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

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Abstract

Background

The spectrum of neurological and psychiatric complications associated with COVID-19 is poorly understood in children. We aimed to describe the size and spectrum of these complications in UK hospitalised children.

Methods

For ten months from April 2020, children and adolescents (<18 years) with neurological or psychiatric disorders were included if paediatric neurologists considered SARS-CoV-2 infection to be relevant to the presentation. Cases were classified as having either a primary neurological disorder associated with COVID-19 (COVID-19 neurology group) or Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) with neurological features (PIMS-TS neurology group). The denominator of all hospitalised children with COVID-19 was collated from National Health Service England data.

Findings

Fifty-two cases were identified, among 1334 children hospitalised with COVID-19 giving an estimated prevalence of 3.8 per 100 children. Twenty-seven (52%) were classified with a primary neurological or psychiatric disorder, 25 (48%) had features associated with PIMS-TS. The median (range) age was 9 (1-17) years. Thirty-six (69%) were from Black or Asian backgrounds. In the COVID-19 neurology group, diagnoses included seven with status epilepticus, five encephalitis, five Guillain-Barré syndrome, three acute demyelinating syndromes, two chorea, two psychosis, two encephalopathy, one transient ischaemic attack. The PIMS-TS neurology group more often had multiple features, which included encephalopathy (22, 88%), peripheral nervous system involvement (10, 40%), behavioural change (9, 36%), hallucinations (6, 24%). A recognised neuro-immune disorder was more

common in the COVID-19 neurology than the PIMS-TS neurology group (13/27 [48%] vs 1/25 [0.04%], p=0.0003). More patients in the PIMS-TS neurology group were admitted to intensive care (20/25 [80%] vs 6/27 [22%], p=0.0001) and received immunomodulatory treatment (22/25 [88%] vs 12/27 [44%]), p=0.045). Seventeen (33%) were discharged with disability; one PIMS-TS child with stroke died.

Interpretation

This first nation-wide study of the neurological and psychiatric manifestations of COVID-19 in children identified key differences between those with a primary disorder versus those with PIMS-TS. More PIMS-TS children needed intensive care, but outcomes were similar overall. Further studies must investigate underlying mechanisms and longer-term outcomes.

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Introduction

Neurological and psychiatric complications of infection with the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been recognised as part of coronavirus disease 2019 (COVID-19) in adults (1-5). In children and adolescents, single case series have identified neurological complications associated with Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS), a rare, newly described severe secondary inflammatory syndrome which occurs weeks after SARS-CoV-2 infection (6-8). Nine children with neurological complications of PIMS-TS, have been described from a single UK centre (8). To date, one international series has described the neuroimaging findings in 38 children (9) and a cohort of 1695 hospitalised children and young people (up to 21 years of age) has described transient neurological involvement in 365 and life threatening neurological conditions in 43 cases (10). However, the prevalence of these complications is not known. We therefore undertook the first nation-wide prospective cohort study in the UK to calculate the size and spectrum of neurological and psychiatric manifestations of COVID-19 in hospitalised children and adolescents.

Methods

Study design and participants

During the first exponential phase of the pandemic, the *Coro*Nerve Study Group (www.coronerve.com) was established to set up an online network of secure rapid-response notification portals via the major UK neuroscience & psychiatry bodies, including the British Paediatric Neurology Association (BPNA). An estimate of the prevalence of cases in England was calculated using hospital admission data in England from the same study dates for children (11). As admission data was only available for England, cases from Scotland, Wales and Northern Ireland were not included in the prevalence calculation. Cases were prospectively recorded using a standardised online Case Report Form (CRF) including demographics, evidence of SARS-CoV-2 infection, clinical characteristics, comorbidities, disease course, requirement for intensive care, laboratory, imaging and neurophysiology results and recovery. The modified Rankin scale (mRS) was assessed at discharge from hospital, or at the most recent clinical assessment, by a neurologist either assessing directly or by using information from the case records (12).

Ethics

The study was approved by the University of Liverpool Institute of Infection Veterinary and Ecological Sciences Ethics Committee (UoL #7725/2020) and the University of Southampton Faculty of Medicine Ethics Committee (ERGO #56504). The electronic CRF was hosted on ALEA (www.aleaclinical.eu) and managed by the Clinical Information Research Unit.

Procedures

Inclusion Criteria

From April 2020, members of the BPNA were invited by the British Paediatric Neurology Surveillance Unit (www.bpnsu.co.uk) to notify any hospitalised children or adolescents (aged <18 years) they considered to have neurological or psychiatric complications associated with COVID-19 (table 1 and 2). Cases were still included if they had a pre-existing neurological disorder. Data lock was the 1st of February 2021.

Table 1: Inclusion criteria for the British Paediatric Neurology Surveillance Unit study of paediatric neurological COVID-19'

• Children or adolescents age <18 years.
• History of laboratory-confirmed of COVID-19 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 contemporaneously or following shortly after COVID-19 infection.
• COVID-19 infection implicated as a possible cause of neurological or psychiatric disorder by a paediatric neurologist.

Table 2: CoroNerve study clinical neurological or neuropsychiatric disorder definitions

Clinical neurological or psychiatric disorders were classified and data were collected as follows: 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 (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); and peripheral neurology (Guillain-Barré syndrome, Miller Fisher syndrome, brachial neuritis, myasthenia gravis, peripheral neuropathy, myopathy, myositis—defined as myopathy with evidence of inflammation (e.g., by MRI or biopsy of muscle with elevated plasma creatine kinase levels), and critical illness neuromyopathy). Further details are available at www.bpnsu.co.uk.

