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# Clinical, thyroid metabolic, and inflammatory features in pediatric patients with post-acute COVID-19 neuropsychiatric symptoms

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## Abstract

**Background** Children are at increased risk for neuropsychiatric disorders following COVID-19. However, information regarding the clinical, metabolic, and cerebrospinal fluid (CSF) characteristics in patients with neuropsychiatric disorders associated with COVID-19 is limited. In this study, we described the clinical features and retrospectively assessed the metabolic and inflammatory profiles of 13 pediatric patients who exhibited subacute neuropsychiatric symptoms within one month of SARS-CoV-2 infection (NP-COVID-19).

**Methods** We retrospectively reviewed and analyzed the clinical and paraclinical data of 13 children with NP-COVID-19 admitted to Qilu hospital from December 15, 2022, to January 31, 2023. Healthy children (HC, $n=21$) and pre-pandemic migraine patients ($n=12$) were included as controls. Systemic metabolic and inflammatory parameters in NP-COVID-19 patients including thyroid hormone levels and neutrophil-to-lymphocyte ratio were compared with HC. Blood-brain barrier (BBB) integrity and CSF biomarkers of intrathecal inflammation including cytokines and immunoglobulin G index were compared with migraine patients.

**Results** CSF SARS-CoV-2 RNA was negative in all patients with NP-COVID-19. No differences in systemic inflammatory parameters were found between NP-COVID-19 patients and HC. However, NP-COVID-19 patients with intact BBB integrity exhibited significantly higher CSF interleukin (IL)-8 levels than migraine controls. In addition, serum free triiodothyronine (FT3) levels were lower in NP-COVID-19 patients than HC and low-T3 syndrome occurred in 61.5% of NP-COVID-19 children.

**Conclusions** Systemic inflammation rarely occurred in children with NP-COVID-19. Low-T3 syndrome is prevalent in NP-COVID-19 pediatric patients and the neuroinflammatory activation is mainly characterized by elevated CSF IL-8. Further study is required to investigate the pathophysiologic mechanisms in NP-COVID-19.

**Keywords** COVID-19, Neuropsychiatric symptoms, Pediatric patients, Low-T3 syndrome

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## Introduction

Although the respiratory system complications of coronavirus disease 2019 (COVID-19) have been the most frequent, mounting evidence indicates that neurological and psychiatric manifestations following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are common [1, 2]. In adults, patients with COVID-19 are at increased risk for developing long-term neuropsychiatric symptoms, such as anxiety, depression, cognitive deficit, dementia, and psychotic disorders [3, 4]. Neuropsychiatric symptoms associated with COVID-19 such as psychosis typically occur within days to weeks after the infection [5] and the post-viral syndrome is seemingly unrelated to COVID-19 severity [6]. In contrast to adults, children were not found to be at greater risk of mood and anxiety disorders after COVID-19, but children are at greater risk of psychotic disorders and cognitive impairment [1]. However, there is limited literature on neuropsychiatric complications associated with COVID-19 in the pediatric population.

A variety of systemic inflammatory processes are upregulated after SARS-CoV-2 infection, and the hyperinflammatory response can promote the development of extrapulmonary manifestations [7, 8]. Evidence has indicated that psychiatric symptoms among adult patients recovered from COVID-19 correlate positively with the baseline levels of systemic inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR) [9]. In addition, a robust innate immune response with circulating inflammatory cytokine production, such as IL-8 and tumor necrosis factor, has also been observed in adults with post-COVID-19 mood disorders and cognitive impairment [10–13]. Furthermore, patients with neurological complications after the acute SARS-CoV-2 infection also exhibit neuroinflammatory activation characterized by blood-brain barrier (BBB) dysfunction and high cerebrospinal fluid (CSF) levels of proinflammatory markers, such as IL-6 and IL-8 [14, 15]. However, systemic and intrathecal inflammatory changes in pediatric patients with post-COVID-19 neuropsychiatric symptoms (NP-COVID-19) remain largely unknown.

Non-thyroidal illness syndrome (NTIS) characterized by the combination of low serum tri-iodothyronine (T3) and serum thyroid-stimulating hormone (TSH) within the reference range, also known as low T3 syndrome, can be detected in many critical illnesses [16] and is closely related to the prognosis of neurological diseases such as stroke and cognitive dysfunction [17]. Increasing data have shown that COVID-19 is associated with thyroid disturbances and NTIS is correlated with the severity the disease [18]. However, information about thyroid function changes in children with NP-COVID-19 is scarce.

Despite the increased risk of neurological and psychiatric disorders following SARS-CoV-2 infection, relevant studies were usually case reports and little is known about the metabolic and inflammatory profiles of NP-COVID-19. Most studies focus on the adult population, which may not be directly comparable to children. Here, we reported a group of 13 pediatric patients with NP-COVID-19 and we analyzed retrospectively metabolic parameters including thyroid hormone levels and inflammatory cytokines in their blood and CSF.

