ORIGINAL ARTICLE

Nationwide observational study of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the Czech Republic

Jan David[1] · Veronika Stara[1] · Ondrej Hradsky[1] · Jana Tuckova[2] · Katerina Slaba[2] · Petr Jabandziev[2,3] · Lumir Sasek[4] · Michal Huml[4] · Iveta Zidkova[5] · Jan Pavlicek[5] · Alzbeta Palatova[6] · Eva Klaskova[6] · Karina Banszka[7] · Eva Terifajova[7] · Radim Vyhnanek[8] · Marketa Bloomfield[8,9] · Sarka Fingerhutova[10] · Pavla Dolezalova[10] · Lucie Prochazkova[11] · Gabriela Chramostova[12] · Filip Fencl[1] · Jan Lebl[1]

Abstract

The worldwide outbreak of the novel 2019 coronavirus disease (COVID-19) has led to recognition of a new immunopathological condition: paediatric inflammatory multisystem syndrome (PIMS-TS). The Czech Republic (CZ) suffered from one of the highest incidences of individuals who tested positive during pandemic waves. The aim of this study was to analyse epidemiological, clinical, and laboratory characteristics of all cases of paediatric inflammatory multisystem syndrome (PIMS-TS) in the Czech Republic (CZ) and their predictors of severe course. We performed a retrospective-prospective nationwide observational study based on patients hospitalised with PIMS-TS in CZ between 1 November 2020 and 31 May 2021. The anonymised data of patients were abstracted from medical record review. Using the inclusion criteria according to World Health Organization definition, 207 patients with PIMS-TS were enrolled in this study. The incidence of PIMS-TS out of all SARS-CoV-2-positive children was 0.9:1,000. The estimated delay between the occurrence of PIMS-TS and the COVID-19 pandemic wave was 3 weeks. The significant initial predictors of myocardial dysfunction included mainly cardiovascular signs (hypotension, oedema, oliguria/anuria, and prolonged capillary refill). During follow-up, most patients (98.8%) had normal cardiac function, with no residual findings. No fatal cases were reported.

Conclusions: A 3-week interval in combination with incidence of COVID-19 could help increase pre-test probability of PIMS-TS during pandemic waves in the suspected cases. Although the parameters of the models do not allow one to completely divide patients into high and low risk groups, knowing the most important predictors surely could help clinical management.

What is Known:
• *Preliminary evidence, majority from relatively small, and mostly single-centre patient cohorts, has shown some insights in the basic epidemiological and clinical data of children with a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).*

What is New:
• *To our knowledge, this is the unique published national population-wide cohort allowing to study the epidemiology (including overall incidence), time gap between viral exposure and clinical symptoms of PIMS-TS, and clinical presentations and outcomes within the individual pandemic waves of COVID-19 that were characterised by various prevailing genetic variants of SARS-CoV-2.*
• *We estimated 3-week interval as a most probable period between SARS-CoV-2 infection and PIMS-TS based on nationwide population data using cross-correlation method.*

Communicated by Peter de Winter

Jan David, Veronika Stara and Ondrej Hradsky shared first authorship.

Filip Fencl and Jan Lebl are senior authors who contributed equally.

✉ Jan David
jan.david@centrum.cz

Extended author information available on the last page of the article

Introduction

Following a temporary success within the first wave of the worldwide pandemic of the novel 2019 coronavirus disease (COVID-19) with very few positive cases in spring 2020, the Czech Republic (CZ) suffered from one of the highest incidences of individuals who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the second and third pandemic waves in late 2020 and in early 2021 (with predominant B.1.258 and B.1.1.7 variants) [1–3]. By May 2021, the number of confirmed COVID-19 cases exceeded 155,873 per one million people (total 1.6 million cases, 15.6% of the population), and the number of deaths hit the 30,000 mark (cumulative mortality 2,829 per one million) according to data of the Institute of Health Information and Statistics (IHIS) of CZ [1, 2]. During the most devastating third wave of the pandemic in January–March 2021, the numbers of newly infected patients reached almost 18,000 per day [1–3].

In parallel, paediatricians faced a serious wave of cases of the multisystem condition resulting from an aberrant immune response to SARS-CoV-2 in children that was already recognised as a novel paediatric disease in spring 2020 [4]. This condition partially resembling Kawasaki disease (KD) was assigned the name paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) or multisystem inflammatory syndrome in children (MIS-C) [4].

PIMS-TS is a severe, heterogeneous disease characterised by multiorgan involvement. Several factors linked to disease severity were described, namely age (older than 5 years), higher concentrations of troponin, brain natriuretic peptide (BNP), ferritin, C-reactive protein (CRP), and D-dimer [5]. However, the majority of previously published studies included relatively small and mostly single-centre patient cohorts [6].

The aim of this study was to analyse epidemiological, clinical, and laboratory characteristics of all cases of PIMS-TS in CZ [7]. We also aimed to identify predictors of a severe course of PIMS-TS.

Materials and methods

We performed a retrospective-prospective nationwide observational study based on patients hospitalised with PIMS-TS in CZ. Data were obtained from nine university hospitals and eight regional hospitals in CZ, which is a middle-sized country with a total population of 10.7 million (2.1 million children and adolescents under 19 years of age) [1]. Data on positive reverse transcription-polymerase chain reaction (RT-PCR) SARS-CoV-2 individuals were retrieved from reviews according to the IHIS of CZ [1–3].

Medical training procedures, data sheet collection, and results evaluation within this study were conducted under the authorisation of the Czech Paediatric Society. Soon after the occurrence of the first cases of PIMS-TS in October 2020, diagnostic and therapeutic guidelines using the already available recommendations were updated [8]. Medical staff from all 59 paediatric departments within CZ participated in an online training programme on the recognition and treatment of PIMS-TS. The recommendations were published using multiple information channels and were also available for all primary care paediatricians. All representative physicians were instructed to collect and report a standard set of data (Supplementary table 1) on all children diagnosed with PIMS-TS.

