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Neurological manifestations of SARS-CoV-2 infection in hospitalised children and adolescents in the UK: a prospective national cohort study

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Summary

Background  The spectrum of neurological and psychiatric complications associated with paediatric SARS-CoV-2 infection is poorly understood. We aimed to analyse the range and prevalence of these complications in hospitalised children and adolescents.

Methods  We did a prospective national cohort study in the UK using an online network of secure rapid-response notification portals established by the CoroNerve study group. Paediatric neurologists were invited to notify any children and adolescents (age <18 years) admitted to hospital with neurological or psychiatric disorders in whom they considered SARS-CoV-2 infection to be relevant to the presentation. Patients were excluded if they did not have a neurological consultation or neurological investigations or both, or did not meet the definition for confirmed SARS-CoV-2 infection (a positive PCR of respiratory or spinal fluid samples, serology for anti-SARS-CoV-2 IgG, or both), or the Royal College of Paediatrics and Child Health criteria for paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Individuals were classified as having either a primary neurological disorder associated with COVID-19 (COVID-19 neurology group) or PIMS-TS with neurological features (PIMS-TS neurology group). The denominator of all hospitalised children and adolescents with COVID-19 was collated as part of COVID-19 in adults.1–5 In children and adolescents (younger than 18 years), single case series have identified neurological complications associated with SARS-CoV-2 infection.6–9

Findings  Between April 2, 2020, and Feb 1, 2021, 52 cases were identified; in England, there were 51 cases among 1334 children and adolescents hospitalised with COVID-19, giving an estimated prevalence of 3.8 (95% CI 2.9–5.0) cases per 100 paediatric patients. 22 (42%) patients were female and 30 (58%) were male; the median age was 9 years (range 1–17). 36 (69%) patients were Black or Asian, 16 (31%) were White. 27 (52%) of 52 patients were classified into the COVID-19 neurology group and 25 (48%) were classified into the PIMS-TS neurology group. In the COVID-19 neurology group, diagnoses included status epilepticus (n=7), encephalitis (n=5), Guillain-Barré syndrome (n=5), acute demyelinating syndrome (n=3), chorea (n=2), psychosis (n=2), isolated encephalopathy (n=2), and transient ischaemic attack (n=1). The PIMS-TS neurology group more often had multiple features, which included encephalopathy (n=22 [88%]), peripheral nervous system involvement (n=10 [40%]), behavioural change (n=9 [36%]), and hallucinations at presentation (n=6 [24%]). Recognised neuroimmune disorders were more common in the COVID-19 neurology group than in the PIMS-TS neurology group (13 [48%] of 27 patients vs 1 [1%] of 25 patients, p=0.0003). Compared with the COVID-19 neurology group, more patients in the PIMS-TS neurology group were admitted to intensive care (20 [80%] vs 12 [44%] patients, p=0.045). 17 (33%) patients (10 [37%] in the COVID-19 neurology group and 7 [28%] in the PIMS-TS neurology group) were discharged with disability; one (2%) died (who had stroke, in the PIMS-TS neurology group).

Interpretation  This study identified key differences between those with a primary neurological disorder versus those with PIMS-TS. Compared with patients with a primary neurological disorder, more patients with PIMS-TS needed intensive care, but outcomes were similar overall. Further studies should investigate underlying mechanisms for neurological involvement in COVID-19 and the longer-term outcomes.

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Introduction  Neurological and psychiatric complications of infection with SARS-CoV-2 have been recognised as part of COVID-19 in adults.1–5 In children and adolescents (younger than 18 years), single case series have identified neurological complications associated with SARS-CoV-2 infection.6–9
Research in context

Evidence before this study
We searched PubMed for studies of children and adolescents with neurological or psychiatric features associated with COVID-19, published from database inception to May 5, 2021, with no language restrictions, and a focus on studies that yielded clinical descriptions and imaging findings in the cohorts described. The search yielded 183 publications, which were mostly case reports or small case series, limiting the description of the spectrum of features in the paediatric population. Two studies described larger series: one international study focused on neuroimaging findings and another described both transient and life-threatening complications from multiple centres in the USA. Two smaller studies described the manifestations of the newly described paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) from two individual centres.

Added value of this study
To our knowledge, this is the first report of a nation-wide study of neurological or psychiatric features of COVID-19 in children and adolescents. Using national hospital admission data for COVID-19 in children and adolescents allowed us to estimate the prevalence of these features for the first time. A wide range of neurological disorders and features were described, with clear differences between those who presented with and without PIMS-TS. Patients presenting without PIMS-TS had a discrete primary neurological disorder; recognised neuroimmune disorders were common in this group (present in approximately half of these patients). Other presentations included status epilepticus, movement disorders, and psychosis. Those with PIMS-TS had multiple overlapping neurological features, and encephalopathy and peripheral nervous system involvement were the most common. Only one patient with PIMS-TS had a recognised neuroimmune disorder, which suggests that perhaps different immune mechanisms underlie neurological manifestations in this newly described inflammatory syndrome. Although patients with PIMS-TS were more likely to require intensive care support, we found that early outcomes were similar in both groups; death was uncommon but one-third had a disability.