## Methods

### Patients and controls

Qilu Hospital of Shandong University is a national regional medical center serving the periphery population and Pediatric Neurology Department contains 45 inpatient beds which admits over 2200 patients per year. Under the dynamic zero-COVID policy implemented by the Chinese government, our department did not receive any pediatric COVID-19 patients until December 7, 2022, when the policy shifted towards reopening [19]. As the Omicron variant of SARS-CoV-2 raged across China, huge numbers of symptomatic COVID-19 cases were reported everywhere. Although the number of patients ultimately diagnosed with neuropsychiatric disorders remained low, our Pediatric Neurology Department did see a notable rise in new-onset neuropsychiatric illnesses among children during this Omicron wave. The distribution of patients with neuropsychiatric disorders from January 1, 2020, to December 31, 2024, is displayed in supplementary File 1. We performed a retrospective review of medical records of children who were hospitalized at the Pediatric Neurology Department of Qilu Hospital between December 15, 2022, and January 31, 2023. Patients under 18 years of age with new-onset neuropsychiatric symptoms within one month of SARS-CoV-2 infection were included. Patients were excluded if they had underlying psychiatric or neurological disorder or were abusing substances. Infection with SARS-CoV-2 was confirmed with real-time positive polymerase chain reaction (RT-PCR) or rapid antigen test of nasopharyngeal swab specimens. The classification of the severity of COVID-19 infection was adapted from Wu and McGoogan [20]. During this period, our ward admitted 156 patients, including 62 pediatric COVID-19 cases, most of whom presented with complications such as seizures or epilepsy, 17 patients with post-COVID-19 neuropsychiatric symptoms (NP-COVID-19), 21 patients with post-COVID-19 neurological diseases, and 56 patients with neurological disorders unrelated to COVID-19. The details were provided in Fig. 1. Thirteen individuals with subacute neuropsychiatric manifestations developing after definite COVID-19 were finally included in the primary cohort. After discharge, all patients were followed up for 6 months by interviewing (directly or by telephone and WeChat) (supplementary

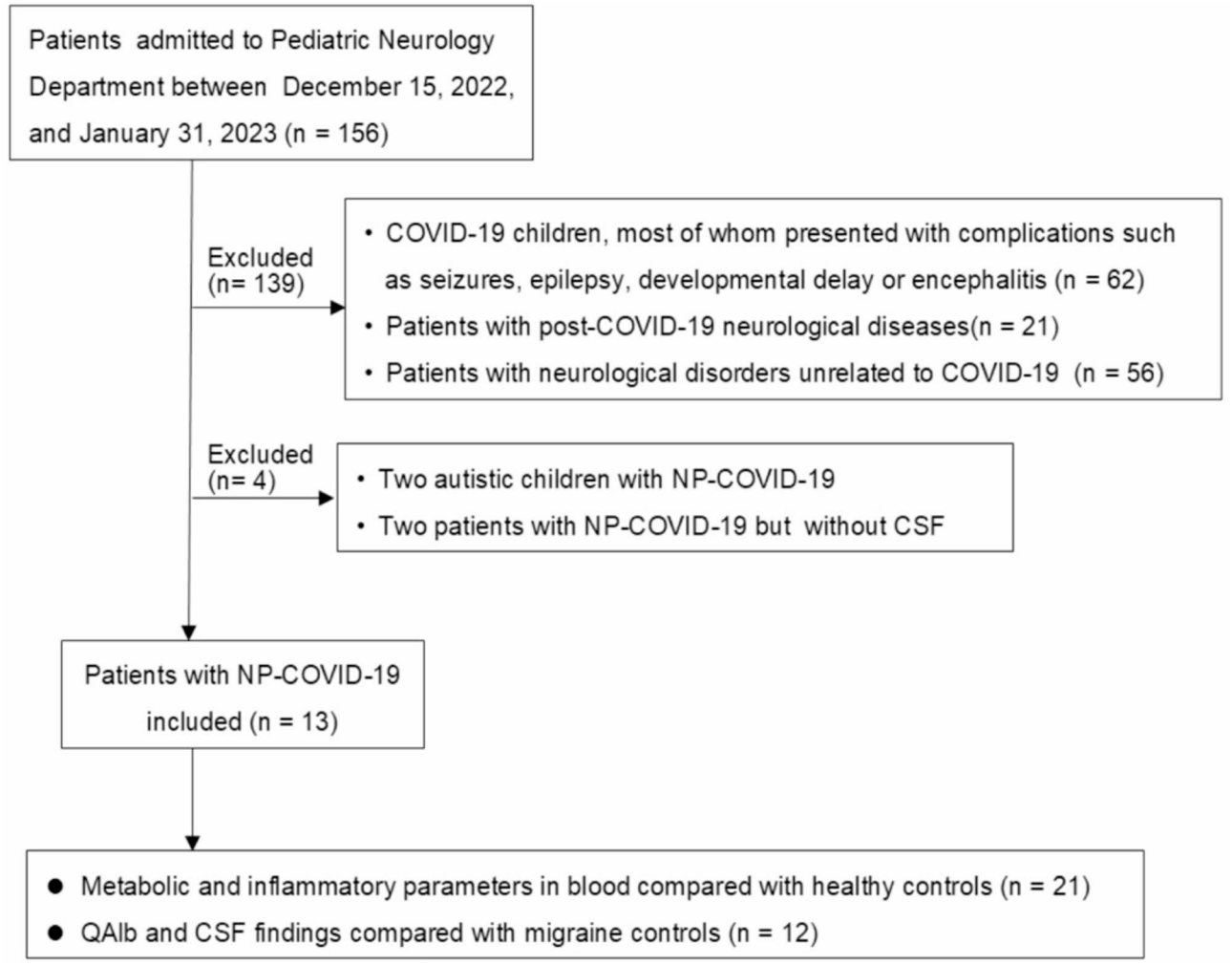


**Fig. 1** Flowchart of patients included in the study. *COVID-19* Coronavirus disease 2019; *NP-COVID-19* COVID-19 associated neuropsychiatric symptoms; *CSF* Cerebrospinal fluid; *QAlb* CSF/serum albumin ratio