Patients with PIMS-TS according to World Health Organization definition (Supplementary Fig. 1) [7] who were admitted to the hospital between 1 November 2020 and 31 May 2021 were included in the study (Fig. 1). The anonymised data of patients (demographic and clinical data, laboratory test results, imaging and echocardiographic findings, and treatments) were abstracted by medical record review. Laboratory evidence of SARS-CoV-2 exposure or a history of contact with a SARS-CoV-2-positive person in the preceding 2 months was required. From each patient, we obtained one nasopharyngeal swab to test for SARS-CoV-2 using RT-PCR and took blood samples to test for IgG antibodies against SARS-CoV-2. Standard cardiology investigations included electrocardiography and echocardiography (initially and 1–6 months apart, individually according to paediatrics department). We defined a coronary artery dilatation as a z-score 2.0–2.5 and an aneurysm as a z-score 2.5 and higher (by the Lopez method) [9]. Myocardial dysfunction was defined by a decreased left ventricular ejection fraction ($<55.0\%$). Resistance to intravenous immunoglobulin (IVIG) treatment was defined as a persistent fever or laboratory evidence of inflammation 36 h of the first immunoglobulin infusion [9].

To ascertain the completeness of the nationwide dataset of patients hospitalised with PIMS-TS, at the end of the observation period, chairs of all inpatient paediatric departments were re-contacted by an e-mail and/or by a direct phone call, which led to identification of an additional five yet unreported cases that were consequently added to the study cohort.

All data were analysed using R statistical software (version 4.0.4). Missing data were imputed using multiple imputation methods within the r package mice (version 3.13.0); missing data in continuous variables were imputed using Predictive Mean Matching Imputation algorithm and categorical variables using Random Forest imputation algorithm. The number of missing values in original dataset were stated in Supplementary table 2. Continuous variables were described as medians and interquartile ranges (IQRs). Categorical variables were described as absolute

Fig. 1 Study profile
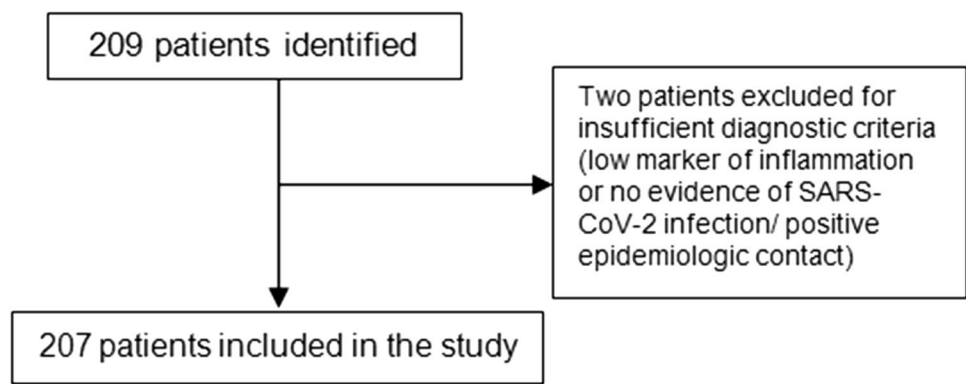
frequencies and percentages. Incidence rate and 95% confidence intervals (CI) were calculated using the epiR package (version 2.0.26). The difference between age categories (0–5 as a reference category) and sex (male sex as a reference category) was tested by generalized linear regression models. The interval between peak of RT-PCR SARS-CoV-2 positivity in children and development of PIMS-TS was estimated using cross-correlation plots. The estimated value was confirmed by comparison of multiple regression models with the most probable intervals as a predictor (based on cross-correlation plots).

The heatmap with dendrogram (based on matrix similarity computation) of the symptom co-occurrence was constructed using R packages "proxy" and "plots". The difference between patients with and without myocardial dysfunction was tested by unadjusted generalized linear regression model. For the purpose of the prediction, categorical data were converted to dummy variables and all missing data of predictors were imputed using k-nearest neighbours algorithm. The prediction models were constructed using R package "caret". Data were divided into training (65.0%) and testing (35.0%) parts. For construction of the models, the modified random forest method, minimising the distance to the perfect model with cross-validation and resampling, was used. The accuracies of these particular models and receiver operator curves (ROCs) were estimated on the testing parts of the datasets.

Results

Using the inclusion criteria, 207 patients with PIMS-TS were enrolled in this study. In the monitored period, the overall incidence of PIMS-TS was 0.1:1,000 of general paediatric population aged 0–19 years and was dependent on age and gender (1:7,400 in 0–5 years; 1:7,200 in 5–10 years; 1:13,900 in 10–15 years; 1:23,900 in 15–19 years; 1:8,100 in males; and 1:13,700 in females). The incidence based on 207 patients with PIMS-TS out of 233,289 SARS-CoV-2 RT-PCR positive children was 0.9:1,000. The incidence rate was 99.0 (95% CI 86.0, 113.0) per 1,000,000 SARS-CoV-2 RT-PCR positive person-months (0–19 years). The incidence rate differed according to age category

as follows: 0–5 years, 136.0 (95% CI 104.0, 174.0); 5–10 years, 140.0 (95% CI 110.0, 173.0); 10–15 years, 72.0 (95% CI 53.0, 96.0); and > 15 years, 42.0 (95% CI 24.0, 68.0) person-months. Using the generalised linear regression model, the frequency of PIMS-TS among SARS-CoV-2 RT-PCR-positive children was lower in the 10–15 years age group (odds ratio (OR) 0.5, 95% CI 0.36, 0.77) and > 15 years (OR 0.3, 95% CI 0.17, 0.52) age group. The estimated OR for girls was nearly half (0.6, 95% CI 0.44, 0.78) that for boys. The data also made it possible to estimate the period between the occurrence of PIMS-TS and the COVID-19 pandemic wave. According to the cross-correlation method, the most likely 3-week interval was found (Supplementary Fig. 2).

Median age at PIMS-TS presentation was 8 years, 132 (63.8%) patients were male and 75 (36.2%) patients were female. Most individuals (196 (94.7%)) were from the Caucasian ethnic group. The demographics, clinical, laboratory parameters, and treatment of patients are summarised in Table 1. The median duration of symptoms before initial treatment was 5 days (range 3–20). Forty-two (20.3%) patients had comorbidities, with the most common being allergies (7.7%) and cardiovascular (2.9%) disorders. An overview of symptom frequency and co-occurrence is displayed in Fig. 2. Among 207 patients, 71 (34.3%) patients had a clearly pathological electrocardiogram: repolarization abnormality ($n=42$), atrioventricular (AV) block ($n=11$), and prolonged QTc interval ($n=2$). Eighty-two (39.6%) individuals had decreased myocardial function and 51 (24.6%) of them required inotropic support. Use of extracorporeal membrane oxygenation was not needed. Only 23 (11.1%) patients had involvement of the coronary arteries. All patients were hospitalised in paediatric departments with accessibility to intensive care monitoring.