Exclusion criteria

Cases were excluded if they did not have a neurological consultation and/or investigations and/or did not meet the definition for confirmed SARS-CoV-2 infection.

Additional data collection

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.

Evidence of COVID-19

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

Case review and categorisation

Those reviewed and diagnosed with a primary neurological or psychiatric disorder associated with COVID-19, either secondary to acute infection e.g. status epilepticus, or a recognised para/post infectious neuro-immune syndrome e.g. GBS, were classified as the 'COVID-19 neurology group'. Those with neurological features in the context of PIMS-TS were classified as the 'PIMS-TS neurology group'. The diagnosis of PIMS-TS was made in tertiary paediatric units by the multi-disciplinary teams responsible for the patient's care. All cases were reviewed by a panel of paediatric neurologists, infectious diseases clinicians and a neuroradiologist. When children fulfilled multiple clinical case definitions, the primary diagnosis was adjudicated by the panel. Children with Guillain-Barré syndrome (GBS), Acute Disseminated Encephalomyelitis (ADEM), other Acute Demyelinating Syndromes (ADS), and autoimmune encephalitis (13-17), which are recognised para or post-infectious immune mediated neurological disorders, were defined as having "neuro-immune disorders". Combined acute phase reactants were defined as lactate dehydrogenase (LDH), ferritin, and D-dimers. Ethnicity was defined by National Health Service (NHS) coding criteria (18).

A good recovery was defined as a Modified Rankin Scale (mRS) 0-1, reflecting no significant disability or no ongoing symptoms or back to baseline for those with a pre-existing neurological disorder; those with a mRS scale of 2-5 were defined as some degree of disability (12). The neurological features or imaging findings of 15 cases (supplementary table 1) have been published previously (8, 9, 19, 20). These cases were included to reflect the full spectrum of neurological complications of paediatric COVID-19 in the UK.

Data management

Data were transferred from the online platform to spreadsheet format (Excel 2016, Windows) using a custom Python script (21). Free text fields describing rationale and context for selections in dropdown lists were manually converted into coded data.

Statistical analysis

Statistical analysis was performed with Stata (version 15.1; StataCorp LLC, 2017) and GraphPad Prism v9.0.0 (GraphPad Software, LLC). 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 chi-squared for categorical variables, with two-sided p values <0.05 considered statistically 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.

Role of the funding source

The funders of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the article. The corresponding authors had full access to all the data and had final responsibility for the decision to submit for publication.

Results

From 2nd April 2020 to 1st February 2021, the *Coro*Nerve Study received notification of 63 paediatric cases that were geographically dispersed across the UK (Figure 1). Six cases were excluded as they did not have a neurological consultation and/or investigations; four of whom had PIMS-TS, one had congenital heart disease and brief encephalopathy and one had a pre-existing psychiatric disorder with worsening of symptoms (appendix 3). A further five cases were excluded due to insufficient evidence of SARS-CoV-2 infection (appendix 4).

Demographics and prevalence

For the 52 remaining cases, the median (range) age was nine (1-17) years; 30 (58%) were male. Thirty-six (69%) were from Black (20 [38%]) or Asian (16 [31%]) backgrounds and 16 (31%) were of White ethnicity. Ten (19%) had a pre-existing neurological or developmental condition. Four (8%) had other pre-existing conditions (table 3; supplementary table 1). Respiratory symptoms were present in 12 (23%) at admission. Eight (15%) had isolated neurological or psychiatric features (PCR for respiratory secretions were positive for SARS-CoV-2). Twenty-seven (52%) were classified as being in the COVID-19 neurology group and 25 (48%) the PIMS-TS neurology group. PIMS-TS cases were more likely to be of Asian or Black ethnicity than those in the COVID-19 neurology group 22/25 (88%) vs 14/25 (56%), p=0.048). During the same period 1,334 children were admitted to English hospitals with COVID-19. Excluding a case from Scotland, the minimum estimated prevalence of neurological and psychiatric complications in hospitalised children with COVID-19 in England was 51/1,334 = 0.038 (C.I 0.029-0.050, SE 0.99) i.e. 3.8 per 100 paediatric cases admitted. The prevalence ranged from 1.8-8.1 cases per 100 depending on the region of referral; the highest prevalence was in London.

Clinical features

Systemic features (fever, rash, hypotension, shock) were present in 40 (77%); with 10 (19%) having cardiovascular shock (nine of whom had PIMS-TS). Systemic features were more common in the PIMS-TS neurology group: 25 out of 25 versus 15 out of 27 (p=0.0234). Other features included respiratory symptoms in 12 (23%), seizures in 12 (23%), 9 (17%) with status epilepticus and cardiovascular shock in 10 (19%), nine of whom had PIMS-TS.

In the COVID-19 neurology group (n=27), 14 (52%) children had encephalopathy compared with 22 (88%) in the PIMS-TS neurology group (p=0.0048). Of these 14, 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. Thirteen (48%) presented with a recognised neuro-immune disorder (five GBS, four ADEM three of whom had myelin oligodendrocyte (MOG) antibodies, three other ADS, one autoimmune [limbic] encephalitis) compared with only one (4%) in the PIMS-TS neurology group (ADEM with MOG antibodies), p=0.0003. Two (7%) presented with acute psychosis and two (7%) with chorea. One child with a previous basal ganglia stroke was diagnosed with a transient ischaemic attack.