file 2). Two separate control groups were retrospectively included. The control group for blood biomarker comparison comprised 21 age- and sex-matched healthy children who underwent physical examination at Department of Health Management Center of Qilu Hospital during 2022. For comparison of biochemical parameters in CSF, 12 pre-pandemic COVID-19 negative patients with migraine served as controls. The study protocol is illustrated in Fig. 1. Our study was approved by the Medical Ethics Committee of Qilu Hospital of Shandong university and we obtained written informed consent from the parents or guardians of all participants. Our study was conducted in accordance with the local legislation and institutional requirements.

### Data collection

We reviewed retrospectively the clinical presentations, laboratory findings, electroencephalographic findings, imaging findings, treatments and outcomes of all patients. Blood biomarker data included complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), folate, vitamin B12, lactic acid, ammonia, homocysteine, cytokines, autoimmune markers [antinuclear antibody (ANA), anti-ds-DNA and rheumatoid factor (RF)], immunoglobulin (Ig) G, IgM, IgA, thyroid hormone and thyroid antibody levels and anti-streptolysin O (ASO) titer. Blood samples were drawn after over-night fasting before examination. Routine CSF biomarker data included white blood cell (WBC) count, protein, glucose, lactic acid, cytokines and meningitis/encephalitis pathogen panel. SARS-CoV-2 virus in the CSF was tested by RT-PCR. Albumin, oligoclonal bands (OCB) and autoimmune encephalitis panel measured in paired CSF and blood samples. The lower detection limit was 2.5 pg/mL for all cytokines.

### Statistical analyses

Data analyses were conducted using IBM SPSS Statistics 26.0 (Armonk, New York, USA). Data are presented

as median, ranges for continuous variables and number (%) for categorical variables. For comparisons, we used the Fisher exact test, Chi square test and Mann-Whitney U test, when appropriate. For group comparisons across thyroid hormone levels and CSF parameters, the Benjamini-Hochberg false discovery rate (FDR) procedure was applied to correct the p values. Two tailed p-values < 0.05 were considered statistically significant.

## Results

### Demographic and clinical findings

The demographic and clinical characteristics of the 13 patients are shown in Table 1. The median age was 168 months (range: 51–196 months), and 8 patients were male (62%). In the acute stage of COVID-19, fever and respiratory symptoms were the most common and most patients were treated with acetaminophen or ibuprofen. The severity of the COVID-19 symptoms of all patients was mild. Nine patients who had undergone SARS-CoV-2 serological tests at admission were seropositive for SARS-CoV-2 IgM. The interval between the onset of symptoms of COVID-19 and the onset of neuropsychiatric symptoms ranged from 13 days to 23 days (median: 15 days). Most patients (10/13, 77%) exhibited psychiatric symptoms, mainly including hallucinations, persecutory delusions and disordered speech and behavior. Mood disorders (7/13, 54%), such as depression, aggression and agitation, were also common. In addition, 11 patients (11/13, 85%) exhibited neurological manifestations, including 6 patients (6/13, 46%) with cognitive and memory impairment. Other neurological disorders included sleep problems, headache, gait disturbance, poor attention and involuntary repetitive movements. Magnetic resonance imaging (MRI) findings were unremarkable for all patients. Electroencephalogram (EEG) findings showed normal in 9 (69%), back ground slowing in 3 (23%), and nonspecific spikes and sharp waves in 1 (8%). In our cohort of patients, targeting psychosis, mood disorders and sleep problems with psychotropic medications provided no benefit in 5 of 7 and was minimally effective in 2 of 7. Thus, most of our patients received immunotherapy. Treatments were combination of intravenous immunoglobulin (IVIg) and corticosteroids in 6, corticosteroids in 4, and supportive care in 3. Ten of 13 made a complete recovery, and 3 of 13 made a partial recovery at the time of follow-up.

### Analysis of hematological and metabolic parameters in the blood of NP-COVID-19 patients and healthy controls

We compared systemic hematological and metabolic parameters in NP-COVID-19 patients and healthy controls (Table 2). No significant differences were observed in the systemic inflammatory marker, NLR, and in the counts of neutrophils as well as lymphocytes between the two groups. The comparison of the metabolic biomarkers, including folate, vitamin B12, lactic acid, ammonia and homocysteine, showed no significant differences between the two groups.

### Analysis of blood inflammatory and autoimmune parameters in NP-COVID-19 patients and healthy controls

Comparison of systemic inflammatory biomarkers between NP-COVID-19 patients and healthy controls revealed no significant differences in the levels of CRP and ESR (Table 3). No significant differences were observed between the two groups in the levels of autoimmune parameters, such as ASO titer, ANA, anti-ds-DNA, RF, IgA, IgG and IgM. The autoimmune encephalitis panel for causes of neuropsychiatric symptoms in the blood of NP-COVID-19 patients was negative. Levels of serum cytokines, including IL-1β, IL-6, IL-8, IL-10, IL-2 and tumor necrosis factor α (TNFα) in NP-COVID-19 patients were all below the detection limits and within the reference ranges.