Sixty-one (29.5%) patients had early neurological symptoms. The most frequent reported neurological symptoms were meningism ($n=24$), disorders of consciousness ($n=21$), headache ($n=11$), and seizures ($n=2$). Six children underwent lumbar puncture, five with negative findings and one with cerebrospinal pleocytosis. Three (1.5%) patients had neuroimaging (computed tomography or magnetic resonance imaging of brain), which revealed a spectrum of findings, including extrapontine myelinolysis, bilateral cortical and cortico-subcortical

hyperintensities, cortical swelling (in posterior reversible encephalopathy syndrome (PRES)), arterial thrombosis, and cerebral ischaemia. Two patients (without known associated risk factors) had major left ventricular thrombi with embolization to the cerebral artery. No known deaths occurred in our cohort. Over 1–6 months of follow-up ($n = 161$), 159 patients (98.8%) had normal cardiac function with no residual findings. Only two patients (1.2%) had persistent left coronary artery dilation, but with normal cardiac function.

In addition to the descriptive characteristics, the objective was to identify possible predictors of a severe course of PIMS-TS from two clinical perspectives: primary and secondary healthcare providers. Figure 3 shows the most important predictors for development of myocardial dysfunction in the training dataset. From the general practitioner's standpoint, cardiovascular signs (hypotension, oedema, oliguria/anuria, and prolonged capillary refill), decreased concentration of haemoglobin, elevated concentration of CRP, and thrombocytopenia have been shown to be the strongest predictors of a cardiac impairment (Fig. 3a). On the other hand, among the hospital healthcare providers with wider laboratory possibilities, these predictors were as follows: cardiovascular signs, elevated concentration of BNP, procalcitonin, troponin, or decreased concentration of haemoglobin (Fig. 3b). ROCs showed characteristics of the models in the testing part of the dataset (Fig. 4). The accuracy of the model from the general practitioner's point of view was 0.8 (95% CI 0.64, 0.87, sensitivity 0.6, specificity 0.9) and 0.8 (95% CI 0.70, 0.90, sensitivity 0.7, specificity 0.7) for the hospital healthcare provider.

Discussion

Thanks to a system of nationwide data collection, we succeeded to summarise data of all patients ($n = 207$) that manifested with clinical symptoms of PIMS-TS and were admitted to a hospital in the entire country within a defined time period of 7 months. To our knowledge, this is one of the first and unique published national population-wide cohort allowing to study the epidemiology (including overall incidence), time gap between viral exposure and clinical symptoms of PIMS-TS, and clinical presentations and outcomes within the individual waves of COVID-19 that were characterised by various prevailing genetic variants of SARS-CoV-2. We are aware that the incidence of PIMS-TS to confirmed paediatric infections is likely a gross overestimation of the true incidence (depending on testing strategy and possible asymptomatically infected children).

Several demographic and clinical characteristics were similar to those reported in previous studies, such as median age (8 years), duration of fever (5 days), and predominant severe multisystem involvement during initial illness (including gastrointestinal symptomatology (84.1%)) [6]. Additionally,

male predominance (63.8%), similarly to other published studies (59.0%), was confirmed [6]. A possible explanation is provided by the androgen-dependency of angiotensin-converting enzyme 2, which acts as a receptor for SARS-CoV-2 to enter the cell [10].

In our cohort, one third of patients showed neurological symptoms, similarly to other previously published studies (15.0–40.0%) [4, 11, 12]. Regarding PIMS-TS, both the peripheral and central nervous systems may be affected. Most commonly, signs include headaches, meningism, confusion, seizures, and unconsciousness [13]. In addition, we diagnosed a paediatric patient with PRES as a complication of PIMS-TS [14]. In contrast, several cases of PRES in acute SARS-CoV-2 infection in adults are described [15]. Nervous system damage associated with SARS-CoV-2 infection can occur through both direct and indirect mechanisms. The proposed aetiological mechanisms include the role of cytokines in endothelial cell dysfunction, failure of cerebral autoregulation, and cerebral ischaemia due to thrombosis [12]. Cerebrospinal fluid testing is usually negative [16].

The majority of patients (90.3%) had SARS-CoV-2 IgG-positive serology at admission. This value proves to be an important predictive diagnostic parameter, which partially allows to distinguish PIMS-TS from an acute course of COVID-19 or KD [17]. The diagnostic yield might drop if progressively more children (as the entire population) have been seroconverted through natural infection (or vaccination). Also, the platelet count may be helpful. In a recent report, compared to a "classical" KD cohort, patients with PIMS-TS had lower platelet counts (188×10^9/L versus 383×10^9/L) [18]. Similarly, in our study, the median of platelet count was 172×10^9/L (range 40–831). A possible explanation may lie within varied underlying immunopathogenesis of both diseases, which are currently intensely studied but not yet fully understood [18–20]. Additionally, the age at disease onset differs, being 4–17 years in PIMS-TS versus 0.5–5 years in KD [21]. Some theories suggest to address this age disparity, such as the protective function of the non-atrophied thymus in younger children [22].

Children with PIMS-TS are at risk for AV conduction disease, especially patients with ventricular dysfunction [23]. In our cohort, 34.3% patients were identified with pathological electrocardiogram findings, however, mostly with repolarization abnormalities ($n = 42$). Only ten patients had first-degree AV block, and one patient had second-degree AV block. These abnormal findings did not persist in any patient and were not detected during follow-up (1–6 months later).