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

In the COVID-19 neurology group, peripheral nervous system involvement occurred independently as a separate disorder: GBS in all 5 cases. In the PIMS-TS neurology group, the PNS involvement was part of the multisystem presentation (appendix 2, figure 1).

The cases presenting with a recognised neuro-immune disorder in the COVID-19 neurology group (table 4 subgroup a) and those in the PIMS-TS neurology group (table 3) were more likely to present later than those in the COVID-19 neurology group (table 4 subgroup b) who did not have a recognised neuro-immune disorder (p=0.027 and p=0.035 respectively).

Laboratory investigations
SARS-CoV-2 PCR was detected by PCR of nasal secretions in 32 (62%) children; 21 (78%) in the COVID-19 neurology and 11 (44 %) in the PIMS-TS groups respectively (p=0.01). SARS-

CoV-2 IgG antibody was detected in 12 (44 %) in the COVID-19 neurology and 19 (76%) in the PIMS-TS neurology groups respectively (p=0.02).

The median (range) CRP was higher in the PIMS-TS neurology group; 290 (80-556) versus 1 (0-161), respectively p<0.0001. Combined acute phase reactants were elevated in all in the PIMS-neurology groups (p<0.0001). Serum MOG antibodies were positive in 5/8 (62.5%) cases with an ADS [four ADEM (one with PIMS-TS), one optic neuritis]. Thirty one (59.6%) underwent a lumbar puncture; 11 (35%) had a cerebrospinal fluid (CSF) pleocytosis, with a median (range) of 11 (6-6075) white cell count/mm3. Of these six had encephalitis; five ADEM, one limbic. The diagnoses in the five remaining patients with a pleocytosis were meningitis (PIMS-TS), other acute demyelinating syndrome, PIMS-TS and encephalopathy, psychosis and GBS. Eight (15.3%) had an elevated CSF protein with a median (range) of 1.8 (0.43-2.63) mg/L: of these, five had GBS, one had ischaemic encephalopathy associated with PIMS-TS, one had ADEM, one had transverse myelitis (TM). Oligoclonal bands (OCB) were positive in the CSF in two of eleven analysed (18%); one child had ADEM and one had encephalopathy associated with PIMS-TS. Glucose analysis of the CSF was undertaken in 26 of 31 (83%) samples and was normal (>2.5 mmol/l) in all. A clinically-indicated viral and bacterial molecular screen of CSF was negative in all 31 CSF samples. In addition, SARS-CoV-2 RNA PCR was negative in six cases when specifically requested (three ADEM and three PIM-TS with encephalopathy). For one child with ADEM, the admission respiratory secretion PCR was positive for SARS-CoV-2 and adenovirus, although only the COVID-19 PCR remained positive on subsequent serial swabs (3). Details of the laboratory investigations are given in table 3 and supplementary table 1.

Neurophysiology investigations

Electroencephalography (EEG) was undertaken in 33 (63%) children: 20 (61%) were abnormal; 18 recorded non-specific focal or generalised background slowing (13 in the PIMS-TS neurology group) and two recorded epileptic discharges: Bilateral Periodic Lateralising Epileptiform Discharges in a PIMS-TS case with ischaemic encephalopathy and

left posterior quadrant discharges in a COVID-19 neurology case with status epilepticus. Seventeen cases had clinical features of PNS involvement: 7 in the COVID-19 neurology and 10 in the PIMS-TS neurology groups respectively. Nerve conduction studies and/or electromyography was performed in 15 (28.8%); 12 (80%) were abnormal. Five with PIMS-TS had diffuse myopathic and/or neuropathic changes, four of the five children with GBS tested had evidence of a primary demyelinating polyneuropathy, two with PIMS-TS had focal changes (one right peroneal and tibial neuropathy and one proximal myopathy and bilateral tibial neuropathies) and one with ADEM had evidence of a unilateral right sided facial nerve injury secondary to brainstem involvement. Details of the individual neurophysiology findings are given in supplementary table 1.

Brain imaging

Cerebral and/or spinal imaging was performed in 48 (92%): 46 MRI and 11 CT, of which 28 (58%) were abnormal. In the COVID-19 neurology group, 11/25 (44%) were abnormal. Of these, four MRI brain scans had diffuse T2 or 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 ADS (Clinically Isolated Syndrome), and one with signal change in the intra-orbital segment of the right optic nerve consistent with optic neuritis. Two had thickening and enhancement of the cauda equina nerve roots supportive of GBS, one had signal changes in the splenium of the corpus collosum consistent with Mild Encephalopathy with Reversible Splenial lesion (MERS), and one, a child with a pre-existing diagnosis of adrenal neuroblastoma, had extensive intramedullary whole spinal cord abnormal T2 signal change supportive of the clinical diagnosis of myelitis.

Within the PIMS-TS neurology group (n=25), 17 (72%) had abnormal neuroimaging. Most notably, seven (28%) had signal changes in the splenium of the corpus callosum consistent with MERS, two had findings consistent with an acute stroke (one ischaemic involving the anterior and middle right cerebral artery, one intraparenchmal haemorrhage in the right frontal lobe) and one had bilateral hyperintensities within the claustra due to ADEM. The

imaging findings for three cases, described as clinical vignettes in the supplementary data, are in figure 2.