### Analysis of thyroid function and antithyroid antibody concentrations in NP-COVID-19 patients and healthy controls

Compared with healthy controls, free triiodothyronine (FT3) levels were significantly lower in NP-COVID-19 patients (FDR-corrected $p < 0.01$) (Table 4). Furthermore, low T3 syndrome occurred in 61.5% of NP-COVID-19 children, which was more prevalent than healthy controls (FDR-corrected $p < 0.03$). However, no significant differences were observed between the two groups in the concentrations of free tetraiodothyronine (FT4), thyroid-stimulating hormone, anti-thyroid peroxidase antibody and anti-thyroglobulin antibody.

### Analysis of CSF biomarkers in NP-COVID-19 patients and controls with migraine

No significant differences were observed between NP-COVID-19 patients and controls with migraine in CSF WBC counts, levels of protein, glucose and lactic acid (Table 5). As a marker of BBB permeability, the CSF/serum albumin ratio (QAlb) was determined. Normal individual age-related QAlb was determined as $QAlb^* = (4 + Age/15) \times 10^{-3}$. BBB dysfunction was defined as $QAlb > QAlb^*$. The QAlb and IgG index reflecting intrathecal IgG synthesis were within the normal range in all patients and no significant differences were found between the two groups. The comparison of the CSF cytokines, including IL-1β, IL-6, IL-10, IL-2 and TNFα showed no significant differences. However, levels of IL-8 in CSF were significantly higher in NP-COVID-19 patients than migraine controls (FDR-corrected $p < 0.02$). The autoimmune encephalitis panel and restricted OCBs in the CSF of NP-COVID-19 patients were negative. CSF

**Table 1** Demographic and clinical characteristics of patients with neuropsychiatric symptoms after COVID-19

| Patients No. sex/ age range (years) | COVID-19 symptoms | COVID-19 diagnosis/severity | COVID-19 treatment | SARS CoV-2 Antibody Test | Time from onset of COVID-19 to neuropsychiatric symptoms (days) | Neuropsychiatric symptoms | Neurologic Treatment | Brain MRI | EEG | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1. M/10–15 | Fever, sore throat, headache, fatigue | Positive antigen rapid test; mild | Ibuprofen | IgM+ | 14 | Psychosis, visual and tactile hallucinations, persecutory delusions, intermittent confusion, agitation, aggression, insomnia, memory impairment, headache | IVIg, IVMP then prednisone taper, olanzapine | Normal | Normal for age | Complete recovery |
| 2. M/15–20 | Fever, vomiting, fatigue | Positive RT-PCR test; mild | Acetaminophen | IgM+ | 16 | Psychosis, visual hallucination, disorganized behavior, aggression, depression, suicidal ideation, sleep disturbances | IVIg, IVMP then prednisone taper, olanzapine | Normal | Normal for age | Complete recovery |
| 3. F/4–9 | Fever, runny nose, cough | Positive RT-PCR test; mild | Acetaminophen | IgM+ | 14 | Psychosis, visual and auditory hallucinations, personality change | Supportive care | Normal | Occasional spikes and sharp waves in the frontal and central zone | Complete recovery |
| 4. F/15–20 | Fever, sore throat, muscle pain | Positive RT-PCR test; mild | Ibuprofen dexamethasone | | 23 | Psychosis, persecutory delusions, ritualistic behavior, nonsensical speech, impaired insight, suicidal ideation, aggression, agitation, reversal of sleep wake cycle, loss of appetite | IVIg, IVMP then prednisone taper, Valproate, olanzapine | Non-specific Changes (enlarged perivascular spaces) | Normal for age | Incomplete recovery |
| 5. F/8–13 | Fever, chills, nasal congestion, runny nose | Positive RT-PCR test; mild | Ibuprofen | IgM+ | 17 | Intermittent confusion, agitation, cognitive impairment; sleep disturbances, gait disturbance, orofacial dyskinesias | IVIg, IVMP then prednisone taper, clonazepam | Normal | Background slowing | Incomplete recovery |
| 6. M/14–19 | Fever, sore throat, muscle pain | Positive RT-PCR test; mild | Acetaminophen dexamethasone | | 19 | Apraxia, cognitive impairment, sleep disturbances, gait disturbance | IVMP then prednisone taper | Normal | Background slowing | Incomplete recovery |
| 7. F/10–15 | Fever, sore throat, cough | Positive RT-PCR test; mild | Ibuprofen | IgM+ | 15 | Psychosis, visual and auditory hallucinations, disorganized behavior, headache | supportive care | Normal | Normal for age | Complete recovery |
| 8. M/9–14 | Fever, sore throat, headache, fatigue | Positive RT-PCR test; mild | Ibuprofen | IgM+ | 14 | Psychosis, persecutory delusions, nonsensical speech, impulsivity, aggression | IVMP then prednisone taper, olanzapine | Normal | Normal for age | Complete recovery |

