalopathy, movement disorder, ataxia, cranial neuropathies, R sided facial weakness, R eye ptosis	PCR -ve/ IgG +ve	CRP <5, WCC 27.3, MOG & AQP4 Ab -ve /CSF WCC 11, P 0.11, G 4.1, viral & bacterial PCR -ve, OCB +ve	N/dysfunction of R facial nucleus	MRI: Brain multiple lesions T2/FLAIR signal change within the deep/juxtacortical & subcortical white matter, brainstem. Spine abnormal signal thoracic spine extending to conus	Encephalitis: ADEM & longitudinally extensive TM	0/N	IVMP, IVIG*	2, unfavourable outcome: Crawling (walking prior to admission)
4	2y, F, White/ post neonatal meningitis ventriculomegaly (no clinical correlate)	Fever, shock/encephalopathy, ataxia, meningism	PCR +ve/ NP	CRP<1, WCC 11.8, MOG Ab +ve/CSF WCC 7, P 0.29, G 3.2, viral & bacterial PCR -ve	NP/NP	MRI: Multiple T2/flair lesions involving the thalami, internal capsules, basal ganglia, parietal white matter, R middle cerebellar peduncle & cerebellar white matter	Encephalitis: ADEM	0/N	IVMP*	0, favourable outcome
5	7y, M, Asian/ neuroblastoma	Fever/neck & back pain, enuresis, ataxia	PCR +ve/ NP	CRP 42, WCC 4, MOG Ab -ve/CSF WCC 4, P 1.9, G 2.5, viral & bacterial PCR -ve	N/NP	MRI: Spine: T2 diffuse hyperintensity of the cord from C1 to conus. Brain T2 diffuse hyperintensities bilaterally	Longitudinally Extensive TM	0/N	Nil (in view of oncology therapy)	4, unfavourable outcome: Using zimmer frame to walk
6	9y, M, Black	None/weakness R arm & leg	PCR -ve; IgG +ve	CRP <5, WCC 9.7, MOG Ab -ve, AQP4 Ab -/CSF WCC 135, P 0.3, G 5, viral & bacterial PCR -ve	NP/NP	MRI: Multiple inflammatory WM lesions in juxtacortical, periventricular, pericallosal & infratentorial, lesions demonstrated 'open ring' contrast enhancement & restricted diffusion	Clinically isolated syndrome (demyelinating)	0/N	IVMP*	1, favourable outcome: Sleep disturbance, functional neurological disorder
7	6y, M, Asian	Fever, cough/relapse R optic neuritis (1 <sup>st</sup> episode 4 weeks before COVID-19)	PCR +ve/ NP	CRP 12, WCC 10.5, MOG Ab +ve/CSF WCC 0, protein N, NA, viral & bacterial PCR -ve, OCB -ve	N/NP	MRI: signal change in intra orbital segment of R optic nerve consistent with optic neuritis; Syrinx (incidental)	R Optic Neuritis	0/N	IVMP, IVIG*	2, unfavourable outcome: Visual disturbance, ongoing care
8	16m, M, Asian	Fever, coryza/progressive weakness, loss of motor skills, hoarse voice, areflexia	PCR -ve/ IgG +ve	CRP 2, WCC 11, glycolipid Ab -ve/CSF WCC 0, P 1.8, G 4.5, viral & bacterial PCR negative, OCB NP	NP/acute, sensorimotor peripheral neuropathy consistent with GBS	MRI: Spine; enhancement of the spinal nerves throughout with florid enhancement of the cauda equina, suggestive of GBS	Guillain Barré Syndrome	1/N	IVIG*	0, favourable outcome