Implications of all the available evidence
By comparing children and adolescents with a primary neurological disorder associated with COVID-19 with those with PIMS-TS, we identified clear differences that could help physicians approach the management of these patients. Patients without PIMS-TS had discrete, often recognised neuroimmune, primary neurological disorders. By contrast, those with PIMS-TS had a recognisable phenotype with multiple overlapping neurological features, often with characteristic findings on brain imaging such as the splenial sign in the corpus callosum. Future studies should investigate the longer-term neurocognitive outcomes and the mechanisms underlying the cause of neurological involvement in COVID-19, particularly in those with PIMS-TS.

Methods

Study design and participants
We did a prospective national cohort study of hospitalised children and adolescents in the UK. During the first exponential phase of the COVID-19 pandemic, the CoroNerve study group was established to set up an online network of secure rapid-response notification portals via the major UK neuroscience and psychiatry institutions, including the British Paediatric Neurology Association (BPNA). From April 2, 2020, members of the BPNA were invited by the British Paediatric Neurology Surveillance Unit (BPNSU) to notify the body of any hospitalised children or adolescents they considered to have neuroimmune or psychiatric complications associated with COVID-19. Children and adolescents aged younger than 18 years were included if they had: history of laboratory-confirmed SARS-CoV-2 infection, or suspected infection, irrespective of clinical signs and symptoms; new-onset neurological or psychiatric disorder or complication of existing neurological or psychiatric disorder occurring at the time of or following shortly after COVID-19 infection; and COVID-19 infection implicated as a possible cause of neurological or psychiatric disorder by a paediatric neurologist. Patients were still included if they had a pre-existing neurological disorder. Patients were excluded if they did not have a neurological consultation or neurological investigations, or did not meet the definition for confirmed SARS-CoV-2 infection.

This study was approved by the University of Liverpool Institute of Infection, Veterinary, and Ecological Sciences ethics committee (7725/2020) and the University of...
Southampton Faculty of Medicine ethics committee (56504). The electronic case report form was hosted on ALEA Clinical and managed by the Clinical Information Research Unit (Southampton, UK).

Procedures
Cases were prospectively recorded using a standardised online case report form including demographics; evidence of SARS-CoV-2 infection; clinical characteristics; comorbidities; disease course; requirement for intensive care; laboratory, imaging, and neurophysiology results; and recovery (outcomes). By requesting reporting physicians to submit their contact details at time of notification, we established confirmation of the veracity of the data in all cases and, where required, additional data to confirm the specific clinical details were obtained from the treating clinical team.

Patients were included for analysis if they had confirmed SARS-CoV-2 infection according to WHO criteria (a positive PCR of respiratory or spinal fluid samples, serology for anti-SARS-CoV-2 IgG, or both),1 or they met Royal College of Paediatrics and Child Health criteria for PIMS-TS and had neurological or psychiatric manifestations.7

Clinical neurological or psychiatric disorders were classified into: cerebrovascular event (ischaemic stroke, intracerebral or subarachnoid haemorrhage, cerebral venous sinus thrombosis, or cerebral vasculitis); altered mental status (encephalopathy, encephalitis—defined as encephalopathy with evidence of inflammation in the CNS [cerebrospinal fluid (CSF) white cell count >5 cells per μL, protein >0·45 g/dL, or MRI consistent with inflammation], seizures [clinical or electroencephalographic evidence], and psychiatric syndromes diagnosed by an attending psychiatrist [psychosis, neurocognitive dementia-like syndrome, personality change, catatonia, mania, anxiety or depression, chronic fatigue syndrome, and post-traumatic stress disorder]); or peripheral neurology (Guillain-Barré syndrome [GBS], Miller-Fisher syndrome, brachial neuritis, myasthenia gravis, peripheral neuropathy, myopathy, myositis—defined as myopathy with evidence of inflammation [eg, by MRI or biopsy of muscle with elevated plasma creatine kinase], and critical illness neuromyopathy). Further details on these classifications are available at the BPNsu website.

Patients who were diagnosed with a primary neurological or psychiatric disorder associated with COVID-19, either secondary to acute infection (eg, status epilepticus), or a recognised para-infectious or post-infectious immune-mediated neurological disorders, were classified as having neuroimmune disorders. Combined acute-phase reactants were defined as: lactate dehydrogenase, ferritin, and D-dimers. Ethnicity was defined by National Health Service (NHS) coding criteria.16

Modified Rankin scale (mRS) score was assessed at discharge from hospital, or at the most recent clinical assessment, by a neurologist either directly or by using information from the case records.7 A good recovery was defined as an mRS score of 0–1, reflecting no substantial disability or ongoing symptoms, or back to baseline for those with a pre-existing neurological disorder; those with an mRS scale score of 2–5 were classified as having some degree of disability.7 The neurological features or imaging findings of 15 cases have been published previously (appendix pp 7–12);8,9,18,19 these cases were included to reflect the full spectrum of neurological complications of paediatric COVID-19 in the UK.