COVID-19 is associated with thrombotic complications, but embolic events are rare in children, in contrast with adult COVID-19. Patients with PIMS-TS have the highest incidence (6.5%, in group > 12 years) versus COVID-19 (2.1%) or asymptomatic SARS-CoV-2 infection (0.7%) [24]. In our study, the median of D-dimer concentration was 2,263 µg/L (range 185–35,000), and only two patients (1.2%) had confirmed

Table 1 Patient demographic, clinical and laboratory characteristics, and treatment

Parameter	Normal myocardial function (n = 125)	Myocardial dysfunction (n = 82)	Odds ratio (confidence intervals)
Age, years (median, IQR)	7.0 (4–11)	8.4 (6–12)	1.1 (0.99, 1.12)
Male (n, %)	74 (59.2)	58 (70.7)	0.6 (0.33, 1.09)
Non-Caucasian ethnicity (n, %)	9 (7.2)	2 (2.4)	3.1 (0.65, 14.88)
SDS Height (median, IQR)	0.05 (-0.90–0.93)	0.29 (-0.60–1.04)	1.1 (0.91, 1.43)
SDS BMI (median, IQR)	-0.26 (-0.90–0.70)	-0.39 (-1.010–0.565)	0.9 (0.75, 1.17)
Comorbidities (n, %)	26 (20.8)	16 (19.5)	1.1 (0.54, 2.18)
Duration of fever, days (median, IQR)	4 (3–6)	5 (4–6)	1.0 (0.90, 1.15)
Cervical lymphadenopathy (n, %)	51 (40.8)	32 (39.0)	1.1 (0.61, 1.91)
Mucocutaneous lesions (n, %)	79 (63.2)	54 (65.9)	0.9 (0.50, 1.60)
Rash (n, %)	89 (71.2)	56 (68.3)	1.1 (0.62, 2.11)
Conjunctival injection (n, %)	87 (70.2)	60 (73.2)	0.9 (0.46, 1.61)
Vomiting (n, %)	45 (36.0)	24 (29.3)	1.3 (0.72, 2.43)
Diarrhoea (n, %)	57 (45.6)	38 (46.3)	0.9 (0.53, 1.64)
Nausea (n, %)	51 (42.1)	27 (32.9)	1.5 (0.82, 2.66)
Abdominal pain (n, %)	64 (51.2)	38 (46.3)	1.1 (0.64, 1.99)
Meningism (n, %)	11 (8.8)	13 (15.9)	0.5 (0.22, 1.21)
Headache (n, %)	3 (2.4)	8 (9.8)	0.2 (0.06, 0.89)
Disorders of consciousness (n, %)	9 (7.2)	12 (14.6)	0.5 (0.18, 1.14)
Seizures (n, %)	2 (1.6)	0 (0)	3,838,542.0 (0, Inf)
Normal electrocardiogram (n, %)	96 (76.8)	40 (48.8)	3.5 (1.90, 6.36)
Leukocytes, ×10⁹/L (median, IQR)	9.4 (6.5–12.5)	9.4 (7.0–11.0)	1.0 (0.93, 1.04)
Neutrophils, ×10⁹/L (median, IQR)	7.2 (4.6–9.8)	7.0 (4.5–9.1)	1.0 (0.92, 1.02)
Lymphocytes, ×10⁹/L (median, IQR)	1.1 (0.7–1.7)	0.9 (0.6–1.4)	0.8 (0.62, 1.03)
Haemoglobin, g/L (median, IQR)	114 (108–124)	115 (103–123)	1.0 (0.97, 1.00)
Platelets, ×10⁹/L (median, IQR)	178 (132–243)	163 (114–203)	1.0 (0.99, 1.00)
C-reactive protein, mg/L (median, IQR)	119.6 (70–178)	159.6 (108–212)	1.0 (1.00, 1.01)
Procalcitonin, μg/L (median, IQR)	1.61 (0.71–5.49)	4.90 (1.90–7.96)	1.0 (1.00, 1.04)
ESR (median, IQR)	54 (37–77)	49 (36–73)	1.0 (0.99, 1.01)
Ferritin, μg/L (median, IQR)	297.5 (167.8–575.0)	516.0 (260.0–887.5)	1.0 (1.00, 1.00)
NT-proBNP, ng/L (median, IQR)	1,500 (413–3,877)	5,013 (1,109–15,857)	1.0 (1.00, 1.00)
Troponin I, ng/L (median, IQR)	11.0 (5–46)	45.5 (13–100)	1.0 (1.00, 1.00)
Fibrinogen, g/L (median, IQR)	5.2 (4.5–6.7)	5.4 (4.6–6.2)	0.9 (0.79, 1.13)
D-dimer, μg/L (median, IQR)	1,992 (1,000–4,000)	2,937 (1,414–4,000)	1.0 (1.00, 1.00)
Urea, mmol/L (median, IQR)	3.9 (2.9–5.1)	4.3 (3.3–6.2)	1.1 (1.02, 1.21)
Creatinine, μmol/L (median, IQR)	41 (30–54)	46 (36–61)	1.0 (1.00, 1.02)
Triacylglycerol, mmol/L (median, IQR)	1.57 (1.23–2.13)	2.02 (1.41–2.74)	1.4 (1.00, 1.90)
Lactate dehydrogenase, μkat/L (median, IQR)	4.9 (4.1–5.7)	4.6 (3.8–5.9)	1.0 (0.80, 1.22)
ALT, μkat/L (median, IQR)	0.40 (0.27–0.70)	0.40 (0.26–0.67)	0.8 (0.53, 1.34)
AST, μkat/L (median, IQR)	0.54 (0.41–0.79)	0.49 (0.36–0.81)	0.8 (0.49, 1.40)
Positive epidemiologic contact in patient history (n, %)	88 (70.4)	56 (68.3)	1.1 (0.60, 2.03)
Symptomatology of COVID-19 in patient history (n, %)	38 (30.4)	24 (29.3)	1.1 (0.57, 1.95)
SARS-CoV-2 PCR positive at admission (n, %)	28 (22.4)	13 (15.9)	0.7 (0.31, 1.36)
SARS-CoV-2 IgG-positive at admission (n, %)	108 (86.4)	79 (96.3)	4.1 (1.17, 14.74)
Intravenous immunoglobulin (n, %)	114 (91.2)	76 (92.7)	0.8 (0.29, 2.32)
Resistance for intravenous immunoglobulin (n, %)	13 (10.4)	4 (4.9)	2.3 (0.71, 7.25)
Systemic corticosteroids (n, %)	97 (77.6)	77 (93.9)	0.2 (0.08, 0.61)
Anakinra (n, %)	5 (4.0)	1 (1.2)	3.4 (0.38, 29.81)
Mechanical ventilation (n, %)	3 (2.4)	7 (8.5)	0.3 (0.07, 1.06)
Inotropic support (n, %)	11 (8.8)	40 (48.8)	0.1 (0.05, 0.22)