Management

Twenty-six (50%) children, 20 (80%) in the PIMS-TS neurology group and six (22%) in the COVID-19 neurology group, required paediatric intensive care unit (PICU) support, for a median (range) of 1 (1 -100) days, p=<00001. Thirty-four children (65%); 22 in the PIMS-TS neurology group and 12 in the COVID-19 neurology group were treated with immunomodulatory medications, p=0.001. Twenty-seven received intravenous immunoglobulin (IVIG), 25 intravenous methylprednisolone (IVMP) for 3-5 days, three high dose oral corticosteroids, two Anakinra, two Tocilizumab, one Infliximab and one five single volume total plasma exchange (PLEX). Twenty-one (40%) received more than one type of treatment. Thirteen children (22%), all PIMS-TS, required inotropic support, p<0.0001. In addition, 16 treated with IVMP were given an oral prednisolone steroid taper over 4-6 weeks.

Outcomes

In the short term follow up of this cohort so far, 34 (65%) children have an apparent good recovery (mRS of 0-1), 17 (33%) children have some degree of disability (mRS 2-5) and one child, with PIMS-TS and an ischaemic stroke (2%), died (mRS 6).

Discussion

This first nation-wide cohort of children and adolescents with neurological and psychiatric manifestations of COVID-19 in the UK, over the first 9 months of the pandemic has identified a wide spectrum of disorders and features. Whilst COVID-19 requiring hospital treatment is very rare in children and young people overall, we found that among these children neurological or psychiatric manifestations are more common (3.8 per 100). Moreover, ethnicity is a risk factor: overall, 36 (69%) cases were Black or Asian compared to 13% of the UK population; a similar percentage has been reported in all children and young people admitted with COVID-19 in the UK (22). Most children presented once their acute COVID-19 illness had resolved; only 12 (23%) had respiratory symptoms on admission.

However, eight (15%) presenting with neurological/psychiatric symptoms only, did have SARS-CoV-2 detected by PCR, underscoring the importance of screening all children with acute neurological disorders for the virus.

All 27 children in the COVID-19 neurology group had discrete neurological or psychiatric disorders; 20 affecting the CNS, five the PNS and two with psychosis. In almost half of these, this was a recognised para- or post-infectious immune mediated (neuro-immune) disorder, e.g. ADEM, other acute demyelinating syndromes or GBS, with MOG antibodies in over 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 neuro-immune disorders are reported in association with a variety of preceding infections (13-17), but whether SARS-CoV-2 infection causes an increase in the incidence of neuro-immune disorders is not clear.

By comparison only one child in the PIMS-TS group had a recognised neuro-immune 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 neuro-immune disorders and neurological manifestations associated with PIMS-TS presented later than those with other neurological or psychiatric manifestations.

Those presenting with PIMS-TS had the most uniform features with encephalopathy being present in 88% (22/25) cases. Two thirds of these cases had abnormal brain imaging with the most common finding in over 40% being a reversible splenial lesion in the corpus callosum consistent with MERS. MERS has been reported previously in PIMS-TS (8, 19), other viral infections (23) and Kawasaki disease (24).
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 (25). Whether the same mechanism is responsible for these imaging findings in PIMS-TS remains to be seen. Ten (40%) with PIMS-TS additionally had peripheral nerve involvement; eight had clinical and/or neurophysiological features consistent with critical illness

neuromyopathy in this group which was more likely to require intensive care support. However, two had focal PNS features suggesting another mechanism, perhaps similar to haemophagocytic lymphohistiocytosis, a genetic or acquired disorder characterised by a cytokine storm which can similarly have acute CNS and PNS involvement (19). Focal peripheral nerve imaging findings have also been reported in children with COVID-19 previously (9). Other features in this group included behavioural change in nine (36%) including six with hallucinations. Comparing those with and without PIMS-TS has therefore identified differences which will help with future neurology consults. Whilst our sample size is small, the differences may infer differing immunopathogenesis.

Our findings are consistent with two other recent paediatric series. Both the international neuro-radiological cohort (9) and multi-centre US cohort (10) also described recognised neuro-immune disorders and PIMS-TS with life threatening neurological features including MERS findings on brain imaging. However, those series, which were not across a whole nation, reported more strokes and deaths than our 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 adult studies (3-5). Similarities between our study and the adult *Coro*Nerve cohort (26) include the range of disorders identified; although stroke was much higher in adults being present in almost half of the cases. Adults were also more likely to have multiple neurological diagnoses (13% of adult cases) perhaps suggesting multiple mechanisms linked to underlying risk factors and co-morbidities. Differences include a higher prevalence of neuro-immune disorders in the paediatric cohort. The case fatality rate was also higher with almost a quarter dying of their neurological disorder. Over the same time period of the adult *Coro*Nerve study, 30 197 adults were admitted with COVID-19. Using this data, we estimate an prevalence of neurological and psychiatric manifestations in adults of 0.9 per 100. Therefore overall, neurological and psychiatric manifestations appear to be four times more common in UK hospitalised children and young people than in adults with COVID-19 requiring admission to hospital: this is likely to represent respiratory and cardiovascular co-morbidities 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 limited evidence demonstrating direct SARS-CoV-2 neurotropism in adults (27, 28), with some evidence emerging of viral invasion of endothelial cells rather than neurons (28, 29). In our cohort, none of the children had features suggesting viral encephalitis caused by direct invasion of brain parenchyma, although SARS-CoV-2 was only tested in the CSF of six of our patients. Postulated neurological mechanisms of SARS-CoV-2 include cytokine driven neuroinflammation (30) or secondary CNS injury from systemic hyperinflammation (27). Both mechanisms would fit the features within our PIMS-TS neurology group. They had significantly higher peripheral inflammatory markers and were more likely to require intensive care and immunomodulatory treatment than the COVID-19 neurology group. Alternatively, adaptive immune mediated disease that we postulate underlies the recognised para- or post-infectious immune mediated disorders within the COVID-19 neurology group, may also mediate the PIMS-TS neuropathogenesis, suggested by the majority being SARS-CoV-2 IgG antibody positive at presentation.