Statistical analysis
The clinical data cutoff date was Feb 1, 2021. Data were transferred from the online platform to spreadsheet format (Excel 2016) using a custom Python (version 3.8.3) script. Free-text fields describing rationale and context for selections in drop-down lists were manually converted into coded data.

An estimate of the prevalence of cases in England was calculated using hospital admission data in England from the same study dates for children and adolescents.20 As admission data were only available for England, cases from Scotland, Wales, and Northern Ireland were not included in the prevalence calculation. Normality of distribution was assessed using D’Agostino-Pearson Omnibus normality tests. Data were analysed using descriptive statistics (median, range, percentages) and group comparison tests with Student’s t tests or Mann-Whitney U tests for continuous variables and χ² for categorical variables, with two-sided p values less than 0·05 considered significant. The Kruskal-Wallis test with Dunn’s multiple group comparison test were used to determine any significant difference in temporality of initial COVID-19-related symptoms to onset of neurological symptoms between groups. Statistical analyses were done with Stata (version 15.1) and GraphPad Prism (version 9.0.0).

Role of the funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
Results
Between April 2, 2020, and Feb 1, 2021, the CoroNerve study group received notification of 63 patients who were geographically dispersed across the UK (62 in England and one in Scotland; figure 1). Six patients were excluded as they did not have a neurological consultation or neurological investigations (appendix p 5), and a further five patients were excluded due to insufficient evidence of prominent neurological involvement of symptoms. 55 patients were included in the study (all with confirmed SARS-CoV-2 infection or PIMS-TS). 52 cases were included in the study: 25 (100%) had systemic features, 22 (88%) had encephalopathy, 21 (81%) had peripheral nervous system involvement, 10 (40%) had headache or meningism, 9 (36%) had behavioural changes, 6 (25%) had CNS signs, and 4 (16%) had seizures.

Figure 1: Study profile and classification of neurological disorders
PIMS-TS—paediatric multisystem inflammatory syndrome temporally associated with COVID-19. ADEM—acute disseminated encephalomyelitis. MERS—mild encephalopathy with reversible splenial lesion. PRES—posterior reversible encephalopathy syndrome. *Recognised para-infectious or post-infectious syndromes. †All were encephalopathic. ‡Patients could have more than one feature.
or developmental condition and four (8%) had other pre-existing conditions (appendix pp 7–12). Respiratory symptoms were present at admission in 12 (23%) patients. Eight (15%) patients had isolated neurological or psychiatric features (PCR for respiratory secretions were positive for SARS-CoV-2). 27 (52%) patients were classified into the COVID-19 neurology group and 25 (48%) into the PIMS-TS neurology group. Patients in the PIMS-TS neurology group were more likely to be Black or Asian than those in the COVID-19 neurology group (22 [88%] of 25 patients vs 14 [52%] of 27 patients, p=0.048). During the same period, 1334 children and adolescents with COVID-19 were admitted to hospitals in England. Excluding one case from Scotland, the minimum estimated prevalence of neurological and psychiatric complications in hospitalised children and adolescents with COVID-19 in England was 51 in 1334, or 0·038 (95% CI 0·029–0·050; SE 0·99); ie, 3·8 (95% CI 2·9–5·0) cases per 100 paediatric patients admitted to hospital. The prevalence ranged from 1·8–8·1 cases per 100 patients depending on the region of referral; the highest prevalence was in London.

Systemic features (fever, rash, hypotension, shock) were present in 40 (77%) patients; ten (19%) had cardiovascular shock (nine of whom had PIMS-TS). Systemic features were more common in the PIMS-TS neurology group than in the COVID-19 neurology group (25 [100%] of 25 patients vs 15 [56%] of 27, p=0·023). Other features included respiratory symptoms in 12 (23%) patients, seizures in 12 (23%), and status epilepticus in nine (17%).

In the COVID-19 neurology group, 14 (52%) of 27 patients had encephalopathy compared with 22 (88%) of 25 in the PIMS-TS neurology group (p=0·0048). Of these 14 patients, seven developed an encephalopathy associated with status epilepticus (three of whom did not have pre-existing epilepsy); five had encephalitis, two had an isolated encephalopathy. 13 (48%) patients in the COVID-19 neurology group presented with a recognised neuroimmune disorder (five had GBS, four had ADEM, three had myelin oligodendrocyte glycoprotein (MOG) antibodies), three had other acute demyelinating syndromes, and one had autoimmune [limbic] encephalitis compared with only one (4%) patient in the PIMS-TS neurology group (who had ADEM with MOG antibodies; p=0·0003). Two (7%) patients presented with acute psychosis and two (7%) with chorea. One patient with a previous basal ganglia stroke was diagnosed with a transient ischaemic attack (table 2).