**Table 1** (continued)

| Patients No. sex/ age range (years) | COVID-19 symptoms | COVID-19 diagnosis/severity | COVID-19 treatment | SARS CoV-2 Antibody Test | Time from onset of COVID-19 to neuropsychiatric symptoms (days) | Neuropsychiatric symptoms | Neurologic Treatment | Brain MRI | EEG | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 9. F/11–15 | Fever, vomiting, fatigue | Positive RT-PCR test; mild | Supportive care | IgM+ | 20 | Suicidal ideation, depression, memory impairment, poor attention | IVIg, IVMP then prednisone taper | Normal | Background slowing | Complete recovery |
| 10. M/10–15 | Fever, nasal congestion, headache | Positive RT-PCR test; mild | Ibuprofen | IgM+ | 14 | Psychosis, visual hallucinations, insomnia, agitation | Supportive care | Normal | Normal for age | Complete recovery |
| 11. M/10–15 | Fever, sore throat, muscle pain | Positive antigen rapid test; mild | Ibuprofen dexamethasone | | 13 | Psychosis, visual hallucinations, nonsensical speech, intermittent confusion, muscle twitching, headache | IVMP then prednisone taper | Normal | Normal for age | Complete recovery |
| 12. M/10–14 | Fever, diarrhea, fatigue | Positive RT-PCR test; mild | Supportive care | IgM+ | 14 | Psychosis, visual and auditory hallucinations, personality change, suspicious, insomnia, poor attention, memory impairment | IVIg, IVMP then prednisone taper, clonazepam | Normal | Normal for age | Complete recovery |
| 13. M/15–20 | Fever, sore throat, fatigue | Positive RT-PCR test; mild | Ibuprofen | | 19 | Psychosis, auditory hallucinations, malaise, fluctuating attention and cognition, orofacial dyskinesia | Prednisone taper, clonazepam | Normal | Normal for age | Complete recovery |

*MRI* magnetic resonance imaging, *EEG* electroencephalography, *M* male, *F* female, *IVMP* intravenous methylprednisolone, *IVIG* intravenous immunoglobulin, *RT-PCR* reverse transcription polymerase chain reaction

**Table 2** Hematological and metabolic parameters in patients with post-COVID-19 neuropsychiatric symptoms (NP-COVID-19) and healthy controls

| Variables | Patients ($n=13$) | Healthy controls ($n=21$) | *P* value |
|---|---|---|---|
| Age, months | 168 (51–196) | 149 (46–198) | 0.51 |
| Male, *n* (%) | 8 (62%) | 15 (71%) | 0.55 |
| Blood Cell Type/Ratio | | | |
| Neutrophils ($\times 10^9$/L) | 4.03 (1.01–7.82) | 3.67 (2.06–6.96) | 0.78 |
| Lymphocytes ($\times 10^9$/L) | 2.58 (1.49–4.66) | 2.9 (1.08–5.17) | 0.89 |
| NLR | 1.38 (0.64–3.03) | 1.35 (0.81–3.16) | 0.99 |
| Folate, nmol/L (Ref > 10.0) | 17.69 (11.9-33.52) | 20 (13.33–35.67) | 0.44 |
| Vitamin B12, pmol/L (Ref: 133–675) | 401.26 (156.21-621.74) | 298.46 (119.26-632.23) | 0.21 |
| Lactic acid, mmol/L (Ref: 0.7–2.1) | 1.78 (1.21–2.56) | 1.66 (0.86–2.64) | 0.58 |
| Ammonia, umol/L (Ref: 9–33) | 28.24 (10.06–52.23) | 20.03 (10.69–50.36) | 0.90 |
| Homocysteine, umol/L (Ref < 15.0) | 11.03 (6.63–17.89) | 10.35 (6.32–18.26) | 0.79 |

*NLR* neutrophil-to-lymphocyte ratio

**Table 3** Blood inflammatory and autoimmune markers in patients with post-COVID-19 neuropsychiatric symptoms (NP-COVID-19) and healthy controls

| Variables | Patients ($n=13$) | Healthy controls ($n=21$) | *P* value |
|---|---|---|---|
| CRP, mg/dL, (Ref: 0–10) | 2.36 (0.2-10.94) | 2.96 (0.2–9.01) | 0.62 |
| ESR, mm/h, (Ref: 0–15) | 6 (2–16) | 5 (2–19) | 0.83 |
| Cytokines (pg/ml) | | | |
| IL-1β (Ref ≤ 12.4) | < 2.5 | ND | NA |
| IL-6 (Ref ≤ 5.3) | < 2.5 | ND | NA |
| IL-8 (Ref ≤ 17.8) | < 2.5 | ND | NA |
| IL-10 (Ref ≤ 4.91) | < 2.5 | ND | NA |
| IL-2 (Ref ≤ 7.42) | < 2.5 | ND | NA |
| TNF-α (Ref ≤ 4.60) | < 2.5 | ND | NA |
| ASO titer, IU/ml, (Ref < 400) | 126 (49–223) | 146 (36–293) | 0.51 |
| Autoimmune markers | | | |
| ANA | All negative | ND | NA |
| Anti-ds-DNA, IU/mL, (Ref ≤ 100.0) | All < 100 | ND | NA |
| RF, IU/mL, (Ref ≤ 15.0) | All < 15 | ND | NA |
| IgA, g/L, (Ref: 0.70-4.00) | 2.94 (1.06–3.69) | 2.64 (1.46–3.97) | 0.72 |
| IgG, g/L, (Ref: 7.00–16.00) | 11.23 (8.64–5.6) | 12.66 (7.69–15.66) | 0.37 |
| IgM, g/L, (Ref: 0.40–2.30) | 1.64 (1.21–2.1) | 1.78 (1.2–2.23) | 0.12 |
| *Autoimmune encephalitis panel | All negative | ND | NA |