The short-term outcome of this cohort has identified almost two thirds (65%) having an apparent good recovery, a third (33%) had some degree of disability and only one (2%), with PIMS-TS and an ischaemic stroke, died.

This study has several strengths; the reporting of cases is facilitated by widespread publicity of the BPNSU studies via the BPNA weekly newsletters, by all patients being managed in the national health care system and by close networks within the paediatric neurology community.

This study has several limitations. The reporting system relies on paediatric neurologists reporting cases they have been consulted about; cases may not have been reported due to the unprecedented workload in the pandemic. Cases may also have been missed as testing for IgG was less available at the beginning of the pandemic; the first case was reported in June 2020. Less severe or cases with transient symptoms were not reported as children and young people are admitted under general paediatricians in the UK; severe cases may have

died before a referral was made. As investigations were not standardised, some complications may be underestimated.

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

Now that we have defined the prevalence, those that appear to be at higher risk, the spectrum of complications and the importance of testing all children and adolescents with neurological disease for SARS-CoV-2, studies are required to define the underlying neuro-immune mechanisms, especially in the novel PIMS-TS neurology group, and the cognitive, psychiatric, and neurological outcomes to better determine the rehabilitation needs of these patients.

Conclusions

This first nation-wide study of the neurological and psychiatric manifestations of COVID in children and adolescents has identified differences between those presenting with a primary neurological or psychiatric disorder versus those with features associated with PIMS-TS. Recognised neuro-immune conditions were common in those with a primary disorder. Those with PIMS-TS had more heterogeneous but overlapping features with encephalopathy, neuromyopathy, behavioural change and hallucinations being common. More PIMS-TS children needed intensive care, but outcomes were similar overall. The estimated prevalence of neurological or psychiatric manifestations is 4 times more common than in adults admitted with COVID-19.

Contributors

STJR, TS, MJG, BDM and RK drafted the first version of the manuscript. The manuscript was revised by all the authors. STJR, OA-M, YH, SA, MJG, ALRR, TS and RK analysed data; STJR,

RK, YH, OA-M, SA adjudicated case assignment; STJR, OA-M, MS, CF, HM, EW, DR, NE, JH, RK, SA, ML, YH contributed data; YH, RK, IG, SP, RHT, BM, TS, NT formed the *Coro*Nerve Studies Group Steering Committee; IG, BDM, SP, RHT and RK lead the *Coro*Nerve Studies Management Group (www.coronerve.com). Additional members of the *Coro*Nerve study group and their contributions are given in the Supplementary data.

Data Sharing

Any reasonable request to share data will be considered by the *Coro*Nerve Studies Group Steering Committee subject to institutional agreements and ethical approvals.

Conflicts of Interest

None for any of the authors

	All cases (n=52)		
	COVID-19 Neurology Group (n=27)	PIMS-TS Neurology Group (n=25)	p value†
Demographics			
Age [years] (range)	9 (1-16)	10 (1-17)	0.26
Gender Male:Female	17 (63):10 (37)	13 (52):12 (48)	0.42
Ethnicity (White:Black:Asian)	13:08:06	03:14:08	0.0048*††
Underlying comorbidity			
Neurological comorbidities	8 (29)	2 (8)	0.048*
Other comorbidities	1 (4)	3 (12)	0.262
Clinical features			
Systemic features (fever, shock, hypotension, rash)	15 (56)	25 (100)	0.0001*
Respiratory involvement at presentation	6 (22)	6 (28)	>0.99
Encephalopathy	14 (52)	22 (84)	0.0048*
Seizures	8 (30)	4 (16)	0.24
Headache/ meningism	4 (15)	10 (40)	0.04*
PNS involvement	7 (26)	10 (40)	0.4
Focal CNS involvement	4 (15)	6 (24)	0.84
Behavioural change	3 (11)	9 (36)	0.08
Hallucinations	1 (3.7)	6 (24)	0.032*
Recognised para/post infectious neurological disease	13 (48)	1 (4)	0.0003*
Investigations			
SARS-CoV-2 PCR positive (%)	21 (78)	11 (44)	0.01 *
SARS-CoV2- IgG positive (%)	12 (44)	19 (76)	0.02*
Median CRP (range)	1 (1-161)	290 (80-556)	<0.0001*
Elevated acute phase reactants (LDH, ferritin, D-Dimers)	4 (14.8)	25 (100)	<0.0001*
WCC (range)	9.9 (4-27.3)	20 (3-44.4)	<0.0001*
CSF WCC > 5 (%)	8 (30)	3 (8)	0.12
Abnormal CNS imaging [CT and/or MRI] (%)	11/25 (44%)	17/23 (73%)	0.036*
Treatment			
PICU admission	6 (22)	20 (80)	<0.0001*
Inotropic support	0	13 (52)	<0.0001*
Immunomodulation	12 (44)	22 (88)	0.001*

