Neuro-PIMS-TS: a single case report and review of the literature

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Abstract: Neurological manifestations related to SARS-CoV-2 infection in adults have been largely reported since the beginning of the pandemic. Subsequent large-scale studies involving children confirmed the occurrence of neurological symptoms associated with SARS-CoV-2 infection also among paediatric patients, especially in the context of paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS). At this regard, we report the challenging case of a 10-month-old baby with PIMS-TS complicated by acute cerebral oedema successfully treated with intravenous immunoglobulins, corticosteroids and anakinra. Our results, combined with the evidence of larger case series suggest that higher inflammatory burden is more frequent in patients with neuro PIMS-TS. As regards neuroimaging, neuroimmune disorders are found to be more common during acute COVID-19, MERS is more frequent during PIMS-TS. Distinct immune mechanisms may underlie these different types of neurological involvement, which are yet to be understood. Further studies are required to better define the physiopathology of neuro PIMS-TS and its possible therapeutical implications.

Keywords: Kawasaki disease, MIS-C, neurological manifestations, PIMS-TS

Introduction
Since the outbreak of coronavirus disease 2019 (COVID-19) pandemic, it was clear that children had an asymptomatic or mild infection course, with minimal hospitalization rate and mortality.1,2

However, starting from April 2020, several countries reported on children with an acute critical condition subsequent to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This new clinical entity was quite similar to other known inflammatory diseases [i.e. Kawasaki disease (KD), septic shock and toxic shock syndrome],3,4 although with peculiar findings. This condition was labelled paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS) by the Royal College of Paediatrics and Child Health.5 Subsequently, the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) referred to this condition as Multisystem inflammatory syndrome in children (MIS-C).6,7

Neurological manifestations related to SARS-CoV-2 infection in adults have been largely reported since the beginning of the pandemic.8 Subsequent large-scale studies involving children confirmed the occurrence of neurological symptoms associated to SARS-CoV-2 infection also among paediatric patients, especially in the context of PIMS-TS.9

LaRovere et al.10 reported that 22% of 1695 children with acute COVID-19 or PIMS-TS in the United States presented a neurological involvement. PIMS-TS patients did not show a higher rate of neurological involvement (35% versus 37%) or life-threatening events (47% versus 53%) than acute COVID-19 patients. Transient symptoms (88%) such as fatigue, confusion, headache, loss of smell or taste and seizures were the most frequently reported (88%). Therefore, a minority of patients (12%) experienced life-threatening conditions: severe encephalopathy (34.9%), ischemic or haemorrhagic stroke (27.9%), acute central nervous system infection or acute disseminated
encephalomyelitis (ADEM; 18.6%), acute fulminating cerebral oedema (9.3%) and Guillain–Barré syndrome (9.3%). These symptoms were more frequent in patients with underlying neurologic disorders and an unfavourable outcome, including death or neurological disability at discharge, was observed in 65% of patients with severe manifestations.

A further prospective cohort study conducted in the United Kingdom involving 1334 patients detected a much lower rate of neurological manifestations (3.8%) among children with acute COVID-19 and PIMS-TS. In the PIMS-TS subgroup (25 patients) encephalopathy (88%), peripheral nervous system involvement (40%), headache or meningism (40%) behavioural changes (36%), hallucinations (24%) and seizures (16%) were observed. Abnormal neuroimaging consistent with mild encephalopathy with reversible splenial lesion (MERS) was detected in 28% of patients. Neuroimmune disorders were more frequently observed in the COVID-19 group (48%) compared with the PIMS-TS one (<1%).

At this regard, we report the challenging case of a 10-month-old baby with PIMS-TS complicated by acute cerebral oedema. Furthermore, we performed a narrative literature review of PIMS-TS cases with neurological involvement, in order to characterize the spectrum of neurological manifestations of this critical condition, to establish the temporal association between PIMS-TS and neurological symptoms as well as to understand the potential underlying mechanisms of neurological involvement during PIMS-TS clinical course.

Materials and methods
A written informed consent for patients’ information and images to be published and written consent to treatment were provided by the legally authorized representatives. CARE guidelines were followed for the case report drafting.

As regards the narrative review of PIMS-TS cases with neurological involvement, the search strategy was carried out in PubMed/Medline and Embase databases using in all fields the key terms [‘Paediatric inflammatory multisystem syndrome temporally associated with COVID-19’ OR ‘PIMS-TS’ OR ‘Multisystem Inflammatory Syndrome in Children Associated With SARS-CoV-2’ OR ‘MIS-C’] AND [‘Neurological’ AND ‘Nervous’ AND ‘encephalopathy’ AND ‘seizures’ AND ‘papilledema’ AND ‘stroke’ AND ‘headache’ AND ‘hallucination’ AND ‘intracranial hypertension’]. The review includes retrospective cohort, prospective cohort studies, case series and case reports. Only articles published in English were included. Studies reporting poor or not-extractable data were excluded, as well as papers published before May 2020 (first PIMS-TS reported case). Double-reported patients were excluded from the total account.

Case report
A previously healthy 10-month-old African infant developed high-grade fever and emesis with a subsequent widespread urticarial rash and bilateral non-secretive conjunctivitis.

He was admitted to our tertiary care hospital after 4 days of persistent fever. At the physical examination, the infant presented marked irritability with tense, wide and bulging anterior fontanelle, shallow breathing and a widespread macular erythematous rash on trunk and limbs. Brain ultrasound did not detect intracranial bleeding or meningitis signs. Blood tests evidenced a remarkable increase of inflammatory markers [C-reactive protein (CRP) 32.08 mg/dl, procalcitonin (PCT) 97.7 ng/ml], neutrophilic leucocytosis, NT-proBNP (92,230 pg/ml) and D-dimer (2547 ug/l FEU) elevation, and a high ferritin value (810 ng/ml). SARS-CoV-2 IgG antibodies were positive, while RT-PCR for SARS-CoV-2 on nasopharyngeal swab was negative. Echocardiography evidenced slight coronary arteries dilatation and hyperkinetic left ventricle, with normal systolic function. Empiric antibiotic and antiviral treatment was started. Clinical and laboratory findings suggested a PIMS-TS diagnosis. Therefore, a single 2 g/kg dose of intravenous immunoglobulin (IVIG) was administered, followed by intravenous continuous infusion of anakinra (10 mg/kg qd). Moreover, a prophylactic antithrombotic therapy with enoxaparine at 100 UI/kg qd was started because of D-dimer elevation and initial coronary arteries dilatation, according to American College of Rheumatology clinical guidelines for PIMS-TS.