9	3y, F, Asian	Fever/ataxia, weakness, areflexia lower limbs	PCR +ve/ IgG -ve	CRP 1, WCC 18, glycolipid Ab screen -ve/CSF WCC 3, P 1.08, G 2.8, viral & bacterial PCR negative, OCB NP	NP/ NP	MRI: Brain N; spine not tolerated	Guillain Barré Syndrome	0/N	Nil	3, unfavourable outcome: Ataxia
10	9y, M, White/epilepsy, ASD, ex-premature infant	None/ataxia, ascending weakness, L sided weakness, areflexia	PCR +ve/ NP	CRP & WCC N/CSF WCC <1, P 2.63, G NA, viral & bacterial PCR -ve, OCB NP	NP/acute, sensorimotor peripheral neuropathy consistent with GBS	MRI: Brain & spine N	Guillain Barré Syndrome	0/N	IVIG*	0, favourable outcome
11	4y, M, White	Coryza/back pain, ascending weakness, unable to weight bear, sensory ataxia, areflexia	PCR +ve/ NP	CRP & WCC 9/CSF WCC 24, P 1.8, G NA, viral & bacterial PCR -ve	NP/acute, sensorimotor peripheral neuropathy consistent with GBS	MRI: brain & spine N	Guillain Barré Syndrome	0/N	IVIG*	0, favourable outcome
12	14y, F, Black/ focal epilepsy	Fever/headache, seizure, urinary incontinence, facial weakness, reduced power, areflexia all 4 limbs	PCR +ve/ NP	CRP<1, WCC 11.8/CSF WCC 0, P 2.1, G3.6, viral & bacterial PCR -ve	NP/acute, sensorimotor peripheral neuropathy consistent with GBS	MRI spine: enhancement of the cranial nerves & cauda equina nerve roots	Guillain Barré Syndrome	0/N	IVIG*	2, unfavourable outcome: Bilateral upper limb weakness
13	4y, M, White	None/ encephalopathy, behavioural change, focal & generalised seizures	PCR +ve/ IgG +ve	CRP <1, WCC 7.5, MOG Ab -ve, NMDR Ab-ve /CSF WCC 6, RBC 2, P 0.2, G NA, viral & bacterial PCR -ve	Diffuse mild background slowing/NP	MRI: brain; T2 signal abnormality involving the hippocampi (not atrophic). Cortical diffusion restriction	Limbic encephalitis	0/N	Dexamethasone*	1, favourable outcome: Walking normally, but mild cognitive impairment, irritable
14	16y, M, Black	Fever, lethargy/encephalopathy, severe headache, photophobia, hyperacusis, meningism	PCR +ve; IgG +ve	CRP 44, WCC 10.8/CSF WCC 2, P 0.25, G 4.9, viral & bacterial PCR -ve	N/NP	MRI: MERS	Encephalopathy	0/N	Dexamethasone*	2, unfavourable outcome: Mild ataxia
15	7y, M, White	Lethargy/ encephalopathy, excessive sleepiness	PCR +ve/ NP	CRP <1, WCC 11.6/NP	Focal background slowing /NP	MRI N	Encephalopathy	0/N	Nil	0, favourable outcome
16	12y, M, Black/epilepsy, ASD, LD	None/ Status Epilepticus/ encephalopathy	PCR +ve/ IgG +ve	CRP 158, WCC 4/CSF WCC<1, P 0.14, G 3.3, viral & bacterial PCR -ve	Diffuse background slowing /NP	CT & MRI N	Status Epilepticus	0/N	Nil	0, favourable outcome
17	15y, M, White/epilepsy, ASD, ex-premature infant	None/ Status Epilepticus/ encephalopathy	PCR +ve/ IgG +ve	CRP 161, WCC 12.6/CSF WCC<1, P 0.29, G 3.2, viral & bacterial PCR -ve	N/N	CT & MRI N	Status Epilepticus	4/N	Nil	0, favourable outcome
18	12y, F, White/epilepsy, CP, R hemiplegia	Fever, rash/ Status Epilepticus/ encephalopathy	PCR +ve/ NP	CRP <1, WCC 12/NP	NP/NP	NP	Status Epilepticus	0/N	Nil	1, favourable outcome
19	12y, M, Asian/epilepsy (Dravet syndrome)	Fever, coryza/ Status Epilepticus/ encephalopathy	PCR +ve/ NP	CRP <1, WCC 7.1/NP	Diffuse background slowing /NP	NP	Status Epilepticus	1/N	Nil	0, favourable outcome
20	2y, F, White	Fever/ encephalopathy, Status Epilepticus, subsequent multiple focal seizures	PCR +ve/ NP	CRP<2, WCC 4.1/NP	N/NP	CT N	Status Epilepticus	0/N	Nil	0, favourable outcome
21	15y, M, Asian	Fever, abdominal pain/headache, encephalopathy, Status Epilepticus	PCR +ve/ NP	CRP 5, WCC 14/CSF WCC 3, P 0.21, G 3.7, viral & bacterial PCR -ve	NP/NP	MRI N	Status Epilepticus	4/N	Nil	1, favourable outcome
22	8y, F, White	Fever/encephalopathy, Status Epilepticus	PCR +ve/ NP	CRP <4, WCC 8/NP	NP/left posterior quadrant discharges	MRI N	Status Epilepticus	0/N	Nil	0, favourable outcome