Outcome			
Disability	10 (37)	7 (28)	0.48
Death	0 (0)	1 (4)	0.29

†p values comparing COVID-19 Neurology Group and PIMS-TS Neurology Group; †† proportion with White ethnicity; PIMS-TS=Paediatric multisystem Inflammatory syndrome temporally associated with COVID-19; CNS, central nervous system; PNS, peripheral nervous system

Table 3: Demographics, clinical features, investigations, management and outcome of study population grouped by COVID-19 Neurology Group and PIMS-TS Neurology Group

	COVID-19 Neurology Group divided into subgroups a) Recognised neuro-immune condition or b) other neurological disorder						
	a) Neuro-Immune COVID-19 Neurology subgroup (n=13)			b) COVID-19 Neurology other subgroup (n=14)			
	ADS (n=7)	**GBS** (n=5)	**Limbic encephalitis** (n=1)	**Severe Encephalopathy** (n=9)	**Psychiatric** (n=2)	**Movement disorder** (n=2)	**Cerebro-vascular** (n=1)
Demographics							
Age [years] (range)	5 (1-10)	6 (1-14)	4	11 (2-16)	12 (10-14)	12 (9-14)	10
Gender Male:Female	4 (57): 3 (43)	3 (60): 2 (40)	1 (100): 0	6 (67): 3 (33)	1 (50): 1 (50)	1 (50): 1 (50)	1 (100): 0
Ethnicity (White:Black:Asian)	02:01:04	02:01:02	01:00:00	05:02:02	00:02:00	02:00:00	01:00:00
Underlying comorbidity							
Neurological comorbidities	1 (29)	2 (40)	0	4 (44)	0	0	1 (100)
Other comorbidities	1 (29)	0	0	0	0	0	0
Clinical features							
Systemic features (fever, shock, hypotension, rash)	6 (86)	3 (60)	0	6 (67)	0	0	0
Respiratory involvement at presentation	2 (29)	2 (40)	0	1 (11)	1 (50)	0	0
Encephalopathy	4 (57)	0	1(100)	9 (100)	0	0	0
Seizures	0	0	1(100)	7 (78)	0	0	0
Headache/ meningism	2 (29)	1 (20)	0	1 (11)	0	0	0
PNS involvement	0	5 (100)	0	0	0	2 (100)	0
Focal CNS involvement	3 (43)	0	0	0	0	0	1 (100)
Behavioural change	0	0	1(100)	0	2 (100)	0	0
Hallucinations	0	0	0	0	1 (50)	0	0
Recognised para/post infectious neurological disease	7 (100)	5 (100)	1(100)	0	0	0	0

Investigations							
SARS-CoV-2 PCR positive (%)	5 (71)	4 (80)	1(100)	10 (100)	1 (50)	0	1 (50)
SARS-CoV2- IgG positive (%)	3 (43)	1 (50)	1(100)	4 (40)	2 (100)	2 (100)	NP
Median CRP (range)	12 (0-42)	1 (1-2)	1	1 (0-158)	8.5 (5-12)	0	NP
Elevated acute phase reactants (LDH, ferritin, D-Dimers)	2 (29)	0	0	1 (10)	0	0	NP
WCC (range)	10 (4-27.3)	11 (7-18)	7.5	9.4 (4-11.6)	7.5 (4-10.5)	6.3 (5.3-7.3)	NP
CSF WCC > 5 (%)	5 (71)	1 (20)	1(100)	1 (10)	1 (50)	NP	NP
Abnormal CNS imaging [CT and/or MRI] (%)	7 (100)	2(40)	1(100)	2/8 (25)	0	0	0
Treatment							
PICU admission	2 (29)	1 (20)	0	5 (50)	0	0	0
Inotropic support	0	0		0	0	0	0
Immunomodulation	6 (86)*	4 (80)	1(100)	2 (20)	0	0	0
Outcome							
Disability	4 (57)	2 (40)	0	1 (10)	1 (50)	1 (50)	0
Death	0	0	0	0	0	0	0

*one not immunomodulated due to underlying malignancy; ADS=Acute demyelinating syndrome; GBS=Guillain-Barré Syndrome; NP=Not performed; CNS, central nervous system; PNS, peripheral nervous system

Table 4: Demographics, clinical features, investigations, management and outcome of the following COVID-19 Neurology subgroups: a) Neuro-Immune COVID-19 Neurology subgroup b) COVID-19 Neurology other subgroup

63 patients rapid reported

6 Excluded for insufficient evidence of prominent neurological involvement
- 4 PIMS-TS
- 1 congenital heart disease and brief encephalopathy
- 1 pre-existing psychiatric disorder with worsening of symptoms

5 Excluded for insufficient evidence of SARS-CoV-2 infection; "possible" COVID
- 1 Neonatal stroke
- 1 Neonatal intraventricular haemorrhage
- 1 Acute Necrotizing Encephalopathy
- 2 New onset psychiatric disorder