Despite this prompt intervention, 24h after admission, a neurological deterioration was observed with drowsiness alternating with extreme irritability. Brain computed tomography (CT) reported an initial cerebral oedema, with
meningeal and cerebral herniation from the anterior fontanelle. The patient continued to get worse and severe hypotension rapidly occurred requiring the admission to the intensive care unit (ICU), hemodynamic support with amines and mechanical ventilation. In order to treat cerebral oedema, dexamethasone and mannitol were administered intravenously. Subsequent cardiological evaluation described increased coronary arteries ectasia.

On day 7 from admission, a new fever rise, and a leucocytosis rebound occurred during the slow tapering of anakinra, therefore, the immunomodulatory regimen was re-intensified. A second 2 g/kg dose of IVIG followed by three boluses of methylprednisolone was administered.

After the maximization of treatment, patient’s clinical conditions gradually improved. He was weaned from ventilation, sedation and vasoactive support. Antibiotics and antiviral therapy were discontinued since all infectious tests resulted negative (aerobic and anaerobic bacteria and fungal blood cultures; Cytomegalovirus, Epstein-Barr virus, Adenovirus, Neisseria meningitidis, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, Listeria monocytogenes, Streptococcus agalactiae, Haemophilus influenzae, Human Herpesvirus-6, Human Herpesvirus-7, Enterovirus, Herpes Simplex virus-1, Herpes Simplex virus-2, Parvovirus on blood samples by real-time polymerase chain reaction (RT-PCR); QuantiFERON for the detection of Mycobacterium tuberculosis).

On day 10, the boy was back at his neurological baseline, with a normal anterior fontanelle. He was persistently afebrile, and the rash completely disappeared. Inflammation indexes slowly decreased, and the patient was moved to the paediatric ward. Dexamethasone regimen was suspended. Two weeks after the admission, the baby presented peeling of the extremities and remarkable thrombocytosis. Right coronary artery (RCA) demonstrated a residual deep aneurismatic remodelling (+5.5 SD). Anti-platelet therapy was started, while enoxaparin was discontinued. Anakinra was slowly tapered and shifted to subcutaneous administration, with no fever relapse.

Brain magnetic resonance imaging (MRI), performed on day 14, showed periventricular hyperintensities without restricted diffusion (Figure 1). Slight cerebral and cerebellar trophism reduction was observed, with mild peri encephalic subarachnoid spaces enlargement. Angiography, venography and post-contrast scan were normal.

Coronary arteries dilatation regressed at its normal size (proximal RCA: +2.2 DS; common trunk of left coronary artery +2 DS; proximal anterior interventricular coronary artery: +1.32 DS; circumflex branch of left coronary artery +1.2 DS) within 2 weeks after its peak (Figure 2). As regards neurological status, the infant presented a regular development without sequelae.

Results
We retrospectively reviewed the clinical history of 75 patients with neuro PIMS-TS reported in literature. We collected epidemiological, clinical, therapeutical, laboratory and instrumental data (Table 1).

Epidemiology
51.6% of patients (33/64) were male. The median age was 9 years. Among those with known ethnicity, the majority (59%, 23/39) were African descent. 28.2% was Asian (11/39); only 12.8% was Caucasian (5/39).

SARS-CoV-2 tests
85% of the patients (51/60) who underwent SARS-CoV-2 serology testing resulted positive, while RT-PCR on nasopharyngeal swab resulted positive in 42.6% of patients (26/61).

Signs and symptoms
Among neuro-PIMS-TS reported patients, fever was the most common finding (97.4%, 38/39). Vomiting (53.8%, 23/39), abdominal pain (53.8%, 21/39), and diarrhoea (41%, 16/39) were also frequent clinical signs, together with skin rash (53.8%, 21/39) and conjunctivitis (33.3%, 13/39). Dyspnoea was reported in 20.5% of these patients (8/39).

Blood tests
Among neuro PIMS-TS patients reported in case reports and case series, 75% (18/24) showed a CRP value higher than 20 mg/dl; a CRP value higher than 30 mg/dl was detected in 45.8% of cases (11/24). 46.6% (7/15) showed a PCT value higher than 30 ng/ml.
Ferritin levels resulted higher than 1000 ng/ml in 50% of these patients (10/20); a D-dimer elevation above 2500 ng/ml was reported in 73.7% of them (14/19).

NT-pro BNP was not routinely performed in neuro PIMS-TS children; 26.9% of cases reported a NT-pro BNP determination during the clinical course with a median value of 13,358 pg/ml.

**Neurological manifestations**

Encephalopathy was the most common neurological finding, involving 82.8% of neuro PIMS-TS patients (53/64). 43.8% of patients (28/64) experienced headache and/or meningism. Behavioural changes were described in 37.5% (24/64) and hallucinations in 21.9% of cases (14/64). Seizures were documented in 9.4% of patients (6/64). 4 stroke episodes (9.4%, 6/64) were also reported.

Signs of intracranial hypertension (abducens palsy 3/39, papilledema 2/39) were described in a minority of cases. Proximal and/or global weakness was sometimes reported, involving 18% of children (7/39). However, Ray et al. reported a higher rate of peripheral nervous system involvement among their patients (40%, 10/25).

**Cardiac manifestations**

Among neuro PIMS-TS patients, 30% (9/30) presented with tachycardia and 52.7% (29/55) with hypotension and/or shock. Indirect cardiovascular signs of intracranial hypertension (hypertension and bradycardia) were reported in two cases.