*CRP* C-reactive protein. *ESR* erythrocyte sedimentation rate, *ND* not determined, *NA* not applicable, *ASO* antistreptolysin O, *ANA* antinuclear antibody, *RF* rheumatoid factor

* Test for NMDAR, AMPA Ab, LGI1, CASPR2, DPPX, GABA-B receptor, GAD65, GFAP, IgLON5, mGLUR, $D_2R$

**Table 4** Thyroid function and antibodies in patients with post-COVID-19 neuropsychiatric symptoms (NP-COVID-19) and healthy controls

| Variables | Patients ($n=13$) | Healthy controls ($n=21$) | *P* value | *P* (FDR corrected) |
|---|---|---|---|---|
| FT3, pmol/L (Ref: 3.93–7.70) | 3.19 (1.14–5.49) | 5.12 (4.21–7.2) | < 0.001 | < 0.01 |
| Low T3 syndrome, n (%) | 8 (61.5%) | 0 (0%) | < 0.001 | < 0.03 |
| FT4, pmol/L (Ref: 12.6–21.00) | 17.66 (13.6–20.1) | 16.8 (13.36–20.3) | 0.35 | 0.61 |
| Thyroid-stimulating hormone, μlU/mL (Ref: 0.51–4.30) | 2.38 (1.09–4.1) | 3.13 (0.89–5.19) | 0.31 | 0.52 |
| Anti-thyroid peroxidase antibody, IU/mL (Ref < 34) | 9.01 (5.6-16.68) | 10.23 (6.26–25.61) | 0.52 | 0.79 |
| Anti-thyroglobulin antibody, IU/mL (Ref < 115) | 19.64 (8.96-36) | 17.56 (9.8-39.46) | 0.58 | 0.81 |

*FDR* false discovery rate, *FT3* free triiodothyronine, *T3* triiodothyronine, *FT4* free tetraiodothyronine

**Table 5** CSF findings in patients with post-COVID-19 neuropsychiatric symptoms (NP-COVID-19) and controls with migraine

| Variables | Patients ($n=13$) | Controls ($n=12$) | *P* value | *P* (FDR corrected) |
|---|---|---|---|---|
| Age, months | 168 (51–196) | 141 (59–201) | 0.40 | 0.64 |
| Male, n (%) | 8 (62%) | 7 (58%) | 0.87 | 0.99 |
| CSF biomarkers | | | | |
| WBC count,/uL | 2 (1–4) | 2 (1–4) | 0.84 | 0.95 |
| Protein levels, mg/dL (Ref 15 ~ 45) | 0.3 (0.13–0.41) | 0.34 (0.12–0.42) | 0.62 | 0.83 |
| Glucose, mmol/L (Ref 2.8 ~ 4.5) | 3.6 (3.1–4.1) | 3.5 (3.0-4.2) | 0.83 | 0.91 |
| Lactic acid, mmol/L (Ref 1.2 ~ 2.1) | 1.8 (1.4–2.3) | 1.6 (1.3–2.4) | 0.21 | 0.46 |
| QAlb | 3.46 (2.03–4.72) | 3.37 (2.21–4.34) | 0.85 | 0.99 |
| Restricted OCBs | All negative | All negative | NA | |
| IgG index (Ref ≤ 0.7) | 0.51 (0.25–0.67) | 0.52 (0.29–0.62) | 0.98 | 0.99 |
| Cytokines, pg/ml | | | | |
| IL-1β (Ref ≤ 2.96) | < 2.50 | < 2.50 | NA | |
| IL-6 (Ref ≤ 6.77) | < 2.50 | < 2.50 | NA | |
| IL-8 (Ref ≤ 15.80) | 78.43 (40.77-308.62) | 13.97 (8.6-22.74) | < 0.001 | < 0.02 |
| IL-10 (Ref ≤ 2.63) | < 2.50 | < 2.50 | NA | |
| IL-2 (Ref ≤ 3.24) | < 2.50 | < 2.50 | NA | |
| TNF-α (Ref ≤ 2.78) | < 2.50 | < 2.50 | NA | |
| *Autoimmune encephalitis panel | Negative | ND | NA | |
| ※Meningitis/encephalitis panel by RT-PCR | Negative | Negative | NA | |
| SARS-CoV-2 RNA by RT-PCR | Negative | ND | NA | |

*CSF* cerebrospinal fluid, *FDR* false discovery rate, *WBC* white blood cell, *QAlb* CSF/serum albumin ratio, *CSF* blood albumin ratio ($\times 10^{-3}$), *OCBs* oligoclonal bands, *NA* not applicable, *ND* not determined, *RT-PCR* reverse transcription polymerase chain reaction

*Test for NMDAR, AMPA Ab, LGI1, CASPR2, DPPX, GABA-B receptor, GAD65, GFAP, IgLON5, mGLUR,

※Test for HSV-1, HSV-2, HHV-6, CMV, Epstein-Barr virus, varicella zoster virus, adenovirus, Japanese encephalitis, enterovirus, mycoplasma, Listeria monocytogenes, Haemophilus influenzae and Escherichia coli

meningitis/encephalitis panel and SARS-CoV-2 RNA by RT-PCR were negative in NP-COVID-19 patients.