Data are n (%), median or interquartile range (IQR). All demographic, clinical, and laboratory parameters were taken initially, before any therapeutic interventions. All data were analysed using R statistical software (version 4.0.4). Missing data were imputed using multiple imputation methods within the r package mice (version 3.13.0); missing data in continuous variables were imputed using Predictive Mean Matching Imputation algorithm and categorical variables using Random Forest imputation algorithm. The number of missing values in original dataset were stated in Supplementary Table 2

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *COVID-19* Novel 2019 coronavirus disease (SARS-CoV-2 infection), *ESR* erythrocyte sedimentation rate, *NT-proBNP* N-terminal pro B-type brain natriuretic peptide, *PCR* polymerase chain reaction, *SDS BMI* standard deviation score of body mass index

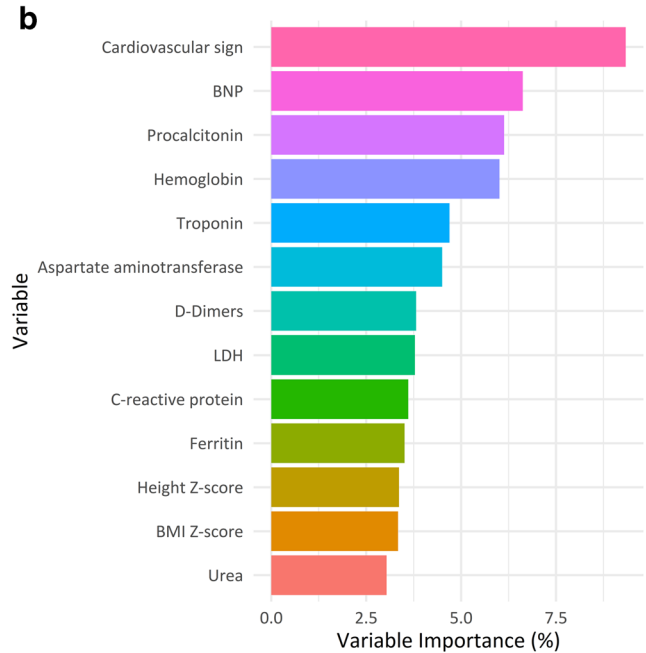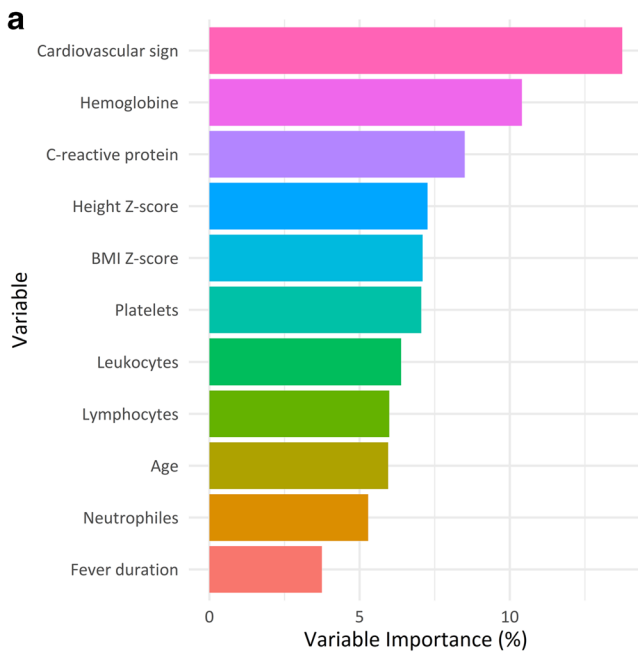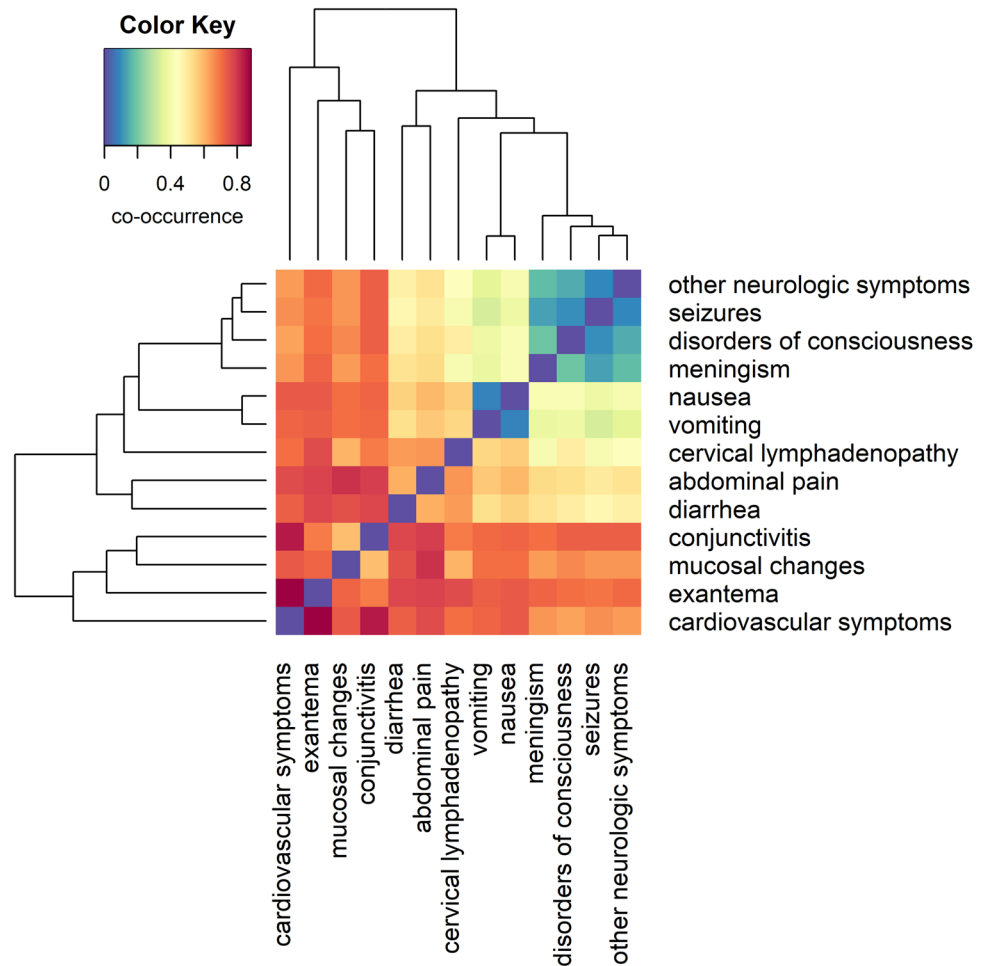**Fig. 2** Overview of symptom frequency and co-occurrence