Coronary arteries dilatation and/or aneurysm were described in 25% of patients (6/24); ventricular dysfunction was reported in 48.6% of cases (18/37).

**Neuro-imaging findings**

Signal changes in the genu and/or splenium of the corpus callosum (consistent with MERS) were the most common imaging findings among all neuro PIMS-TS patients, accounting on 30.4%
of cases (21/69). 11.6% of them presented with radiological signs of stroke (8/69).

Among neuro PIMS-TS patients reported in case reports and case series, normal brain imaging was quite frequent, being documented in 42.4% of patients (14/33). Cerebral oedema and anomalies of optic nerves were both described in 2 cases. Lindan et al. also reported two cases of cranial nerve enhancement (18.2%, 2/11) among their patients; myositis of the facial or neck musculature was a common finding, involving 36.4% of children (4/11).

**Treatment**

A first-line immunomodulatory treatment with IVIG and methylprednisolone was received by 84.6% (33/39) of neuro PIMS-TS patients. 23.1% of them (6/26) also required the recourse to anakinra. Antibiotics were administered in 18% of patients (7/39). Vasooactive support was necessary in 34.3% of cases (9/26). 30.8% of patients (12/39) underwent anticoagulant treatment, while aspirin was administered in 10.3% (4/39).

Ray et al. reported a high rate of paediatric intensive care unit admission (80%, 20/25), with inotropic support in 52% of cases (13/25) and immunomodulatory treatment in 88% of patients (22/25).

**Outcomes**

A complete recovery without sequelae was reported in most cases (64%, 48/75). However, a variable degree of residual disability was observed, involving 32% of patients (24/75) and ranging from hemiparesis and wheelchair bounding to mild behavioural changes. Death was a rare adverse event (4%, 3/62).
### Table 1. Neuro PIMS-TS previously reported cases.