52 patients included
(All confirmed COVID infection and/or PIMS-TS)

COVID Neurology (no PIMS-TS) (n=27)

PIMS-TS with prominent neurology (n=25)

Systemic features 25 (100%)
Encephalopathy 22 (88%) [MERS 7]
PNS involvement 10 (40%)
Behavioural changes 9 (36%)
Headache/meningism 10 (40%)
Focal neurological signs 6 (24%)
Seizures 4 (16%)

Acute demyelinating Syndromes (n=7)

Severe Encephalopathy (n=10)

Peripheral (n=5)

Movement disorder (n=2)

Neuropsychiatric (n=2)

Cerebrovascular (n=1)

5 Specific mechanisms for encephalopathy

Recognised Para/postinfectious Neurological syndrome

{ 1 Optic Neuritis | 1 Clinically isolated syndrome | 1 Transverse myelitis | 4 ADEM * | 1 Limbic encephalitis | 5 Gillian Barre

1 ADEM | 1 PRES | 2 Stroke 1 haemorrhagic 1 Ischaemic | Global ischaemic cortical damage

7 Encephalopathy & status epilepticus
(4 pre-existing epilepsy)
2 Isolated encephalopathy (1 MERS)

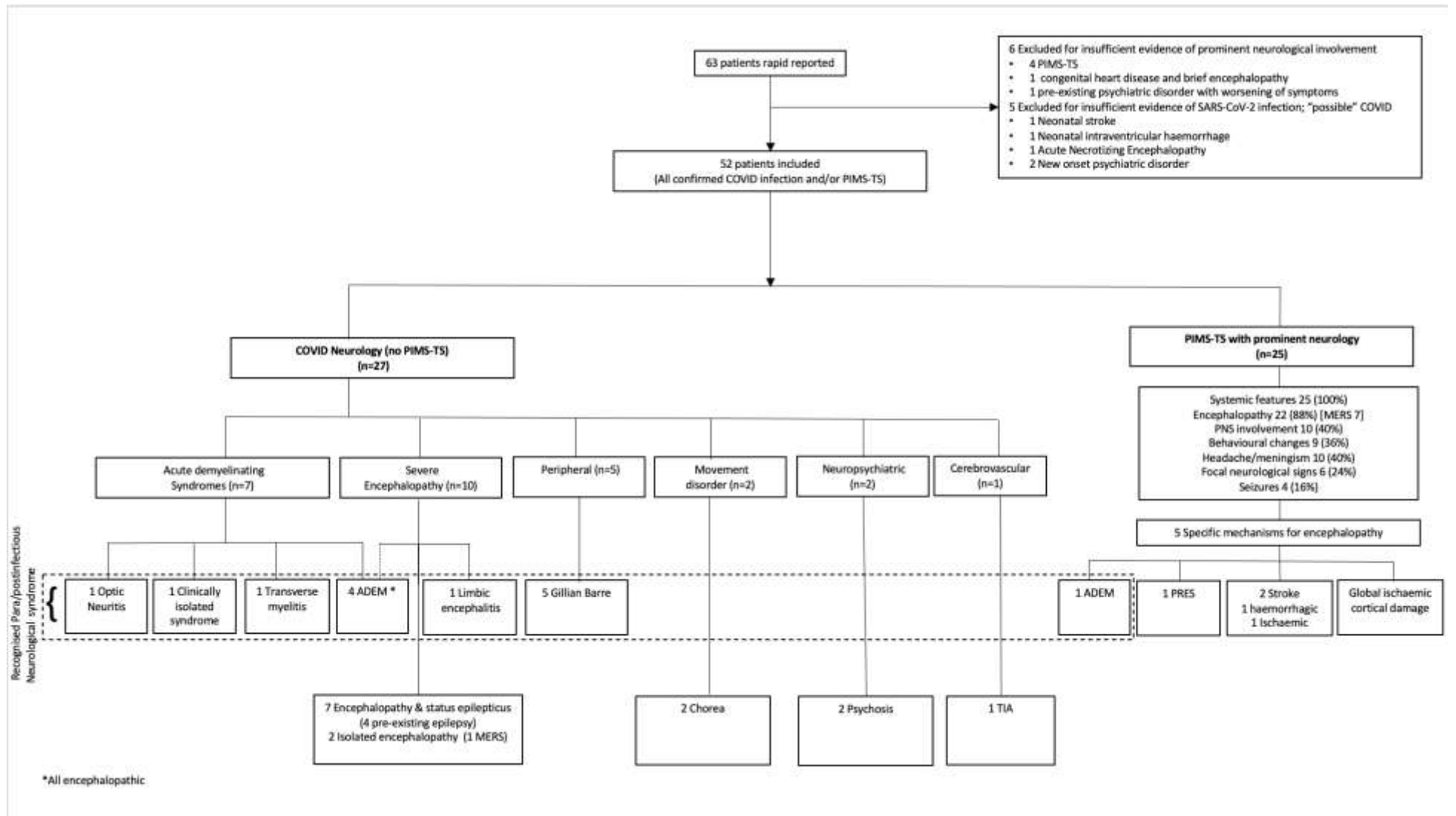2 Chorea

2 Psychosis

1 TIA

*All encephalopathic

23

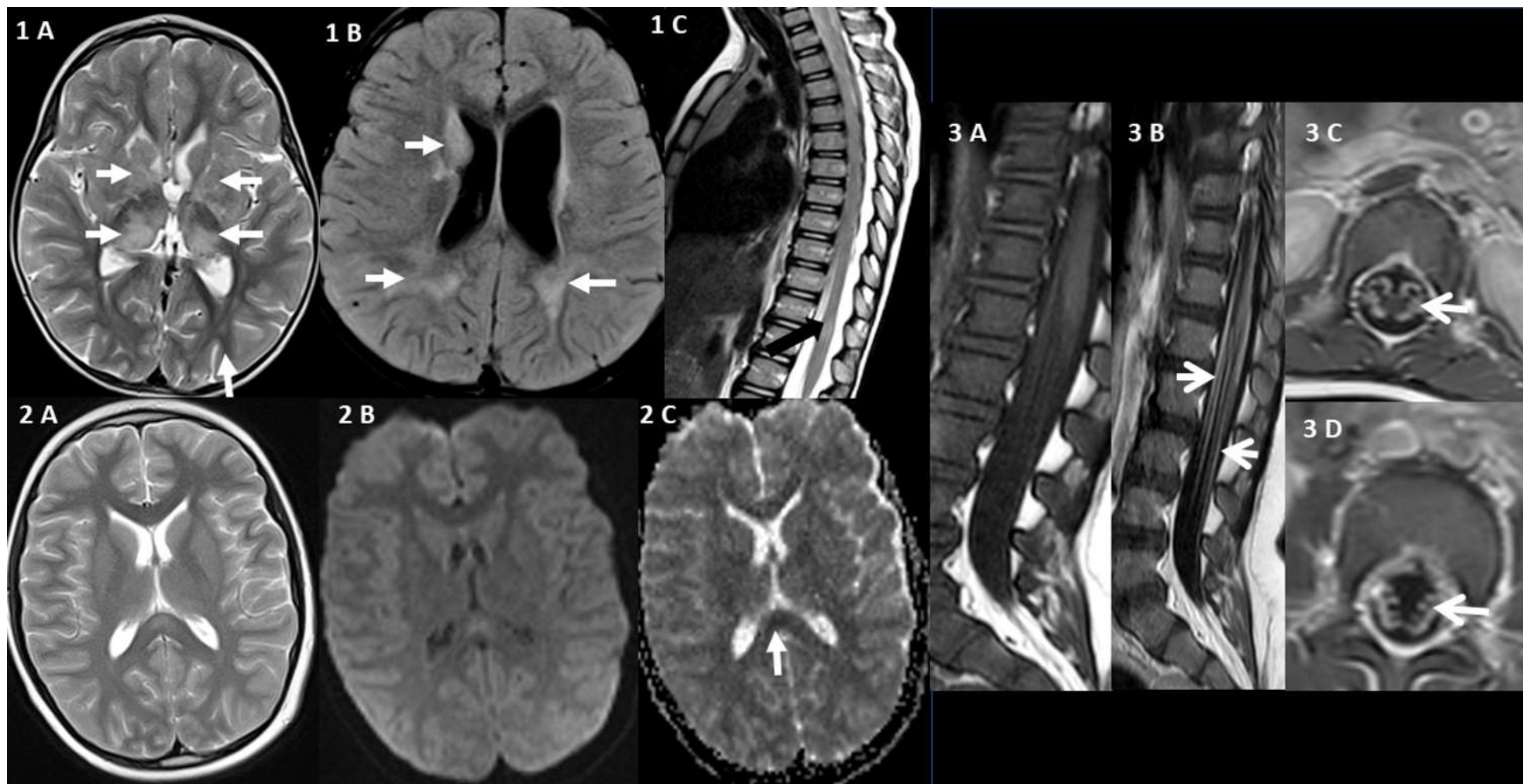Figure 1: Recruitment flow diagram and classification of neurological diseases

Figure 2: Magnetic Resonance (MR) imaging demonstrating the range of neurological complications seen in this study