23	10y, F, Black	Cough & coryza/aggression, self-harm, auditory & visual hallucinations	PCR +ve/ IgG +ve	CRP 5, WCC 4, metabolic investigations N/CSF WCC 1, P 0.13, G 3.5, viral & bacterial PCR -ve, NMDAR Ab -ve, OCB NP	N/NP	CT & MRI N	Psychosis	0/N	Nil	2, unfavourable outcome: Severe mental health problems, antipsychotic medication
24	14y, M, Black	None/acute behavioural changes	PCR -ve/ IgG +ve	CRP 12, WCC 10.5/CSF WCC 6, P 0.2, G 3, viral & bacterial PCR -ve, OCB -ve	N/NP	MRI N	Psychosis	0/N	Nil	2, unfavourable outcome: Residual psychotic symptoms, antipsychotic medication
25	14y, F, White	None/involuntary movements of the R shoulder, chorea of the R>L arm & R foot	PCR -ve/ IgG +ve	WCC 5.3, CRP NP/NP	N/NP	MRI N	Chorea	0/N	Nil	2, unfavourable outcome: Ongoing chorea
26	9y, M, White	None/bilateral chorea with dyskinesia & limb posturing	PCR -ve/ IgG +ve	CRP<5, WCC 7.3/NP	N/NP	MRI: N	Chorea	0/N	Nil	0, favourable outcome
27	10y, M, White/ previous L basal ganglia stroke	Headache, anosmia/Unable to walk, R sided weakness	PCR +ve/ NP	NP/NP	N/NP	MRI no acute changes. Established L anterior basal ganglia stroke	Transient ischaemic attack	0	Nil	0, favourable outcome

**Paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (PIMS-TS) with neurological manifestations (n=25)**

28 [8]	14y, M, Black	Fever, ARDS, diarrhoea, impaired cardiac ventricular function, cardiovascular shock/encephalopathy, headache, brain stem signs	PCR +ve/ IgG +ve	CRP 556, WCC 39/LP contraindicated	NP/NP	CT: Acute R anterior & middle cerebral artery territory infarction	Ischaemic stroke	8/Y	Nil	6, unfavourable outcome: Died
29 [8]	10y, M, Black/SSD	Fever, dorsal, chest & thigh pain (sickle cell crisis), abdominal pain & vomiting/encephalopathy, L hemiplegia	PCR -ve/ IgG +ve	CRP 296, WCC 16/LP contraindicated	NP/NP	CT: Large intraparenchymal haemorrhage R frontal lobe with midline shift	Haemorrhagic stroke	1/N	Nil	4, unfavourable outcome: L hemiparesis
30	11y, M, Asian	Fever, abdominal pain, diarrhoea, vomiting, dry conjunctiva/encephalopathy, visual & auditory hallucinations, ataxia, L sided weakness, myelopathy, urinary retention	PCR -ve/IgG +ve	CRP 221, WCC 24.9, MOG Ab +ve/CSF WCC 20 P 0.43, G4.5, viral & bacterial PCR (including SARS-COV-2) -ve, OCB -ve	Severe background slowing/lower limb mild myopathy	MRI: T2 Hyperintensity seen within the claustra bilaterally, generalised parenchymal volume loss, spine N	Encephalitis: ADEM & clinical TM	6/Y	IVMP, IVIG, PLEX*	2, unfavourable outcome: After intensive rehabilitation walking, proximal myopathy & long tract signs
31 [18]	16y, F, Black/ Cornelia de Lange syndrome; LD, epilepsy	Fever, cough, dyspnoea/encephalopathy, status epilepticus	PCR +ve/ NP	CRP 275, WCC 3/CSF WCC 3, P 0.9, G 4.4, viral & bacterial PCR -ve	Bilateral independent periodic lateralized epileptiform discharges (BI-PLEDS)/NP	MRI: Extensive cortical & thalamic signal change without diffusion restriction secondary to hypoxic ischaemic injury	Encephalopathy (ischaemic)	100/N	IVMP	5, unfavourable outcome: Severe disability; bedridden, incontinent; substantial deterioration from baseline
32	11y, F, Black	Fever, headache, vomiting, diarrhoea, shock/encephalopathy, proximal weakness	PCR +ve/ IgG +ve	CRP 459, WCC 15/LP NP	NP/NP	CT: N, MRI: MERS	Encephalopathy & neuromyopathy	4/Y	IVMP, IVIG	1, favourable outcome