| Study          | Age    | Sex | Ethnicity | SARS-CoV-2 tests       | Blood tests                                      | Neurological manifestations                  | Cardiovascular findings                     | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy                              | Outcome                  |
|----------------|--------|-----|-----------|------------------------|-------------------------------------------------|-----------------------------------------------|---------------------------------------------|-------------------------------------------|--------------------------|----------------------|--------------------------------------|-------------------------|
| Abel et al.    | 33 months | M   | NA        | RT-PCR: negative/inde-terminate | PLT 23,000/dl CRP 25.2 mg/dl Ferritin 2000 ng/ml NT-pro-BNP 29.4 pg/ml | CNS Irritability Somnolence Hypotension PNS None | ECG: Sinus tachycardia | Fever Emsesis Rash | MRI: normal MRI (day 7): restricted diffusion in the bilateral lateral thalamic nuclei without T2/FLAIR changes MRI (day 15): normal | Normal | Antibiotics Anakinra Methylprednisolone Anticoagulants | Mild residual weakness requiring physical therapy |
| Baccarella et al. | 9 years | M   | NA        | RT-PCR: negative Serology: positive | CNS Headache Diplopia Right abducens palsy PNS None | Fever Abdominal pain | MRI and venography: normal | Elevated opening pressure: 34 cm H2O Sars-CoV-2: RT-PCR: negative Other CSF studies: normal | | PIMS-TS protocol Acetazolamide | Complete recovery |
| Becker et al.  | 14 years | F   | NA        | RT-PCR: negative Serology: positive | CNS Blurry vision Abducens palsy Bilateral papilledema PNS None | Tachycardia Hypotension US: Left ventricular dysfunction Right coronary artery dilatation (day 7): z score 3.15 | Fever Dyspnea Headache Emsesis Diarrhoea Rash | MRI: restricted diffusion of optic nerve sheaths, flattening of the posterior sclera, and oedema of the optic discs Venography: flattening of the left transverse and sigmoid sinuses | Elevated opening pressure: >36 cm H2O Sars-CoV-2 RT-PCR: negative Other CSF studies: normal | | PIMS-TS protocol Acetazolamide IVIG Anakinra Methylprednisolone Hydrocortisone | Recovery of papilledema after 5 months |
| 6 years        | F      | NA  | RT-PCR: negative (day1)/positive (day 2) low viral load Serology: positive | CNS Altered mental status Irritability Nucal rigidity PNS None | US: Moderate left ventricular dysfunction | Fever Rash Conjuctisitis Emsesis Diarrhoea | MRI: restricted diffusion of optic nerve sheaths, flattening of the posterior sclera, and oedema of the optic discs Venography: flattening of the left transverse and sigmoid sinuses | Elevated opening pressure: 31 cm H2O Sars-CoV-2 RT-PCR: negative Pleocytosis | | IVIG Anakinra Methylprednisolone Epinephrine Nor epinephrine | Discharged on day 12 at neurological baseline |
| Study | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy | Outcome |
|-------|-----|-----|-----------|------------------|-------------|-----------------------------|------------------------|-------------------------|-----------------|----------------|----------|---------|
| 13 years | F   | NA  | RT-PCR: negative | Serology: positive | WBC 13,300/ul | N 94.8% L 3.5% PLT 107,000/ul CRP 23.2 mg/dl PCT 1.5 ng/ml NT-pro-BNP: normal Troponin: normal | CNS Headache Neck pain Waning mental status Nuchal rigidity Encephalopathy Intracranial hypertension PNS None | EEG: no seizures | CT: normal MRI: normal | Elevated opening pressure: > 38 cm H₂O Pleocytosis Elevated protein | Ceftazidime Doxycycline Hypertonic saline IVIG Hydrocortisone Methylprednisolone Tacrolimus Meprobamate Epinephrine Noradrenaline Vasopressin Milrinone Enoxaparin Aspirin | Discharged on day 27 at neurological baseline |
| 12 years | M   | NA  | RT-PCR: negative | Serology: positive | WBC 10,300/ul | N 84.6% L 6.7% PLT 204,000/ul CRP 22.4 mg/dl ESR 62 mm/h PCT 38.1 mg/dl NT-pro-BNP 230 pg/ml Troponin 4.4 mg/ml Na 123 mEq/l | CNS Waning mental status Nuchal rigidity PNS None | EEG: diffuse slowing, no seizures | CT: normal | Elevated opening pressure: 34 cm H₂O Epinephrine Milrinone IVIG Methylprednisolone Enoxaparin Aspirin | Discharged on day 16 at neurological baseline |
| Tiwari et al. | 9 years | F | RT-PCR: positive | Serology: positive (week 4 of admission) | PLT 250,000/ul | CRP 6.49 mg/dl ESR 50 mm/h Ferritin 614 ng/ml D-dimer 3570 ng/ml Troponin 1 normal Na 132 mEq/l ALT 126 UI/L LDH 1000 UI/L | CNS Right facial nerve palsy Frontal headache Right hemiparesis Brisk deep tendon reflexes Extension right plantar response Worsening GCS (day 3) PNS None | Hypertension Bradycardia Cardiac arrest US: normal ECG: normal | Fever (14 days) | Emesis Conjunctivitis | CT: infarcts in the genu and adjacent body of corpus callosum, (left basal ganglia and bilateral thalami; mild oedema and mild mass effect over the lateral ventricle CT angiography: multifocal smooth stenosis of both intracranial internal carotid arteries, right middle cerebral artery, and anterior cerebral arteries. Diffuse narrowing of the M2 and M3 segment branches of both middle cerebral arteries | Sars-CoV-2 RT-PCR: negative Pleocytosis (80% lymphocytes) Slightly increased protein | Mechanic ventilation Sedation Head elevation (30°) Glycerol 3% Hypertonic saline Mannitol Supportive care Ceftriaxone Vancomycin Azithromycin IVIG Methylprednisolone Dexame the sone Remdesivir LMWH | GCS 13 power: 2–3/5 On psychomotor rehabilitation | (Continued) |
| Study                        | Age  | Sex | Ethnicity | SARS-CoV-2 tests            | Blood tests                                      | Neurological manifestations                                      | Cardiovascular findings                                      | Other symptoms and sings          | Neuro-Imaging                                           | Lumbar puncture | Therapy                        | Outcome                           |
|-----------------------------|------|-----|-----------|-----------------------------|--------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|----------------------------------|--------------------------------------------------------|----------------|--------------------------------|----------------------------------|
| **Kim et al.**              | 7 yrs | M   | NA        | RT-PCR: positive (his parents had positive nasopharyngeal swab 4 weeks before) | CRP 22 mg/dl ESR 38 mm/h PCT 8.6 mg/l Fibrin: 1601.2 ug/l D-dimer 17,650 ng/ml | CNS: Headache Neck pain Allergic mental status              | ECG: normal                                              | Fever Emesis Abdominal pain       | CT angiography: negative CT scan: diffuse cerebral oedema | Elevated opening pressure: 103.3 cm H2O | Levetiracetam Lorazepam Vancomycin | Brain death                        |
| **Shenker et al.**          | 12 yrs | M   | NA        | RT-PCR: positive Serology: positive (day 9) | WBC: 28,000/ul PLT 109,000/ul CRP 42.14 mg/dl Ferritin 633 ng/ml D-dimer 816 ng/ml NT-pro-BNP 1067 pg/ml Troponin: negative | CNS: Hyperactivity Emotional lability Tangential speech Allergic mental status Decreased level of consciousness | Tachycardia Hypotension                                    | Fever Right-sided neck swelling Conjunctivitis Abdominal rash Trismus | Neck CT: retropharyngeal fluid collection Head CT: normal MRI: normal MR angiography: normal | Normal SARS-CoV-2 RT-PCR: negative | Enoxaparin Clindamycin Ampicillin-sulbactam Vancomycin Furosemide IVIG Epinephrine Remdesivir Anakinra Levetiracetam Lorazepam Fosphenytoin Oxcarbazepine | Discharged on day 26 at neurological baseline |
| **Abdel-Mannan et al.**     | 8 yrs | M   | South Asian | RT-PCR: positive | CRP 44.8 mg/dl Ferritin 1414 ng/ml D-dimer 1,625,400 ng/ml ml LDH 1016 U/l | CNS: Agitation Meningism Headache Generalized proximal weakness | Circulatory shock US: —Mild to moderate left ventricular dysfunction ECG: pericarditis | Fever Abdominal pain Palmar rash Emesis | CT (day 3): hypodensity of the splenium of the corpus callosum (SCC) T2 MRI: persistent signal changes in the genu and SCC without restricted diffusion | Sars-CoV-2 RT-PCR: negative WBC 8,000 cell/ul Protein 2 g/dl | ICU admission IVIG Dexa methasone Methylprednisolone Anakinra | Encephalopathy resolved, wheelchair bound |
| **9 years**                 | M    | Afro-Caribbean | RT-PCR: positive | CRP 31.3 mg/dl Ferritin 1192 ng/ml D-dimer 494,500 ng/ml Na 129 mEq/L LDH 900 U/l | CNS: Confusion Ataxia Dysesthesia Dysphagia Bilateral proximal leg weakness Urinary retention | Circulatory shock US: —Mild to moderate parietal dysfunction ECG: supraventricular | Fever Palmar rash Emesis | T2 MRI (day 1): signal changes of the genu and SCC with restricted diffusion | Sars-CoV-2 RT-PCR: negative WBC: 2,000 cell/ul Protein 1.9 g/dl | ICU admission | Discharged on day 11 at neurological baseline | (Continued) |