Ten (40%) of 25 patients in the PIMS-TS neurology group had features of peripheral nervous system involvement. Nine (36%) patients had behavioural changes, including six (24%) with hallucinations (at presentation) and ten (40%) with headache or meningism. Six (24%) patients had CNS signs (three had ataxia, one had hemiplegia associated with haemorrhagic stroke, one had brainstem signs associated with ischaemic stroke, and one had left hemiplegia associated with ADEM). Four (16%) patients had seizures; three had focal seizures (status epilepticus in one) and one had subtle motor seizures associated with ongoing subclinical ictal activity.

In the COVID-19 neurology group, peripheral nervous system involvement occurred independently as a separate disorder (GBS in all five cases). In the PIMS-TS neurology
Peripheral nervous system involvement was part of the multisystem presentation (appendix pp 3–4, figure 1).

Patients who presented with a recognised neuroimmune disorder in the COVID-19 neurology group (p=0.027) and patients in the PIMS-TS neurology group (p=0.035) were more likely to present later than those in the COVID-19 neurology group who did not have a recognised neuroimmune disorder.

SARS-CoV-2 was detected by PCR of nasal secretions in 32 (62%) of 52 patients; 21 (78%) in the COVID-19 Recognised neuroimmune condition subgroup (n=13) Other neurological disorder subgroup (n=14)

| Recognised neuroimmune condition subgroup (n=13) | Other neurological disorder subgroup (n=14) |
|-----------------------------------------------|------------------------------------------|
| **Acute demyelinating syndromes (n=7)**       | **Severe encephalopathy (n=9)**           |
| **GBS (n=5)**                                 | **Psychiatric disorder (n=2)**            |
| **Limbic encephalitis (n=1)**                  | **Movement disorder (n=2)**               |
|                                               | **Cerebrovascular disorder (n=1)**        |
| Age, years                                    | 11 (2–16)                                 |
| 5 (1–10)                                      | 12 (10–14)                                |
| 6 (1–14)                                      | 12 (9–14)                                 |
| Sex                                           | 10                                         |
| Female                                        |                                               |
| 3 (43%)                                       | 3 (33%)                                   |
| 4 (57%)                                       | 6 (67%)                                   |
| Male                                          | 1 (50%)                                   |
| 2 (40%)                                       | 1 (50%)                                   |
| 3 (60%)                                       | 1 (100%)                                  |
| 1 (100%)                                      | 1 (100%)                                  |
| **Ethnicity**                                 | 1 (100%)                                  |
| White                                         | 5 (56%)                                   |
| 2 (29%)                                       | 0                                          |
| 2 (40%)                                       | 2 (100%)                                  |
| 1 (100%)                                      | 1 (100%)                                  |
| Black                                         | 2 (22%)                                   |
| 1 (14%)                                       | 2 (100%)                                  |
| 1 (20%)                                       | 0                                          |
| Asian                                         | 2 (22%)                                   |
| 4 (57%)                                       | 0                                          |
| 2 (40%)                                       | 0                                          |
| **Underlying comorbidity**                    | 2 (100%)                                  |
| Neurological comorbidities                    |                                               |
| 1 (14%)                                       | 4 (44%)                                   |
| 2 (40%)                                       | 0                                          |
| Male                                          | 0                                          |
| 2 (40%)                                       | 0                                          |
| 4 (57%)                                       | 0                                          |
| **Clinical features**                         |                                               |
| Systemic features*                            | 6 (67%)                                   |
| 6 (86%)                                       | 0                                          |
| 3 (60%)                                       | 0                                          |
| Febrile or shock                              | 1 (11%)                                   |
| 2 (29%)                                       | 1 (100%)                                  |
| Respiratory involvement at presentation       | 9 (100%)                                  |
| 2 (29%)                                       | 0                                          |
| 2 (40%)                                       | 1 (100%)                                  |
| Acute respiratory distress or hypoxemia       | 7 (78%)                                   |
| Seizures                                      | 0                                          |
| 0                                             | 1 (100%)                                  |
| 0                                             | 0                                          |
| Encephalopathy                                | 1 (11%)                                   |
| 2 (29%)                                       | 0                                          |
| 1 (20%)                                       | 0                                          |
| Peripheral nervous system involvement         | 2 (22%)                                   |
| 1 (100%)                                      | 0                                          |
| 0                                             | 0                                          |
| **Focal CNS involvement**                     | 0                                          |
| 3 (43%)                                       | 0                                          |
| 3 (60%)                                       | 0                                          |
| Behavioural change                            | 0                                          |
| 0                                             | 0                                          |
| 1 (100%)                                      | 1 (100%)                                  |
| Headache or meningism                         | 1 (11%)                                   |
| 1 (29%)                                       | 0                                          |
| 1 (20%)                                       | 0                                          |
| 1 (100%)                                      | 0                                          |
| 2 (22%)                                       | 0                                          |
| Peripheral nervous system involvement         | 0                                          |
| 0                                             | 2 (100%)                                  |
| 0                                             | 0                                          |
| 0                                             | 2 (100%)                                  |
| **Recognised para-infectious or post-infectious neurological disease** | 0                                          |
| 7 (100%)                                      | 1 (100%)                                  |
| 7 (100%)                                      | 0                                          |
| **Investigations**                            | 0                                          |
| SARS-CoV-2 PCR positive                       | 5 (71%)                                   |
| 5 (71%)                                       | 2 (29%)                                   |
| SARS-CoV2- IgG positive                       | 3 (43%)                                   |
| 3 (43%)                                       | 1 (20%)                                   |
| C-reactive protein, mg/L                      | 12 (0–42)                                 |
| 12 (0–42)                                     | 1 (0–12–2)                                |
| Elevated acute-phase reactants†              | 4 (57%)                                   |
| 2 (29%)                                       | 0                                          |
| Plasma white cell count, cells per µL         | 10 (0–27.3)                               |
| 10 (0–27.3)                                   | 11 (90–18.0)                              |
| CSF white cell count >5 cells per µL          | 7.5                                        |
| 7.5                                           | 4 (4.0–11.6)                              |
| Abnormal neuroimaging                         | 9 (100%)                                  |
| 7 (100%)                                      | 1 (100%)                                  |
| 1 (100%)                                      | 1 (100%)                                  |
| 1 (100%)                                      | 2 (25%)                                   |
| Treatment                                     | 2 (29%)                                   |
| 2 (29%)                                       | 1 (20%)                                   |
| PICU admission                                | 0                                          |
| 0                                             | 0                                          |
| Inotropic support                             | 0                                          |
| 0                                             | 0                                          |
| Immunomodulation                              | 0                                          |
| 0                                             | 0                                          |
| Disability§                                   | 4 (57%)                                   |
| 4 (57%)                                       | 5 (56%)                                   |
| Death                                         | 0                                          |
| 0                                             | 0                                          |
| 0                                             | 0                                          |
| 0                                             | 0                                          |