Fig. 3 The most important predictors for development of myocardial dysfunction according to general practitioners (Fig. 3**a**) and hospital care providers (Fig. 3**b**). Predictors with importance less than 3% were not displayed. BMI = body mass index. BNP = brain natriuretic peptide. LDH = lactate dehydrogenase
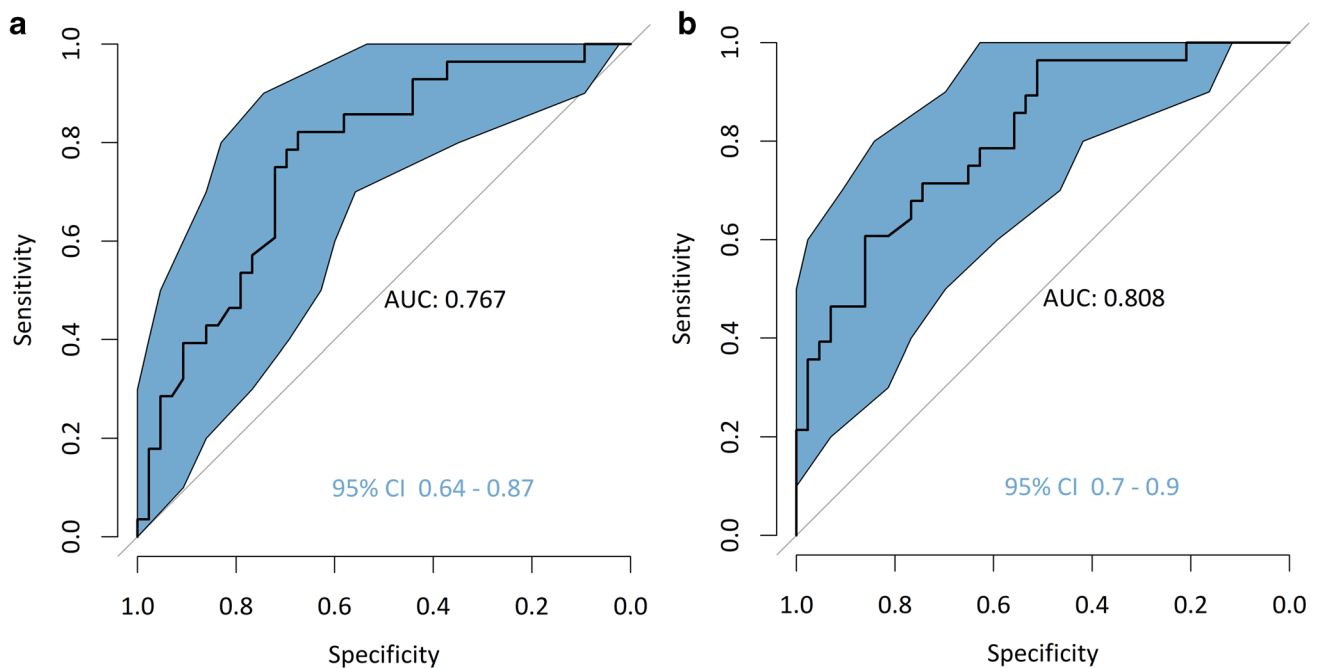
Fig. 4 Receiver operator curves (ROCs) with characteristics of the models on the testing parts of the datasets according to general practitioners (Fig. 4**a**) and hospital care providers (Fig. 4**b**). AUC = area under the curve. CI = confidence intervals

clinically relevant thrombosis (major left ventricular thrombi) at the time of admission: an 8-year-old girl and 17-year-old young man [25]. Both had an unremarkable medical and family history. We can speculate that a low incidence rate in our cohort is due to a combined anticoagulant and antiplatelet treatment that was administered routinely [8].

In a published systematic review on PIMS-TS (n = 953), 18 deaths occurred (1.9%) [6]. Unlike in other countries, in CZ, there was no report of a fatal case of PIMS-TS. However, residual cardiac finding was present only in two patients (1.2%, n = 161). This is less than the previously published data (7.3%) [6]. Except for one patient with neurological deficit, no other residual morbidity was reported.

In our cohort, 83.0% patients received combined treatment with IVIG (2 g/kg per dose) and systemic corticosteroids. According to local guidelines [8], a dual regimen in corticosteroids dosing was made possible. Higher doses of methylprednisolone (10–30 mg/kg per day) are earmarked for serious/life-threatening conditions. In less severe conditions, a lower dose of methylprednisolone (0.8–2.0 mg/kg per day) may be administered. This combination of IVIG and systemic corticosteroids could be associated with a better course of fever in PIMS-TS and can thus contribute to low morbidity and mortality in our national cohort [26]. It should also be noted that all reported patients were hospitalised in paediatric departments with accessibility to intensive care monitoring. This might have played an important role, due to rigorous monitoring and early detection of disease progression. Also, a later onset of a pandemic in CZ allowed to learn from international experiences.