(Continued)
| Study | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy | Outcome |
|-------|-----|-----|-----------|------------------|-------------|--------------------------|------------------------|------------------------|----------------|---------------|---------|---------|
| 15 years | F | South Asian | RT-PCR: positive | Serology: positive | CRP 28.9 mg/dl | Ferritin 54,145 ng/ml | D-dimer 1,479,800 ng/ml | LDH 4331 U/V | CNS | Confusion | Dysarthria | Dizziness | Global flaccid weakness | Reduced reflexes | PNS | None | EEG: mild excess of slow activity over the anterior region | EMG: mild myopathic or neuromyopathic changes |
| 15 years | F | Afro-Caribbean | RT-PCR: positive | Serology: positive | CRP 32.8 mg/dl | Ferritin 1218 ng/ml | D-dimer 1,248,600 ng/ml | LDH 1168 U/V | CNS | Confusion | Disorientation | Headache | Global proximal weakness | Reduced reflexes | PNS | None | EMG: mild myopathic changes |
| Bektaş et al.21 | 10 years | M | NA | RT-PCR: negative | Serology: positive 1 week after discharge | PLT 124,000/µl | CRP 39.2 mg/dl | Ferritin 341 ng/ml | D-dimer 595 ng/ml | NT-pro-BNP 15,800 pg/ml | Troponin I 324 ng/ml | Na 131 mmol/l | CNS | Hallucinations | Agitation | Disorientation | Personality changes | PNS | None | EEG: diffuse slowing |
| | 11 years | NA | RT-PCR: negative | Serology: positive | PLT 133,000/µl | CRP 45.6 mg/dl | Ferritin 533 ng/ml | D-dimer 850 ng/ml | NT-pro-BNP 35,000 pg/ml | Troponin I 182 ng/ml | Na 132 mmol/l | CNS | Agitation | Personality changes | PNS | None | EEG: diffuse slowing |

(Continued)
| Study | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and sings | Neuro-Imaging | Lumbar puncture | Therapy | Outcome |
|-------|-----|-----|-----------|-----------------|-------------|--------------------------|------------------------|--------------------------|---------------|---------------|----------|---------|
| Sa et al. | 14 years | M | African-American | RT-PCR: negative | CRP 30.8 mg/dl | CNS | Restlessness, Agitation, Confusion | Tachycardia, Hypotension, Circulatory shock | Fever, Abdominal pain, Truncal rash, Tachypnoea | MRI: normal | NA | Antibiotics, Fluid resuscitation, Noradrenaline, Ketamine, Midazolam, Doxome, Drotrecogin, LMWH, Methylprednisolone, Anakinra, Milrinone, Haloperidol, Lorazepam, Olanzapine, IVIG | Discharged on day 12 at neurological baseline |
| 2 years | F | Afro-Caribbean | RT-PCR: positive, Serology: positive | CRP 18.9 mg/dl | Altered consciousness, PNS | US: Mild left ventricular dysfunction, Coronary atherosclerosis | Fever, Lymphadenopathy, Periorbital and lip oedema, Abdominal pain | Normal, SARS-CoV-2 RT-PCR: negative | MRI: normal | NA | IVIG, Methylprednisolone | Complete recovery at 3 months follow-up |
| 4 years | F | Caucasian | RT-PCR: negative, Serology: negative | CRP 28.3 mg/dl | CNS | US: Hyperchogenicity of coronary arteries, Ectasia of left anterior descending coronary artery | Fever, Abdominal pain, Diarrhoea, Vomits, Altered consciousness, Behavioural changes | MRI: normal | Normal, CSF: mixed oligoclonal bands (serum and CSF) | IVIG, Methylprednisolone | Behavioural changes at 3 months follow-up |
| 6 years | F | Asian | RT-PCR: positive, Serology: positive | CRP 8 mg/dl | CNS | Severe behavioural changes, PNS | US: Coronary atherosclerosis, | Fever, Rash, Face and feet Oedema, Abdominal pain, Vomits, Severe behavioural changes, | NA | NA | Oral prednisolone | Complete recovery at 4 months follow-up |
| 8 years | F | Afro-Caribbean | RT-PCR: negative, Serology: positive | CRP 57 mg/dl | CNS | Altered consciousness, Visual hallucinations, PNS | Circulatory shock, Ventricular dysfunction | Fever, Sore throat, Vomits, Diarrhoea | MRI: normal | NA | IVIG, Methylprednisolone | Complete recovery at 4 months follow-up |