Data are n (%) or median (range). GBS=Guillain-Barré syndrome. NP=not performed. CSF=cerebrospinal fluid. PICU=pediatric intensive care unit. *Systemic features were fever, shock, hypotension, or rash. †Combined acute-phase reactants were defined as lactate dehydrogenase, ferritin, and D-dimers. §One patient did not receive immunomodulation because of underlying malignancy. Disability was defined as a modified Rankin scale score of 2–5.

Table 2: Demographics, clinical features, investigations, management, and outcomes in the COVID-19 neurology group by condition subgroup

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group, peripheral nervous system involvement was part of the multisystem presentation (appendix pp 3–4, figure 1).

Patients who presented with a recognised neuroimmune disorder in the COVID-19 neurology group (p=0.027) and patients in the PIMS-TS neurology group (p=0.035) were more likely to present later than those in the COVID-19 neurology group who did not have a recognised neuroimmune disorder.

SARS-CoV-2 was detected by PCR of nasal secretions in 32 (62%) of 52 patients; 21 (78%) in the COVID-19
neurology group and 11 (44%) in the PIMS-TS neurology group (p=0.012). SARS-CoV-2 IgG antibody was detected in 12 (44%) patients in the COVID-19 neurology group and 19 (76%) in the PIMS-TS neurology group (p=0.021; table 1).

The median C-reactive protein was higher in the PIMS-TS neurology group than in the COVID-19 neurology group (290 mg/L [range 80–556] vs 1 mg/L [0–161], p<0.0001; table 1). Combined acute-phase reactants were elevated in all 25 (100%) patients in the PIMS-neurology group compared with four (15%) in the COVID-19 neurology group (p<0.0001). Serum MOG antibodies were positive in five (63%) of eight patients with an acute demyelinating syndrome (four with ADEM [one with PIMS-TS], one with optic neuritis). 31 (60%) of 52 patients had a lumbar puncture; 11 (35%) of whom had an abnormal result. Five patients with PIMS-TS had diffuse T2 or fluid-attenuated inversion recovery (FLAIR) signal abnormalities of the cerebral white matter or deep grey matter consistent with ADEM, one had abnormal T2 signal involving the hippocampi and cortical diffusion restriction due to limbic encephalitis, one had abnormal T2 signal in the periventricular and infratentorial regions consistent with demyelination in a child with an acute demyelinating syndrome (clinically isolated syndrome), and one had signal change in the intraorbital segment of the right optic nerve consistent with optic neuritis. Two patients had thickening and enhancement of the cauda equina nerve roots supportive of GBS, one had signal changes in the splenium of the corpus callosum consistent with mild encephalopathy with reversible splenial lesion (MERS), and one, a child with a pre-existing diagnosis of adenral neuroblastoma, had extensive intramedullary whole spinal cord abnormal T2 signal change supportive of the clinical diagnosis of myelitis.