33	13y, F, Black	Fever, abdominal & chest pain, vomiting/ataxia, bilateral foot drop, mild encephalopathy, weak L arm	PCR -ve/ IgG +ve	CRP 253, WCC 26.8/CSF WCC<1, P 0.25, G 3.6, viral & bacterial PCR -ve, OCB -ve	Diffuse background slowing/Myopathy & mild bilateral tibialis neuropathy	MRI: Developmental venous anomaly (incidental finding)	Encephalopathy & neuromyopathy	1/N	IVMP, IVIG	2, unfavourable outcome: Reduced co-ordination, residual L arm weakness
34 [9,17]	15y, F, Asian	Fever, vomiting, rash, shock/ encephalopathy, dysarthria, dysphagia, proximal weakness	PCR +ve/ IgG +ve	CRP 290, WCC 37/LP NP	Mild background slowing anterior regions/ myopathic & neuropathic changes	MRI: MERS & bilateral parietal white matter lesions; scattered micro-haemorrhages	Encephalopathy & neuromyopathy	14/Y	IVMP, IVIG, Anakinra, Ciclosporin, Rituximab	0, favourable outcome
35 [9,17]	15y, F, Black	Fever, dyspnoea, vomiting, rash/ encephalopathy, headache, proximal weakness	PCR +ve/ IgG +ve	CRP 328, WCC 37.1/LP NP	Mild background slowing anterior regions/ myopathic & neuropathic changes	MRI: MERS	Encephalopathy & neuromyopathy	4/Y	IVIG	0, favourable outcome
36 [9,17]	9y, M, Black	Fever, vomiting, rash, shock/encephalopathy, dysarthria, headache, ataxia, proximal weakness	PCR +ve/ IgG +ve	CRP 313, WCC 13.6/CSF WCC 2, P 0.19, G 5, viral & bacterial PCR (including SARS-COV-2)-ve, OCB -ve	Diffuse background slowing/NP	MRI: MERS & bilateral subcortical parietal white matter lesions	Encephalopathy & neuromyopathy	2/N	IVIG	0, favourable outcome
37	9y, F, Asian	Fever, rash, vomiting, diarrhoea, abdominal pain/visual hallucinations, encephalopathy, R lower limb neuropathic pain	PCR -ve/IgG +ve	CRP 378, WCC 19.5/NP	NP/proximal neuropathy of R peroneal & tibial nerve	MRI: Isolated area of leptomeningeal inflammation L post-parietal lobe. Spine N	Encephalopathy & neuromyopathy	4/Y	IVMP, IVIG	4, unfavourable outcome: R peroneal nerve damage; foot drop, crutches to mobilise
38	16m, F, Asian/ Type 1 Diabetes Mellitus	Fever, vomiting, diarrhoea/ encephalopathy, headache, ataxia, dysphasia, dysphonia, left Horner's syndrome, R sided LMN facial weakness, R upper limb hypertonia	PCR -ve/ IgG -ve	CRP 161, WCC 35.6/CSF WCC<1, P 0.39, G 3.4, viral & bacterial PCR -ve	Diffuse background slowing/N	MRI: Bi-frontal multiple focal areas of diffusion restriction	Encephalopathy & neuromyopathy	6/Y	IVIG, high dose oral prednisolone	1, favourable outcome: Required physiotherapy to optimise strength & balance, now fully recovered
39	10y, M, Asian/ Asthma	Fever, vomiting, diarrhoea, dyspnoea / encephalopathy, visual hallucinations, dysphonia, subtle dysmetria bilaterally, R arm weakness (areflexia), L leg weakness	PCR -ve/ IgG +ve	CRP 267, WCC 14.5/NP	Mild diffuse background slowing/myopathic changes	MRI: diffuse microhaemorrhages	Encephalopathy & neuromyopathy	2/Y	IVMP, IVIG	0, favourable outcome
40 [9, 17]	9y, M, Asian	Fever, abdominal pain, rash, vomiting, circulatory shock/ encephalopathy, agitation, meningism, headache, generalised proximal weakness	PCR +ve/ IgG -ve	CRP 448, WCC 38.7/CSF WCC 8, P 0.2, G NA, viral & bacterial PCR (including SARS-CoV-2) -ve, OCB -ve	Mild diffuse background slowing/patchy myopathic changes	CT: N, MRI: MERS	Encephalopathy & neuromyopathy	9/Y	IVMP, IVIG Anakinra	0, favourable outcome
41	13y, F, Black	Fever, cough, dyspnoea, abdominal pain, vomiting, shock/ encephalopathy, seizures	NP/ IgG +ve	CRP 302, WCC 21.8/LP NP	Diffuse background slowing/ NP	CT N	Encephalopathy	4/N	IVMP, IVIG	0, favourable outcome
42 [8]	2y, F, Black	Fever, lymphadenopathy, abdominal pain/encephalopathy	PCR +ve/ IgG +ve	CRP 189, WCC 20/CSF WCC 3, P 0.1, G 2.6, viral & bacterial PCR -ve, OCB -ve	Fluctuating mild background slowing/ NP	CT & MRI N	Encephalopathy	0/N	IVMP, IVIG Tocilizab	0, favourable outcome