Table 1. (Continued)
| Study | Age  | Sex | Ethnicity  | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-imaging | Lumbar puncture | Therapy | Outcome |
|-------|------|-----|------------|------------------|-------------|-----------------------------|-----------------------|------------------------|--------------|---------------|---------|---------|
| 12 years M | Caucasian | RT-PCR: negative | Serology: negative | CRP 9.4 mg/dl | Persistent severe headache, Sleepiness | PNS | Hypotension | Pedal oedema, Conjunctivitis | MRI: normal | NA | IVIG, Methylprednisolone | Complete recovery at 3 months follow-up |
| 12 years F | Afro-Caribbean | RT-PCR: negative | Serology: positive | CRP 34.3 mg/dl | Behavioural changes, Cognitive dysfunction | PNS | Circulatory shock | Rash, Crackled lips | MRI: subtle cortical changes | NA | IVIG, Methylprednisolone, Infliximab | Mild behavioural changes/low mood at 4 months follow-up |
| 14 years M | Afro-Caribbean | RT-PCR: positive | Serology: positive | CRP 55.6 mg/dl | Headaches, Focal neurology with asymmetric pupils (stroke) | PNS | Circulatory shock | ARDS | CT: acute right anterior circulation infarct | NA | No treatment | Death |
| 15 years F | Afro-Caribbean | RT-PCR: negative | Serology: negative | CRP 9.9 mg/dl | Behavioural changes, Visual and auditory hallucinations | Seizures | Circulatory shock | ARDS | MRI: splenium of corpus callosum and hippocampal mild diffusion restriction | Normal | RT-PCR SARS-CoV-2: negative | IVIG, Methylprednisolone | Mild memory difficulties at 3 months follow-up |
| 10 years M | Afro-Caribbean | RT-PCR: negative | Serology: positive | CRP 29.6 mg/dl | Left-sided facial weakness, Hypertension and bradycardia (raised intracranial pressure: stroke) | PNS | Hypertension | Dorsal, chest, and thighs pain (sickle cell crisis) | CT/MRI: right frontal intraparenchymal haemorrhage and infarction | NA | IVIG, Methylprednisolone, Tocilizumab | Left hemiparesis |
| Study | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy | Outcome |
|-------|-----|-----|-----------|------------------|-------------|-----------------------------|------------------------|--------------------------|----------------|---------------|----------|---------|
| Lacinel Gürlevik et al. | 3 years | M | NA | RT-PCR: negative | Serology: positive | NA | CNS: Irritability, Lethargy, Headache, Meningism, Visual hallucinations, PNS, None | Hypotension | Fever, Rash, Conjunctivitis, Hepatospino-megaly | CT: normal | Glucose: 58 mg/dl, Protein: 40 mg/dl, Direct microscop-ic examination: no cell, CSF culture: negative, Viral encephalitis panel: negative | IVIG, Steroids, Immunomodulators, Plasma exchange, Prophylactic anticoagulation, Antiviral | Complete recovery |
| 14 years | F | NA | RT-PCR: negative | Serology: positive | NA | CNS: Visual and auditory hallucinations, Delirium, Fluctuating attention and cognition, Blurred vision, PNS, None, EKG (1 month later): normal | Hemodynamic impairment | Fever, Rash, Abdominal pain, Diarrhea, Rash | MRI (day 25): multiple microhemor-rages and bilateral MCA stenosis consist-ent with small- and medium-vessel vasculitis, MRI (day 36): PRES, MRI (day 54): PRES regression | NA | IVIG, Steroids, Immunomodulators, Plasma exchange, ECMO, Prophylactic anticoagulation, Antiviral | Discharged with moderate muscle strength loss and need assistance for walking, Difficulty in climbing stairs and tremors onset to 6 months follow-up |
| 15 years | F | NA | RT-PCR: negative | Serology: positive | NA | CNS: Irritability, Visual hallucinations, Fluctuating cognition, Agitation, Delirium, PNS, None, EMG: myopathic changes | Hypotension | Fever, Rash, Abdominal pain, Conjunctivitis | CT: normal | NA | IVIG, Steroids, Immunomodulators, Plasma exchange, Prophylactic anticoagulation, Antiviral | Complete recovery |
| 6 years | F | NA | RT-PCR: negative | Serology: positive | NA | CNS: Headache, Irritability, Lethargy, Fluctuating cognition, Meningism, On extubation (26th day): weakness is lower > upper limbs, muscle atrophy, PNS, EMG (2 months later): motor axonal poly-neuropathy in lower extremities | Hypotension | Tachycardia | CT: normal | Glucose: 58 mg/dl, Protein: 23 mg/dl, Direct microscop-ic examination: no cell, CSF culture: negative | IVIG, Steroids, Immunomodulators, Plasma exchange, Prophylactic anticoagulation, Antiviral | Discharged with mild muscle strength loss and need assistance for walking |
| 17 years | M | NA | RT-PCR: negative | Serology: positive | NA | CNS: Headache, Irritability, Lethargy, Fluctuating cognition, Meningism, On extubation (26th day): weakness is lower > upper limbs, muscle atrophy, PNS, EMG (2 months later): motor axonal poly-neuropathy in lower extremities | Hypotension | Tachycardia, CT angiography: stenosis in the upper truncus of the right MCA and paucity of distal branches of the MCA | CT: normal | Glucose: 58 mg/dl, Protein: 23 mg/dl, Direct microscop-ic examination: no cell, CSF culture: negative | IVIG, Steroids, Immunomodulators, Plasma exchange, Prophylactic anticoagulation, Antiviral | Discharged with moderate muscle strength loss and need assistance for walking, Steppage gait, impaired vibra-tion sensation in the lower limbs on up to 5 months follow-up |
**Table 1.** (Continued)

| Study | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy | Outcome |
|-------|-----|-----|-----------|------------------|-------------|---------------------------|------------------------|-------------------------|----------------|----------------|---------|---------|
| A Scarcella, MV Mastrolia et al. | 13 years | M | NA | RT-PCR: negative | NA | CNS None PNS | NA | Fever Rash Conjunctionitis Diarrhoea Abdominal pain | NA | NA | IVIG Steroids Immunosuppressants | Recovered with gabapentin |
| | 5 years | M | NA | Serology: positive | ↑ CRP ↑ PCT ↑ ESR ↑ D-dimer ↑ NT-pro BNP Troponin T: normal ↑ IL-6 ↓ PLT Hyponatremia Hyponatremia Hyponatremia Lyphocytopenia | CNS Headache Drowsiness Irritability Mood deflection Sleep disorder Photophobia Diffuse limb pain Lower limb weakness and areflexia Gait disorder Speech disorder Oculomotor apraxia PNS None | None | Mild dysfunction (EF 49-50%) | Fever Asthemia Abdominal pain Emesis Diarrhoea | Normal | Normal | IVIG Methylprednisolone | Full recovery |
| | 3 years | F | NA | Serology: positive | ↑ CRP ↑ PCT ↑ ESR ↑ D-dimer ↑ NT-pro BNP Troponin T: normal ↑ IL-6 ↓ PLT Hyponatremia Hyponatremia Hyponatremia Lyphocytopenia Proteinuria | CNS Irritability Mood deflection Drowsiness PNS None | None | None | Fever Rash Conjunctionitis Lower limb oedema | MRI: normal | Normal | IVIG Methylprednisolone | Full recovery |
| | 3 years | F | NA | RT-PCR: positive | ↑ D-dimer ↑ NT-pro BNP ↑ Troponin T ↑ PLT Neutrophilia Hyponatremia Hyponatremia Hyponatremia | CNS Generalized tonic-clonic seizures Irritability Drowsiness Hyporeactivity Mood deflection PNS None | None | Severe dysfunction (EF <35%) | Fever Abdominal pain Diarrhoea Femoral artery thrombosis Subpleural thickenings and pleural effusion | MRI: normal | Normal | ICU admission IVIG Methylprednisolone | Full recovery |