In the PIMS-TS neurology group, 17 (74%) of 23 patients had abnormal neuroimaging. Notably, seven (28%) patients had signal changes in the splenium of the corpus callosum consistent with MERS, two (8%) had findings consistent with an acute stroke (one ischaemic involving the anterior and middle right cerebral artery, one intraparenchymal haemorrhage in the right frontotemporal lobe) and one (1%) had bilateral hyperintensities within the claustra due to ADEM. The imaging findings for three cases, described as clinical vignettes in the appendix (pp 1–2), are shown in figure 2.

26 (50%) of 52 patients (20 [80%] in the PIMS-TS neurology group and six [22%] in the COVID-19 neurology group) required admission to the paediatric intensive care unit for a median of 1 days (range 1–100; p<0.0001). 34 (65%) patients (22 in the PIMS-TS neurology group and 12 in the COVID-19 neurology group; p=0.0010) received immunomodulatory medications; 27 had intravenous immunoglobulin, 25 had intravenous methylprednisolone for 3–5 days, three had high-dose oral corticosteroids, two had anakinra, two had tocilizumab, one had infliximab, and one had five single-volume total plasma exchange. 21 (40%) patients received more than one type of treatment. 13 (22%) patients, all in the PIMS-TS neurology group (p<0.0001), required inotropic support. In addition, 16 patients treated with intravenous methylprednisolone were given an oral prednisolone steroid taper over 4–6 weeks.
In the short-term follow-up (assessed at discharge from hospital, or at the most recent clinical assessment [range 1–6 months after discharge], by a neurologist) of this cohort so far, 34 (65%) patients had an apparent good recovery (mRS score 0–1), 17 (33%) had some degree of disability (mRS score 2–5), and one (2%) died (with ischaemic stroke in the PIMS-TS neurology group; mRS score 6).

**Discussion**

This first nation-wide cohort study of hospitalised children and adolescents with neurological and psychiatric manifestations of SARS-CoV-2 infection in the UK, during the first 9 months of the COVID-19 pandemic, has identified a wide range of disorders and features. Although COVID-19 requiring hospital treatment is very rare in children and young people overall, we found that among hospitalised children and adolescents neurological or psychiatric manifestations are common (3·8 cases per 100 hospitalised patients). Moreover, these neurological or psychiatric manifestations disproportionately affected children from minoritised ethnic groups: 36 (69%) of the 52 patients identified were Black or Asian compared with 13% of the UK population; a similar percentage of Black or Asian patients has been reported in all children and young people admitted to hospital with COVID-19 in the UK (64%). Most patients presented after their acute COVID-19 illness had resolved; only 12 (23%) had respiratory symptoms on admission. However, eight (15%) patients presenting with neurological or psychiatric symptoms only did have SARS-CoV-2 detected by PCR, highlighting the importance of screening for the virus in all children and adolescents with acute neurological disorders.

All 27 patients in the COVID-19 neurology group had discrete neurological or psychiatric disorders; 20 affecting the CNS, five affecting the peripheral nervous system, and two with psychosis. In almost half of these, this was a recognised para-infectious or post-infectious immune-mediated (neuroimmune) disorder—e.g., ADEM, other acute demyelinating syndromes, or GBS—with MOG antibodies in more than half of those presenting with an acute demyelinating syndrome. One case with ADEM was atypical: at presentation there were over 6000 white cells in the CSF; the initial brain imaging was normal with changes consistent with ADEM only noted during recovery on day 44. These recognised neuroimmune disorders are reported in association with a variety of preceding infections, but whether SARS-CoV-2 infection causes an increase in the incidence of neuroimmune disorders is not clear.

By comparison, only one child in the PIMS-TS group had a recognised neuroimmune disorder (ADEM), suggesting that different immune mechanisms are the cause of neurological manifestations in this newly described inflammatory syndrome. Immune-mediated mechanisms would also be supported by the finding that...
patients with recognised neuroimmune disorders and neurological manifestations associated with PIMS-TS presented later than those with other neurological or psychiatric manifestations.

Patients presenting with PIMS-TS had the most uniform features, with encephalopathy being present in 22 (88%) of 25 cases. Two-thirds of these patients had abnormal brain imaging, with the most common finding in more than 40% being a reversible splenial lesion in the corpus callosum consistent with MERS. MERS has been reported previously in PIMS-TS,18 other viral infections,22 and Kawasaki disease.23

The lesions in MERS are postulated to represent intramyelinic oedema in the corpus callosum as a result of cytokine-mediated glutamate release caused by inflammation.24 Whether the same mechanism is responsible for these imaging findings in PIMS-TS remains to be seen. Ten (40%) patients with PIMS-TS additionally had peripheral nerve involvement; eight had clinical or neurophysiological features consistent with critical illness neuromyopathy in this group, which was more likely to require intensive care support. However, two patients had focal peripheral nervous system features suggesting another mechanism, perhaps similar to haemophagocytic lymphohistiocytosis, a genetic or acquired disorder characterised by a cytotoxic storm, which can similarly have acute CNS and peripheral nervous system involvement.25 Focal peripheral nerve imaging findings have also been reported in children with COVID-19 previously.26 Other features in this group included behavioural change in nine (36%) patients, including six with hallucinations at presentation. Comparing those with and without PIMS-TS has therefore identified differences that will help with future neurology consults. Although our sample size was small, the differences identified here might infer differing immunopathogenesis.