1. MRI brain and spine of a 2 year old White girl with ADEM (case 4 supplementary table 1). Full history given in vignette a) supplementary appendix 1. There are multiple hyperintense foci on the axial T2 weighted (A) and T2 FLAIR (B) images involving both cerebral hemispheres including the basal ganglia, thalami, subcortical and periventricular white matter (white arrows). Sagittal T2 weighted image of the spine (C) demonstrates a focus of hyperintensity within the cord close to the conus (black arrow).

2. MRI brain of an 11 year old Asian boy presenting with PIMS-TS, encephalopathy and MERS (case 48 supplementary table 1). Full history given in vignette b) supplementary appendix 1. Axial T2 weighted image (A) demonstrates a focus of hyperintensity involving the splenium of the corpus callosum along the midline (white arrow). The b1000 (B) and the ADC maps (C) from the diffusion weighted imaging demonstrates subtle diffusion restriction involving the lesion.

3. MRI spine of a 16 month-old Asian boy presenting with Guillain-Barré syndrome (case 8 supplementary table 1). Full history given in vignette c) supplementary appendix 1. Sagittal T1 weighted image prior to (A) and following contrast (B) showing enhancement of the lumbosacral nerve roots (white arrows). The axial T1 weighted post contrast images (C & D) depict bilateral enhancement of the nerve roots.

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