## Discussion

During the wave of the Omicron variant of SARS-CoV-2, there was a spike in children presenting with neuropsychiatric disorders in our pediatric neurology department. The potential pathophysiological connection between COVID-19 and these neuropsychiatric symptoms is supported by two key observations: (i) the onset of symptoms occurred following the actual infection, and (ii) there was no other plausible clinical explanation to justify the occurrence of these symptoms other than the former infection [21]. Our study included 13 pediatric patients who exhibited neuropsychiatric symptoms including psychosis, mood disorders, sleep disorders and cognitive impairment after COVID-19 despite the absence of SARS-CoV-2 RNA in CSF. None of the patients had neuronal autoantibodies in their CSF and blood. Furthermore, we found that patients with NP-COVID-19 had higher CSF IL-8 than migraine controls. However, no differences were seen in blood systemic inflammatory biomarkers between NP-COVID-19 patients and healthy children. These findings showed that systemic inflammation rarely occurred in pediatric patients after SARS-CoV-2 infection. In addition, we also observed lower serum FT3 levels and prevalent low T3 syndrome in COVID-19 patients with neuropsychiatric involvement.

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and peripheral blood neutrophil-to-lymphocyte ratio (NLR) are indicators of the systemic inflammatory response and elevated NLR is associated with neuropsychiatric disorders as well as poor clinical outcome in adult patients with COVID-19 [22–24]. Recent studies have also found increased CRP and NLR in patients with psychotic disorders compared to healthy population [25, 26]. However, we observed no significant difference in NLR, CRP and ESR between patients with NP-COVID-19 and healthy controls. Moreover, more specific markers of systemic inflammation, including IL-6, IL-8, IL-1β and TNF-α, were all below lower limit of quantification in the present study. As a matter of fact, clinical features of children with COVID-19 are much milder and systemic inflammation rarely happens, highlighting the possibility that systemic inflammation may not be a trigger of COVID-19 associated neuropsychiatric impairments in pediatric patients [27].

Patients who underwent serological tests for SARS-CoV-2 upon admission were all found to be seropositive for SARS-CoV-2 IgM, supporting the fact of recent infection. The absence of SARS-CoV-2 RNA and pleocytosis in the CSF of our cohort, along with the delayed onset of neuropsychiatric symptoms after SARS-CoV-2

infection, clearly distinguishes COVID-19 from typical CNS invasive infections [28]. Furthermore, targeting psychiatric symptoms with psychotropic medications provided no benefit or was minimally effective in patients with NP-COVID-19 while their symptoms remitted after immunotherapy. These findings highlight the possibility of the immune-mediated mechanisms other than direct viral invasion and infection in the pathogenesis of NP-COVID-19 [29]. Accumulating evidence indicates elevated levels of intrathecal pro-inflammatory cytokines, such as IL-8 and IL-6, in patients with COVID-19 who present with neuropsychiatric symptoms [30–33]. Additionally, recent studies have reported persistently elevated CSF levels of cytokines, including IL-18, IL-6, and IL-8, along with sustained BBB dysfunction in patients experiencing post-COVID-19 neurological disorders, such as acute disseminated encephalomyelitis, limbic encephalitis, and cognitive deficits [14, 34, 35]. In contrast, a study by Kanberg et al. found no evidence of ongoing immune activation in CSF or BBB dysfunction in patients suffering from post-COVID neurocognitive complications [36]. The discrepancies among these findings may be attributed to differences in neurological complications, variations in the timing of CSF sampling after symptom onset, and differences in patient populations. In our cohort of 13 patients with NP-COVID-19, we observed a significant increase in CSF levels of IL-8 compared to migraine controls. Other cytokines, including IL-1β, IL-6, IL-10, IL-2, and TNFα, did not show significant differences between the two groups. Furthermore, BBB permeability, as indicated by QAlb, was within normal reference ranges, suggesting intact BBB function in patients with NP-COVID-19. Notably, serum levels of IL-8 were below the detection limit. The elevated levels of IL-8 in CSF but not in sera in NP-COVID-19 patients with intact BBB integrity indicate that production of IL-8 happened in the CNS, potentially supporting the notion of an active CNS process. Additionally, other chemokines such as monocyte chemoattractant protein-1, macrophage-derived chemokine, and C-C motif chemokine 11 have also been found to be elevated in the CSF of patients with NP-COVID-19, making IL-8 a relatively nonspecific marker for this condition [1, 33]. Interestingly, recent data show that adult patients with schizophrenia spectrum disorders exhibit significantly higher IL-8 levels in their CSF compared to healthy controls [37]. This raises two critical questions: First, was the elevation of CSF IL-8 in our NP-COVID-19 cohort a result of SARS-CoV-2 infection or a direct consequence of the neuropsychiatric complications? Second, is the high level of CSF IL-8 a cause or a consequence of the neuropsychiatric symptoms? To investigate the cause of the increased CSF IL-8, it would be beneficial to include two additional groups: children who did not develop neuropsychiatric symptoms following COVID-19 and children with acute-onset neuropsychiatric symptoms who have had no prior SARS-CoV-2 infection. Hypothetically, if CSF IL-8 levels in these two groups were found to be normal, we could infer that sustained intrathecal IL-8 production triggered by SARS-CoV-2 infection, may contribute to the pathogenesis of NP-COVID-19. However, due to the retrospective nature of this study and ethical considerations, performing lumbar punctures on children who did not experience neuropsychiatric symptoms following COVID-19 is not feasible. The role of neuroinflammation, such as IL-8 in the pathogenesis of NP-COVID-19 still remains unclear. Future studies should aim to recruit a larger number of subjects, including healthy volunteers, post-COVID-19 individuals who are free of neuropsychiatric symptoms, and individuals with neuropsychiatric symptoms but without a prior COVID-19 infection. Additionally, conducting follow-up lumbar punctures would help us to understand the mechanisms underlying NP-COVID-19. If elevated CSF cytokine levels are proven to be the cause, effective agents to block the key cytokines will be necessary to prevent the onset of NP-COVID-19.