Our findings are consistent with those from two other paediatric series published in 2021. Both the international neuroradiological cohort14 and multicentre US cohort15 described recognised neuroimmune disorders and PIMS-TS with life-threatening neurological features including MERS findings on brain imaging. However, those series, which were not studies done across a whole nation, reported more strokes and deaths than we found in this cohort, perhaps suggesting they were not representative of the larger patient group.

The neurological and psychiatric manifestations of COVID-19 have been reported in several studies in adults (age 18 years or older).1,11 Similarities between our study and the adult CoroNerve cohort12 include the range of disorders identified; although stroke prevalence was much higher in adults, present in almost half of the cases. Adults were also more likely to have multiple neurological diagnoses (13% of adult cases) than children and adolescents, perhaps suggesting there are multiple mechanisms linked to underlying risk factors and comorbidities. Differences also included a higher prevalence of neuroimmune disorders in the paediatric cohort. The case fatality rate was also higher in adults with almost one-quarter dying of their neurological disorder. Over the same time period of the adult CoroNerve study, 30,197 adults were admitted to hospital with COVID-19. Using this data, we estimated a prevalence of neurological and psychiatric manifestations of COVID-19 in adults of 0·9 cases per 100 hospitalised patients. Therefore, overall, neurological and psychiatric manifestations appear to be four times more common in hospitalised children and adolescents than in hospitalised adults with COVID-19 in the UK; this difference is likely to be due in part to respiratory and cardiovascular comorbidities in adults.

In the absence of detailed immunological studies investigating cell-mediated and adaptive immune responses to SARS-CoV-2 in children, the underlying pathogenesis of neurological disease of COVID-19 is unclear. There is little evidence showing direct SARS-CoV-2 neurotropism in adults,26,27 and some evidence emerging of viral invasion of endothelial cells rather than neurons.28,29 In this cohort, none of the patients had features suggesting viral encephalitis caused by direct invasion of brain parenchyma, although SARS-CoV-2 was only tested for in the CSF of six patients. Postulated mechanisms for neurological manifestations of SARS-CoV-2 include cytokine-driven neuroinflammation29 or secondary CNS injury from systemic hyperinflammation.30 Both mechanisms would fit the features found in the PIMS-TS neurology group in this study. Patients in this group had significantly higher peripheral inflammatory markers and were more likely to require intensive care and immunomodulatory treatment than patients in the COVID-19 neurology group. Alternatively, adaptive immune-mediated disease, which we postulate underlies the recognised para-infectious or post-infectious immune-mediated disorders within the COVID-19 neurology group, might also mediate the PIMS-TS neuropathogenesis, suggested by the majority being positive for SARS-CoV-2 IgG antibodies at presentation.

The short-term follow-up of this cohort showed almost two-thirds (65%) of patients had an apparent good recovery, one-third (33%) had some degree of disability, and only one (2%) died.

A strength of this study is that the reporting of cases is facilitated by widespread publicity of the BPNSU studies via the BPA weekly newsletters, by all patients being managed in the national health-care system, and by close networks within the paediatric neurology community, and therefore the sample could be considered nationally representative.

This study has several limitations. The reporting system relies on paediatric neurologists reporting cases that they have been consulted about; however, cases might not have been reported due to the unprecedented workload in the pandemic. Cases might also have been missed as testing for IgG antibodies was less available.
at the beginning of the pandemic; the first case was reported in June, 2020. Less severe cases or cases with transient symptoms were not reported as children and adolescents are admitted to hospital under general paediatricians in the UK; severe cases might have died before a referral to a neurologist was made. As investigations were not standardised, some complications might be underestimated.

The only cases included with psychiatric features are patients who were referred to neurologists, therefore this group is likely to be under-reported. The reporting of the outcomes of children and adolescents in this study is functional, with the mRS being a crude tool. The scale being made by chart extraction in some cases is also a limitation. Although short-term outcomes were apparently good in two-thirds of this cohort, we were likely to have underestimated substantial evolving cognitive and behavioural problems.

This study has identified differences between patients presenting with a primary neurological or psychiatric disorder versus those with features associated with PIMS-TS. Recognised neuroimmune conditions were common in patients with a primary disorder; whereas those with PIMS-TS had more heterogeneous but overlapping features, with encephalopathy, neuromyopathy, behavioural change, and hallucinations being common. More patients with PIMS-TS needed intensive care, but outcomes were similar overall. The estimated prevalence of neurological or psychiatric manifestations of COVID-19 was four times more common in hospitalised children and adolescents than in hospitalised adults in the UK. Further studies are required to define the underlying neuroimmune mechanisms for these manifestations, especially in the novel PIMS-TS neurology group, and the cognitive, psychiatric, and neurological outcomes, to better determine the rehabilitation needs of these patients.