(Continued)
### Table 1. (Continued)

| Study | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy | Outcome |
|-------|-----|-----|-----------|-----------------|-------------|-----------------------------|-------------------------|------------------------|---------------|---------------|---------|---------|
| 7 years | F | NA | Serology: positive | ↑ CRP | Neutrophilia |
| 8 years | F | NA | Serology: positive | ↑ CRP | Neutrophilia |
| 10 years | M | NA | RT-PCR: positive | ↑ NT-pro BNP | Troponin T: normal |
| Ray et al. | 25 PIMS-TS patients | 10 (1-17) years | White (3/25, 12%) Black (14/25, 56%) Asian (8/25, 32%) | RT-PCR positive: 11/25 (44%) Serology positive: 19/25 (76%) | CRP: 2 mg/dl (55.6) Elevated acute-phase reactants: 25/25 (100%) WBC: 20,000/μl (3000-44,400) |

CT or MRI: 23/25 (92%) Abnormal neuro-imaging: 17/23 (74%) —MERS: 7/23 (28%) —Stroke: 2/23 (8%) EEG: non-specific focal or generalized background slowing: 13/25 (52%) Pleocytosis: 3/25 (12%) PICU admission: 20/25 (80%) Inotropic support: 13/25 (52%) Immunomodulation: 22/25 (88%) Disability: 7/25 (28%) Death: 1/25 (4%)
### Table 1. (Continued)

| Study                          | Age | Sex | Ethnicity | SARS-CoV-2 tests | Blood tests | Neurological manifestations | Cardiovascular findings | Other symptoms and signs | Neuro-Imaging | Lumbar puncture | Therapy | Outcome                        |
|--------------------------------|-----|-----|-----------|------------------|-------------|----------------------------|-------------------------|------------------------|---------------|----------------|---------|--------------------------------|
| Lindan et al.                  | 25  | 11  | PIMS-TS   | NA               | NA          | CNS                        | NA                      | 7/11 (64%): splenial lesion of the corpus callosum | NA            | NA             | NA      | 5/11 (45%): clinically normal at hospital discharge |
|                                |     |     | patients  | NA               | NA          | CNS                        | NA                      | 4/11 (36%): enhancing myositis of the facial or neck musculature | NA            | NA             | NA      | 4/11 (55%): clinically improved at hospital discharge |
|                                |     |     |           | NA               | NA          | PNS                        | NA                      | 2/11 (18%): cranial nerve enhancement | 1/11 (9%): cauda equina enhancement |               |               |         |                                |
|                                |     |     |           | NA               | NA          | NA                         | NA                      | 1/11 (9%): myelitis                              |               |               |         |                                |
|                                |     |     |           | NA               | NA          | 1/11 (9%): multiple microthrombi |               | 5/11 (45%): clinically normal at hospital discharge |               |               |         |                                |

ADEM, acute disseminated encephalomyelitis; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computer tomography; ECG, electrocardiography; ECMO, extracorporeal membrane oxygenation; EEG, electroencephalography; EF, ejection fraction; EMG, electromyography; ESR, erythrocyte sedimentation rate; FLAIR, fluid-attenuated inversion recovery; GCS, glasgow coma scale; HFNC, high flow nasal cannula; ICU, intensive care unit; IVIG, intravenous immunoglobulin; L, lymphocytes; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; MCA, middle cerebral artery; MERS, Mild Encephalitis/Encephalopathy with Reversible Splenial Lesion; MRI, magnetic resonance imaging; N, neutrophils; Na, sodium; NA, not available; NT-pro-BNP, brain natriuretic peptide; PCT, procalcitonin; PICU, paediatric intensive care unit; PIMS-TS, pediatric inflammatory multisystem syndrome tempo rally associated with COVID-19; PLT, platelets; PNS, peripheral nervous system; PRES, posterior reversible encephalopathy syndrome; RT-PCR, real time polymerase chain reaction; US, ultrasonography; WBC, white blood cells.
Discussion

To the best of our knowledge, we reported the youngest PIMS-TS patient presenting a neurological involvement. Four case reports, five case series, one prospective cohort study and one multicentre study have previously described neuro PIMS-TS patients, recording a total amount of 75 children, with a median age of 9 years (Table 1).

As regards ethnicity, our infant was of African descent. It is well known that most of the PIMS-TS patients are African/Afro-Caribbean, Hispanic and South Asian, mainly in Western countries. Only few cases were described in East Asia, probably because of the lack of knowledge of this new clinical entity at the beginning of pandemic. African ancestry was also one of the most represented in neuro PIMS-TS.

Our patient presented a positive SARS-CoV-2 serology, with negative RT-PCR on nasopharyngeal swab. LaRovere et al. described a 22% of patients reporting neurological symptoms between COVID-19 and PIMS-TS patients and a concomitant positivity of both serology and RT-PCR was often reported making difficult to distinguish between acute hyperinflammatory COVID-19 and PIMS-TS. Patients with and without neurological involvement presented a similar rate of PIMS-TS diagnosis and life-threatening neurologic events did not show a predominance among neuro-PIMS-TS cases.

Considering clinical features, our patient presented high-grade fever, emesis and widespread skin rash as reported in previous cases.

In this group of patients, a severe neurological involvement was associated to a remarkable inflammatory state, similarly to KD patients. Our infant presented with acute cerebral oedema and deep increase of inflammatory markers. A CRP value >30 mg/dl, a PCT value >30 ng/ml and a ferritin level >1000 ng/ml were observed in about half of the reported neuro PIMS-TS cases.

Our patient presented with wide, tense and bulging anterior fontanelle, with a rapid subsequent neurological impairment and a deep increase of NT-pro BNP (92,230 pg/ml) at the clinical onset, without any sign of myocardial dysfunction. NT-pro BNP represents a marker of left ventricular dysfunction in heart failure patients since it regulates systemic fluid volume through vasodilatation and natriuresis. However, the wide distribution of BNP receptors in the brain may suggest a novel pathway between heart and brain and a potential additional role for NT-pro BNP in the development of cerebral oedema.