According to our data, we propose several initial predictors of severe cardiac involvement in patients with PIMS-TS, such as cardiovascular signs, concentration of selected laboratory parameters of inflammation or cardiac impairment. These factors are similar to those reported previously [5, 27, 28]. However, our results allow specifying predictors according to the level of healthcare provider, which may be very beneficial for clinical practice. In particular, for primary care paediatricians, these predictors may be relevant if full PIMS-TS diagnostic criteria are not met and a decision is made on whether to refer the patient for hospital admission. However, it has to be mentioned that the accuracy of these models do not allow strictly selected patients who do not need intensive treatment [28]. Apart from the relatively low number of included patients, the relatively low accuracy could be explained by treatment titration according to actual patient condition.

In summary, individuals from our study had nearly 40.0% decreased myocardial function and 11.1% coronary artery involvement. Over 1–6 months of follow-up (n = 161), all patients had normal cardiac function. Only two patients (1.2%) had persistent left coronary artery dilation, which is much less than previously published [6]. It is important to keep in mind that the dilatation of coronary arteries could be a nonspecific consequence of increased coronary blood flow due to higher myocardial oxygen demand caused by febrile illness [29]. We speculate that the use of Z-scores of coronary artery dimensions may perhaps increase the threshold of abnormal findings on echocardiography in PIMS-TS. In a similar way, it

has increased the sensitivity of echocardiographic detection of coronary artery changes in KD [9].

The results of our study may have some practical consequences. Firstly, our data allowed clarification of the incidence of PIMS-TS out of all SARS-CoV-2 positive children, which was 0.9:1,000. Secondly, 3-week intervals in combination with incidence of COVID-19 could help increase pre-test probability of PIMS-TS during pandemic waves in the suspected cases. Thirdly, using information campaigns and an intensive treatment protocol (combined IVIG and systemic corticosteroids), there were no reported fatalities from PIMS-TS within the country in that monitored period. Fourthly, we confirmed predictors of PIMS-TS severity from two clinical perspectives. They may serve as a clue to an early detection of patients at higher risk of developing myocardial dysfunction. Finally, during follow-up, all patients had normal cardiac function. Only two patients (1.2%) had persistent left coronary artery dilation. Additionally, the PIMS-TS incidence this group has found (0.9:1,000 of SARS-CoV-2 positive children) is higher than previously reported [30]. It emphasizes importance of COVID-19 vaccination strategies in young and healthy children.

Study limitations

This study had several limitations that are partly linked to the combined retrospective and prospective design. The data were collected from 17 paediatric departments from all over the country and no specific standardisation of laboratory testing methodology could be done. Despite the online training of all medical staff, mild differences in establishing diagnosis, evaluating clinical findings, and thus individualising treatment procedures cannot be excluded. However, all potential participating hospital staff were trained according to national diagnostic and treatment guidelines. As a nationwide study, validation on an external group was not possible. Also, the exact distribution of SARS-CoV-2 variants in the Czech population was not known, so we could only estimate by dominant variant in individual pandemic waves. The strength of this study includes the country-wide surveillance of all affected patients, detected by a double-checked method, and evaluated on the background of the national epidemiological data on COVID-19.

Abbreviations AV: Atrioventricular; BNP: Brain natriuretic peptide; CI: Confidence interval; COVID-19: The novel 2019 coronavirus disease; CRP: C-reactive protein; CZ: Czech Republic; IHIS: Institute of Health Information and Statistics; IQRs: Interquartile ranges; IVIG: Intravenous immunoglobulin; KD: Kawasaki disease; MIS-C: Multisystem inflammatory syndrome in children; OR: Odds ratio; PIMS-TS: Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2; PRES: Posterior reversible encephalopathy syndrome; ROCs: Receiver operator curves; RT-PCR: Reverse transcription-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00431-022-04593-7.

Authors' contributions All authors contributed to the study conception, design, material preparation, and data collection. Analysis were performed by Ondrej Hradsky and Jan David. The first draft of the manuscript was written by Jan David, Ondrej Hradsky, Filip Fencl, and Jan Lebl, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability Any reasonable requests to share deidentified data (including study protocol) will be considered by the senior authors and corresponding author subject to institutional agreements and ethics approvals. Data requests should be sent to the corresponding author (jan.david@fnmotol.cz). Authors whose names appear on the submission have contributed sufficiently to the scientific work and therefore share collective responsibility and accountability for the results.

Declarations

Ethics approval The observational study was approved by the Ethics Committee of the University Hospital Motol (number 705/21).

Consent to participate Data were collected from clinical reviews only and further analysed in the anonymous form, consent from patients (parents) was not required.

Competing interests The authors declare no competing interests.

References

1. Institute of Health Information and Statistics of the Czech Republic (2021). https://www.uzis.cz. Accessed 7 May 2021
2. Komenda M, Bulhart V, Karolyi M et al (2020) Complex reporting of coronavirus disease (COVID-19) epidemic in the Czech Republic: use of interactive web-based application in practice. J Med Internet Res 22:e19367. https://doi.org/10.2196/19367
3. Jirincova H, Nagy A (2021) SARS-CoV-2 variant surveillance in the Czech Republic. http://www.szu.cz/uploads/Epidemiologie/Coronavirus/WGS_covid/SARSvariantS_surveillance_final_CZ_ECDC.pdf. Accessed 7 May 2021
4. Feldstein L (2021) Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 325:1074–1087
5. Abrams JY, Oster ME, Godfred-Cato SE et al (2021) Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health 5:323–331

6. Hoste L, Van Paemel R, Haerynck F (2021) Multisystem inflammatory syndrome in children related to COVID-19: a systematic review. Eur J Pediatr 180:2019–2034

7. World Health Organization (2020) Multisystem inflammatory syndrome in children and adolescents with COVID-19. https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. Accessed 7 May 2021

8. Fencl F, Sibikova M, David J, Malcova H (2021) Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Czech guidelines. (in Czech, Syndrom multisystémové zánětlivé odpovědi asociovaný s COVID-19 u dětí. Doporučený postup ČPS ČLS JEP). Ces-slov Pediat 76:4–9

9. McCrindle BW, Rowley AH, Newburger JW et al (2017) Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 135:e927-999

10. Mihalopoulos M, Levine AC, Marayati NF, Chubak BM, Archer M, Badani KK, Tewari AK, Mohamed N, Ferrer F, Kyprianou N (2020) The resilient child: sex-steroid hormones and COVID-19 incidence in pediatric patients. J Endocr Soc 4:bvaa106