43 [8]	4y, M, White	Fever, abdominal pain, diarrhoea, vomiting/encephalopathy & behavioural changes	PCR -ve/ IgG -ve	CRP 283, WCC 19/CSF WCC<1, protein 0.14, G NA, viral & bacterial PCR (including SARS-COV-2) -ve, OCB +ve	N/NP	MRI N	Encephalopathy	0/N	IVMP, IVIG	0, favourable outcome
44 [8]	5y, F, Asian	Fever, rash, face & foot oedema, abdominal pain, vomiting/encephalopathy & behavioural changes	PCR +ve/ IgG +ve	CRP 80, WCC 21/LP NP	NP/NP	NP	Encephalopathy	0/N	Nil	3, unfavourable outcome: Persistent behavioural changes
45 [8]	8y, F, Black	Fever, vomiting, diarrhoea, cardiac shock/encephalopathy, visual hallucinations	PCR -ve/ IgG +ve	CRP 470, WCC 18/LP NP	NP/NP	MRI N	Encephalopathy	7/Y	IVMP, IVIG	0, favourable outcome
46 [8]	12y, F, Black	Fever, rash, cracked lips, conjunctivitis, lymphadenopathy, ARDS, abdominal pain, diarrhoea, vomiting, shock/ behavioural changes (delirium), cognitive regression	PCR +ve/ IgG +ve	CRP 343, WCC 32/LP NP	Slow waves posterior L hemisphere/NP	MRI: Diffuse cortical signal abnormality both cerebral hemispheres	Encephalopathy	11/Y	IVMP, IVIG, Infliximab	1, favourable outcome: Mild behavioural changes, low mood
47 [8]	15y, F, Black	Fever, ARDS, shock/encephalopathy & behavioural change, visual & auditory hallucinations, focal seizures	PCR -ve/ IgG -ve	CRP 99, WCC 17/CSF WCC 2, P 0.25, G 3.5, viral & bacterial PCR -ve, OCB -ve	Slow waves R temporal region/NP	MRI: MERS & multi-focal hazy signal change of WM (no diffusion restriction)	Encephalopathy	19/Y	IVMP, IVIG	2, unfavourable outcome: Memory difficulties
48	10y, M, Asian	Fever, conjunctival injection, lip erythema, diarrhoea, vomiting/encephalopathy, headache	PCR -ve/IgG +ve	CRP 328, WCC 12/CSF WCC <3, P 0.22, G 4.3, viral & bacterial PCR -ve	NP/NP	MRI: MERS & cortical/subcortical diffusion restriction L frontal & R occipital lobes	Encephalopathy	0/N	IVMP, IVIG	1, favourable outcome
49	5y, M, Black/ SSD, ASD	Fever, abdominal & leg pain (sickle crisis)/encephalopathy, focal & generalised seizures, Status Epilepticus	PCR -ve/ IgG +ve	CRP 119, WCC 34//LP NP	Diffuse background slowing more prominent L hemisphere/NP	MRI: Abnormal cortical T2 signal in the occipito-parietal regions (L > R) consistent with PRES. Mild diffusion restriction of the L hippocampus & thalamus (seizure-associated); MRA N	Status Epilepticus	4/N	IVMP, IVIG	0, favourable outcome
50	9y, M, Black	Fever, widespread maculopapular rash, abdominal pain/headache, meningism, L leg weakness	PCR -ve/ IgG +ve	CRP 194, WCC 21.6/CSF WCC 118, P 0.31, G 4.6, viral & bacterial PCR -ve	NP/NP	MRI: Small non-specific T2/FLAIR hyperintensities bi-parietal subcortical white matter	Meningitis & neuromyopathy	1/Y	IVMP, IVIG	0, favourable outcome
51	9y, M, White	Fever, myalgia, injected sclera, abdominal pain/headache, meningism	PCR +ve/ IgG +ve	CRP 351, WCC 4/CSF WCC 0, P 0.32, G 4.2, viral & bacterial PCR -ve	NP/NP	NP	Severe eadache/meningism	0/N	IVMP, IVIG	0, favourable outcome
52 [8]	12y, M, White	Fever, rash, foot oedema, conjunctivitis, abdominal pain, vomiting, hypotension/severe headaches	PCR -ve/ IgG -ve	CRP 94, WCC 5/LP NP	NP/NP	MRI N	Severe headache	1/N	IVMP, IVIG	0, favourable outcome