Contributors
STJR, TS, MJG, BDM, and RK drafted the first version of the manuscript. The manuscript was revised by all authors. STJR, OAM, YH, SA, MJG, ALRR, TS, and RK analysed the data. STJR, RK, YH, OAM, and SA adjudicated case assignment. STJR, OAM, MS, CF, HM, EW, DR, NE, JH, RK, SA, ML, and YH contributed data. STJR, RK, BDM, MJG, and TS accessed and verified the data. TS and LAB led the CoroNerve studies group steering committee. IG, BDM, SP, RHT, and RK led the CoroNerve studies management group. Additional members of the CoroNerve study group and their contributions are shown in the appendix (pp 14–16). All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests
We declare no competing interests.

Data sharing
Any reasonable requests to share data will be considered by the CoroNerve studies group steering committee subject to institutional agreements and ethics approvals. Data requests should be sent to the corresponding author.

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References
1 Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767–83.
2 Kushwaha S, Seth V, Bapat P, et al. Neurological associations of COVID-19—do we know enough? a tertiary care hospital based study. Front Neurol 2020; 11: 588879.
3 Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol 2020; 77: 683–90.
4 Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurological: clinical, radiological and laboratory findings. Brain 2020; 143: 3104–20.
5 Varatharaj A, Thomas N, Ellul MA, et al. Neurological and neuropsychiatric complications of COVID-19 in 153 patients: a UK-wide surveillance study. Lancet Psychiatry 2020; 7: 875–82.
6 Jiang L, Tang K, Levin M, et al. COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 2020; 20: e276–88.
7 Royal College of Paediatrics and Child Health. Guidance—paediatric multisystem inflammatory syndrome temporally associated with COVID-19. 2020. https://www.rcpch.ac.uk/resources/paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19-pims-guidance (accessed Sept 18, 2020).
8 Sa M, Mirza L, Carter M, et al. Systemic inflammation is associated with neurologic involvement in pediatric inflammatory multisystem syndrome associated with SARS-CoV-2. Neurol Neuroimmunol Neuroinflamm 2021; 8: e999.
9 Lindsay CE, Mankad K, Ram D, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health 2021; 5: 167–77.
10 LaRovere KL, Riggs BJ, Poussaint TY, et al. Neurologic involvement in children and adolescents hospitalized in the United States for COVID-19 or multisystem inflammatory syndrome associated with SARS-CoV-2. Neurol Neuroimmunol Neuroinflamm 2021; 8: e999.
11 Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. Mult Scler 2013; 19: 1261–67.
12 Cellucci T, Van Mater H, Graus F, et al. Clinical approach to the diagnosis of autoimmune encephalitis in the pediatric patient. Neurol Neuroimmunol Neuroinflamm 2020; 7: e663.
Hacohen Y, Mankad K, Chong WK, et al. Diagnostic algorithm for relapsing acquired demyelinating syndromes in children. Neurology 2017; 89: 269–78.

Wells E, Hacohen Y, Waldman A, et al. Neuroimmune disorders of the central nervous system in children in the molecular era. Nat Rev Neurol 2018; 14: 433–45.

Höftberger R, Lassmann H. Inflammatory demyelinating diseases of the central nervous system. In: Kovacs GG, Alafuzoff I, eds. Handbook of Clinical Neurology. Amsterdam: Elsevier; 2018: 263–83.

NHS England. NHS data model and dictionary. 2021. https://www.datadictionary.nhs.uk/ (accessed April 20, 2021).

Bigi S, Fischer U, Wehrli E, et al. Acute ischemic stroke in children versus young adults. Ann Neurol 2011; 70: 245–54.

Abdel-Mannan O, Eyre M, Löbel U, et al. Neurologic and Radiographic Findings Associated With COVID-19 Infection in Children. JAMA Neurol 2020; 77: 1440–45.

Zombori L, Bacon M, Wood H, et al. Severe cortical damage associated with COVID-19 case report. Seizure 2021; 84: 66–68.

NHS England. COVID-19 hospital activity. 2021. https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19-hospital-activity/ (accessed March 22, 2021).

Swann OV, Holden KA, Turtle I, et al. Clinical characteristics of children and young people admitted to hospital with COVID-19 in United Kingdom: prospective multicentre observational cohort study. BMJ 2020; 370: m3249.

Iadecola C, Anrather J, Kamel H. Effects of COVID-19 on the nervous system. Cell 2020; 183: 16–27.e1.

Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol 2020; 92: 699–702.

Solomon T. Neurological infection with SARS-CoV-2—the story so far. Nat Rev Neurol 2021; 17: 65–66.

Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol 2020; 19: 919–29.