11. Chen TH (2020) Neurological involvement associated with COVID-19 infection in children. J Neurol Sci 418:117096

12. Aghagoli G, Gallo Marin B, Katchur NJ, Chaves-Sell F, Asaad WF, Murphy SA (2021) Neurological involvement in COVID-19 and potential mechanisms: a review. Neurocrit Care 34:1062–1071

13. Abdel-Mannan O, Eyre M, Löbel U, Bamford A, Eltze C, Hameed B, Hemingway C, Hacohen Y (2020) Neurologic and radiographic findings associated with COVID-19 infection in children. JAMA Neurol 77:1440–1445

14. Lindan CE, Mankad K, Ram D et al (2021) Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health 5:167–177

15. Kishfy L, Casasola M, Banankhah P, Parvez A, Jan YJ, Shenoy AM, Thomson C, AbdelRazek MA (2020) Posterior reversible encephalopathy syndrome (PRES) as a neurological association in severe Covid-19. J Neurol Sci 414:116943

16. Lad SS, Kait SP, Suryawanshi PB et al (2021) Neurological manifestations in pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS). Indian J Pediatr 88:294–295

17. Rostad CA, Chahroudi A, Mantus G et al (2020) Quantitative SARS-CoV-2 serology in children with multisystem inflammatory syndrome (MIS-C). Pediatrics 146:e2020018242

18. Yeo WS, Ng QX (2020) Distinguishing between typical Kawasaki disease and multisystem inflammatory syndrome in children (MIS-C) associated with SARS-CoV-2. Med Hypotheses 144:110263

19. Sancho-Shimizu V, Brodin P, Cobat A et al (2021) SARS-CoV-2-related MIS-C: A key to the viral and genetic causes of Kawasaki disease? J Exp Med 218:e20210446. https://doi.org/10.1084/jem.20210446

20. Consiglio CR, Cotugno N, Sardh F et al (2020) The Immunology of Multisystem Inflammatory Syndrome in Children with COVID-19. Cell 183:968–981

21. Toubiana J, Poirault C, Corsia A et al (2020) Kawasaki-like multisystem inflammatory syndrome in children during the covid-19 pandemic in Paris, France: prospective observational study. BMJ 369:m2094. https://doi.org/10.1136/bmj.m2094

22. Güneş H, Dinçer S, Acıpayam C, Yurttutan S, Özkars MY (2021) What chances do children have against COVID-19? Is the answer hidden within the thymus? Eur J Pediatr 180:983–986

23. Dionne A, Mah DY, Son MBF et al (2020) Atrioventricular block in children with multisystem inflammatory syndrome. Pediatrics 146:e2020009704

24. Whitworth HB, Sartain SE, Kumar R et al (2021) Rate of thrombosis in children and adolescents hospitalized with COVID-19 or MIS-C. Blood 138:190–198. https://doi.org/10.1182/blood.2020010218

25. Materna O, Koubský K, Pádr R, Janoušek J (2021) Major left ventricular thrombi in an adolescent with COVID-19-associated inflammatory syndrome. Eur Heart J ehab165. https://doi.org/10.1093/eurheartj/ehab165

26. Ouldali N, Toubiana J, Antona D et al (2021) Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA 325:855–864

27. Pignatelli R, Antona CV, Rivera IR et al (2021) Pediatric multisystem SARS COV2 with versus without cardiac involvement: a multicenter study from Latin America. Eur J Pediatr 180:2879–2888

28. Ward JL, Harwood R, Smith C et al (2022) Risk factors for PICU admission and death among children and young people hospitalized with COVID-19 and PIMS-TS in England during the first pandemic year. Nat Med 28:193–200

29. Muniz JC, Dummer K, Gauvreau K, Colan SD, Fulton DR, Newburger JW (2013) Coronary artery dimensions in febrile children without Kawasaki disease. Circ Cardiovasc Imaging 6:239–244

30. Payne AB, Gilani Z, Godfred-Cato S et al (2021) Incidence of multisystem inflammatory syndrome in children among US persons infected with SARS-CoV-2. JAMA Netw Open 4:e2116420. https://doi.org/10.1001/jamanetworkopen.2021.16420

Authors and Affiliations

Jan David[1] · Veronika Stara[1] · Ondrej Hradsky[1] · Jana Tuckova[2] · Katerina Slaba[2] · Petr Jabandziev[2,3] · Lumir Sasek[4] · Michal Huml[4] · Iveta Zidkova[5] · Jan Pavlicek[5] · Alzbeta Palatova[6] · Eva Klaskova[6] · Karina Banszka[7] · Eva Terifajova[7] · Radim Vyhnanek[8] · Marketa Bloomfield[8,9] · Sarka Fingerhutova[10] · Pavla Dolezalova[10] · Lucie Prochazkova[11] · Gabriela Chramostova[12] · Filip Fencl[1] · Jan Lebl[1]

[1] Department of Paediatrics, Second Faculty of Medicine, Charles University and University Hospital Motol, V Úvalu 84, 150 06, Prague, Czech Republic

[2] Department of Paediatrics, Faculty of Medicine, Masaryk University and University Hospital Brno, Brno, Czech Republic

[3] Central European Institute of Technology, Masaryk University, Brno, Czech Republic

[4] Department of Paediatrics, Faculty of Medicine, Charles University and University Hospital Plzeň, Plzeň, Czech Republic

[5] Department of Paediatrics, Faculty of Medicine, University of Ostrava and University Hospital Ostrava, Ostrava, Czech Republic

[6] Department of Paediatrics, Faculty of Medicine, Palacky University and University Hospital Olomouc, Olomouc, Czech Republic

[7] Department of Paediatrics, Faculty of Medicine, Charles University and University Hospital Hradec Králové, Hradec Králové, Czech Republic

[8] Department of Paediatrics, First Faculty of Medicine, Charles University and University Thomayer Hospital, Prague, Czech Republic

[9] Department of Immunology, Second Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic

[10] Department of Paediatrics and Inherited Metabolic Disorders, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic

[11] Department of Paediatrics, Regional Bata Hospital, Zlín, Czech Republic

[12] Department of Paediatrics, Regional Hospital, Kolín, Czech Republic