As regards the pathogenesis of the neurological involvement observed in our case and in the most of the neuro-PIMS-TS patients, it is reasonable to suppose that is due to an immune-mediated pathophysiological mechanism triggered by previous SARS-CoV-2 infection rather than a direct viral invasion. This hypothesis is supported by the fact that the neurological symptoms occurred during a post-infectious multisystem inflammatory condition. Moreover, cytopathological evaluation of cerebrospinal fluid samples of previous neuro-PIMS-TS cases were negative for SARS-CoV-2 RNA by RT-PCR and reported increased numbers of lymphocytes and macrophages suggesting that the production of cytokines induced by the inflammatory response is responsible of the neurological manifestations. This hypothesis is also supported by the excellent response to immunomodulatory treatment for neurological complications in this group of patients.

Encephalopathy, headache and/or meningism and behavioural changes (33.3%) were the most reported symptoms in neuro PIMS-TS patients. Signs of intracranial hypertension (abducens nerve palsy, papilledema) and cerebral oedema were observed in a minority of cases.

A clinical hallmark was the concomitant presence of myocardial disfunction. Cardiovascular impairment frequently coexists with neurological symptoms since hypotension and/or shock and ventricular dysfunction were frequently observed. Coronary arteries ectasia and/or aneurysm were also reported even if typically transient, usually occurring at the onset of fever and rarely progressing to aneurysms.

As regards neuroimaging, a non-specific periventricular hyperintensities and a slight cerebral and cerebellar atrophy was observed in our patient. According to previous data, MERS is a common finding in neuro PIMS-TS patients. MERS is a distinct radiological entity characterized by hyperintensities of the genu and/or the splenium of corpus callosum on MRI T2-weighted, fluid-attenuated inversion recovery and diffusion-weighted images. MERS may have different causes; primarily viral infections as most frequent triggers, although its exact
pathophysiology is still unknown. The most accredited hypothesis is that pro-inflammatory cytokines lead to glutamate release and oxidative stress in neurons, resulting in cytotoxic oedema.34 MERS cases following SARS-CoV-2 infection have been reported.35 Similarly, anecdotal cases of KD-associated MERS have reported,25,36 strengthening the hypothesis that MERS may be a consequence of systemic hyper-inflammation.

Lindan et al.25 collected 38 cases of neuroimaging abnormalities in COVID-19 and PIMS-TS children. In the acute COVID-19 subgroup, 50% of patients presented a neuroimmune disorder (ADEM-like and neuritis); 33.3% had fulminant co-infections (tuberculosis, chickenpox, bacterial sepsis) and rapidly died; one patient (8.3%) showed an aggressive necrotizing myelitis; a 27-weeks pregnant adolescent girl presented with posterior reversible encephalopathy syndrome and occipital infarction. In the PIMS-TS subgroup, 64% of patients presented splenial lesions; two patients (18%) had cranial nerve enhancement; one patient (9%) reported cauda equina enhancement and myelitis was observed in one case (9%). Four patients (36%) had enhancing myositis of the facial and neck muscles; one patient (9%) reported multiple brain microthrombi.

These results suggest that neuroimmune disorders (i.e. ADEM-like changes, neuritis, Guillain Barré syndrome) may be more frequently observed during acute COVID-19 and neurological symptoms during COVID-19 and PIMS-TS may be caused by different immune mechanisms.

Focusing on treatment, our patient presented with a refractory disease and maximal therapy was performed, including IVIG, steroids and anakinra. Considering previous data, IVIG and methylprednisolone were the most common adopted treatment. Anakinra was administered in 23% of these patients, mostly in case of first-line treatment-resistant cases.

As regards thromboprophylaxis, our patient was treated with enoxaparine, while in the subacute phase anti-platelet regimen was started. Anticoagulants were used in 23% of neuro-PIMS-TS patients, while aspirin was used in 15.3% of cases.

Despite being a life-threatening condition with high rates of ICU admission,10,11 PIMS-TS patients, if promptly treated, report a complete recovery. As regards neuro PIMS-TS subgroup, a complete recovery was observed in most of the patients although a significant rate of disability (32%) was reported, thus underlying the importance of a timely diagnosis and treatment.

In conclusion, neurological involvement may be frequent in PIMS-TS patients as expression of the hyperinflammatory state. Symptoms are acute and reversible in most of the patients with a favourable response to immunomodulatory treatment. Available data suggest that paediatric patients experience different types of neurological involvement during acute COVID-19 and PIMS-TS. Further studies are needed to better characterize these different neurological manifestations related to SARS-CoV-2 infection suggesting the opportunity of different patient-tailored therapeutic strategies.

**Declarations**

**Ethics approval and consent to participate**

Ethics approval was not required by our institution for case reports.

**Consent for publication**

Written informed consent for patients' information and images to be published were provided by the legally authorized representatives.

**Author contributions**

**Antonio Scarcella**: Data curation; Formal analysis; Investigation; Writing – original draft.

**Maria Vincenza Mastrolia**: Conceptualization; Methodology; Project administration; Supervision; Writing – review & editing.

**Edoardo Marrani**: Investigation; Validation.

**Ilaria Maccora**: Investigation; Validation.

**Ilaria Pagnini**: Investigation; Validation.

**Gabriele Simonini**: Conceptualization; Methodology; Supervision.

**Acknowledgements**

None.

**Funding**

The authors disclosed receipt of the following financial support for the research, authorship and/or publication of this article: ‘Registro COVASAKI: sorveglianza di casi di Sindrome di
Kawasaki e di Malattia Infiammatoria Multisistemica Pediatrica associata ad infezione da SARS CoV-2 tramite la Rete Pediatrica TOSCANA’ founded by Tuscany Region.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Availability of data and materials
The authors confirm that the data supporting the findings of this study are available at request.

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