Abbreviations: M, Male; F, female; CSF, cerebrospinal fluid; mRS, modified Rankin Score; NP, not performed; N, normal; ARDS, Acute Respiratory Distress Syndrome; ASD, Autism Spectrum Disorder; SSD, Sickle Cell Disease; CP, cerebral palsy; PCR, polymerase chain reaction; IgG, immunoglobulin G; CT, computed tomography; MRI, magnetic resonance imaging; MRA, magnetic resonance angiography; WM, white matter; EEG, electroencephalogram; NCS, Nerve Conduction Studies; ADEM, Acute Disseminated Encephalomyelitis; TM, transverse myelitis; CRP, GBS, Guillain Barré Syndrome; NMDAR, N-methyl-D-aspartate receptor; PICU, paediatric intensive care unit; mRS, +ve, positive; -ve, negative; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin; MERS, Mild Encephalopathy with Reversible Splenial Lesion; LP, Lumbar Puncture; WCC, white cell count/mm<sup>3</sup>; P, protein g/L; G, glucose mmol/L; Ab, antibody; MOG, myelin oligodendrocyte; AQP4, aquaporin 4; OCB, Oligoclonal Bands; CRP, C-Reactive Protein mg/L; L, left; R, right; LMN, Lower Motor Neuron; Ab, antibodies; L, Left; R, Right; PLEX, plasma exchange; D, day; \*, indicates immunotherapy administered primarily for neurological symptoms [for the PIMS-TS neurology group, immunotherapy was administered for a multisystem severe presentation, that included neurological features, and may have improved these neurological symptoms, but was not primarily neuro-directed therapy]

**Table 1 appendix. Clinical features, investigation results and outcome of 52 children and young people with neurological or psychiatric features associated with COVID-19 from the UK listed by diagnostic syndrome**

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## **Appendix 5:**

### **Case Report Form**

This appendix outlines the CRF within the ALEA platform that was completed by clinicians as part of the CoroNerve project. The CRF is annotated to outline sections of the form that appear when particular fields have specific values inserted by the user. These annotations are highlighted with the following outline. Please see CRF in separate supplementary PDF entitled "ALEA CRF" due to size of file.

## **Appendix 6:**

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