Thyroid hormones have a profound influence on the human brain and behavior [38], and thyroid dysfunction is common in COVID-19 patients [39]. In our study, the serum FT3 levels were significantly lower in NP-COVID-19 patients than healthy controls. Low T3 syndrome occurred in 61.5% of our patients, indicating that NTIS is prevalent in pediatric patients who develop neuropsychiatric symptoms after SARS-CoV-2 infection. Indeed, NTIS may occur in a variety of systemic illnesses and stress states and accumulating evidence has demonstrated that NTIS was associated with poor clinical outcomes in patients with neurological diseases [17]. As a matter of fact, low T3 syndrome is recognized as a nonspecific adaptive response to acute psychiatric or underlying systemic illnesses, aimed at reducing energy expenditure and preventing catabolism, rather than acting as a pathogenic factor [38, 40]. The implications of this observation for the progression and prognosis of patients with NP-COVID-19 remain largely unclear. We propose that low T3 syndrome may serve as an adaptive response to NP-COVID-19 rather than a contributor to disease progression. The role of low T3 syndrome in the progression and prognosis of NP-COVID-19 warrants further investigation.

Our study has several limitations, mainly due to its retrospective design and ethical considerations. First, it is important to address the inclusion of a control group consisting of migraine patients, as neuroinflammation has been implicated in migraine through altered cytokine levels. Although a previous study found no significant differences in CSF IL-8 levels between migraine patients and healthy controls [41], the underlying

pathophysiology of migraine may have influenced the group differences, potentially resulting in an overestimation or underestimation of the pathology in the NP-COVID-19 cohort. Second, due to the absence of control groups consisting of individuals who did not develop neuropsychiatric symptoms following COVID-19, the role of neuroinflammation, such as IL-8, in the pathogenesis of NP-COVID-19 remains unclear. Consequently, our study should be considered preliminary. Third, given the widespread presence of the virus, the relatively low incidence of NP-COVID-19, and the confounding factors that can lead to neuropsychiatric symptoms, we cannot rule out the possibility that NP-COVID-19 occurred as coincidental conditions rather than as a consequence of the virus.

## Conclusions

Despite the limitations, we demonstrate that neuropsychiatric disorders can occur after mild SARS-CoV-2 infection in pediatric patients. In contrast to adult COVID-19 population, systemic inflammatory responses rarely occur in children with NP-COVID-19. Low T3 syndrome and neuroinflammation characterized by elevated CSF IL-8 levels are observed in pediatric patients with post-COVID-19 neuropsychiatric disorders. Future studies would benefit from recruiting a larger number of subjects, including post-COVID-19 neuropsychiatric-free volunteers, conducting follow-up lumbar punctures and performing animal studies to help to elucidate the mechanisms underlying neuropsychiatric complications associated with COVID-19 and guide treatment.

### Abbreviations

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| NP-COVID-19 | COVID-19 associated neuropsychiatric symptoms |
| HC | healthy children |
| CSF | Cerebrospinal fluid |
| SARS-CoV-2 | Syndrome coronavirus 2 |
| IL | Interleukin |
| FDR | false discovery rate |
| T3 | triiodothyronine |
| FT3 | free triiodothyronine |
| NLR | neutrophil-to-lymphocyte ratio |
| NTIS | non-thyroidal illness syndrome |
| TSH | thyroid-stimulating hormone |
| RT-PCR | real-time positive polymerase chain reaction |
| CRP | C-reactive protein |
| ESR | erythrocyte sedimentation rate |
| Anti-ds-DNA | anti-double stranded DNA |
| Ig | immunoglobulin |
| ASO | anti-streptolysin O |
| WBC | white blood cell |
| OCB | oligoclonal bands |
| MRI | magnetic resonance imaging |
| EEG | electroencephalogram |
| IVIg | intravenous immunoglobulin |
| TNF | tumor necrosis factor |
| QAlb | Cerebrospinal fluid /serum albumin ratio |
| CSF | blood albumin ratio |
| BBB | blood-brain barrier integrity |
| CNS | central nervous system |

## Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Not applicable.

### Authors' contributions

P.Y. contributed to the study conception and design, performed the data analysis, wrote and revised the manuscript. D.Z. and B.L. contributed to the conception and design of the study and wrote the first draft. G.L. contributed to the study conception and design, performed the data analysis, and revised the manuscript. X.F. retrieved medical records, conducted data analysis, and revised the manuscript. All the authors have read and approved the final manuscript.

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### Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.We declare it in the manuscript. We aegree to the data availability policy of BMC infectious disease.

## Declarations

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of Qilu Hospital of Shandong University and adhered to the principles outlined in the Declaration of Helsinki. We obtained written informed consent from all participant's parents or guardians.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

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