Prevalence of thrombotic complications in children with SARS-CoV-2

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ABSTRACT

Knowledge of thrombosis in children with SARS-CoV-2 is scarce. In this multicentre national cohort of children with SARS-CoV-2 involving 49 hospitals, 4 patients out of 537 infected children developed a thrombotic complication (prevalence of 0.7% (95% CI: 0.2% to 1.9%) out of the global cohort and 1.1% (95% CI: 0.3% to 2.8%) out of the hospitalised patients). We describe their characteristics and review other published paediatric cases. Three out of the four patients were adolescent girls, and only two cases had significant thrombotic risk factors. In this paediatric cohort, D-dimer value was not specific enough to predict thrombotic complications. Adolescence and previous thrombotic risk factors may be considered when initiating anticoagulant prophylaxis on children with SARS-CoV-2 disease (COVID-19).

INTRODUCTION

The disease caused by SARS-CoV-2, named COVID-19, has spread rapidly. Among adult patients, a significant prevalence of thrombotic complications has been described. This risk has been linked to a hypercoagulability state, which has conditioned the publication of guidelines on anticoagulant management in patients with COVID-19.[1 2]

However, due to the lower experience in COVID-19 disease in children, these guidelines have not included specific recommendations for paediatric patients. Based on adult recommendations, several authors have proposed some indications for anticoagulant prophylaxis that take into account individual risk factors.[3] Nevertheless, to date, there is scarce information about thrombotic complications in children with COVID-19. We aimed to describe thrombotic complications among children infected with SARS-CoV-2.

METHODS

The Epidemiological Study of COVID-19 in children was launched and supported by the Spanish Society of Pediatrics (EPICO-AEP) as a multicentre prospective national cohort study aiming to describe paediatric COVID-19 in Spain. Children younger than 18 years of age infected by SARS-CoV-2 and attended at 49 hospitals are currently being enrolled in this registry. Inclusion criteria include positivity in real-time PCR (RT-PCR), IgM or IgG in lateral-flow rapid test, ELISA or chemiluminescence serology, or disease suggestive of multi-inflammatory syndrome related to SARS-CoV-2 in children (MIS-C). From 1 March to 30 September 2020, children with thrombotic complications associated with SARS-CoV-2 enrolled in EPICO-AEP were included in this study.

Thrombotic complications associated with SARS-CoV-2 infection were defined as any radiologically confirmed thrombosis, arterial or venous, occurring close to the diagnosis of SARS-CoV-2 infection (up to 3 weeks). Microthrombi phenomena related or suspected to be related to SARS-CoV-2 (eg, acral chilblains) were not included. Two-sided 95% Clopper-Pearson exact CIs (95% CI) for binomial proportions were calculated for prevalence. Data were analysed using the Stata V.15 (College Station, Texas, USA).

RESULTS

By 30 September, 537 children were diagnosed with SARS-CoV-2 infection and included in the EPICO-AEP cohort. The median age was 61 months (IQR: 6–140 months), and 293 (54.6%) were boys. Of those, 368 (68.5%) were hospitalised, requiring paediatric intensive care unit admission (PICU), 58 (10.8%) cases. Forty-seven (8.8%) cases were diagnosed with MIS-C.

D-dimer was available from 169 patients, with a median of 1071 µg/L (IQR: 291–2858 µg/L). Anticoagulant drugs (heparin in all cases) were administered to 29 (5.4%) patients: as prophylaxis in 24 (82.8%) cases, and as treatment in 5 (17.2%) cases. Most of the patients on thromboprophylaxis had severe COVID-19 (79.2% admitted to PICU and 56.5% received inotropic support). Four cases, which correspond to 0.7% (95% CI: 0.2% to 1.9%) out of the global cohort and 1.1% (95% CI: 0.3% to 2.8%) out of the hospitalised patients, developed some thrombotic complication. A fifth case receiving anticoagulant treatment was a patient who had a history of venous thrombosis not related to SARS-CoV-2 infection and was not included in this report.

Three out of these four patients were adolescent girls (table 1, cases 1–4). None of the cases was diagnosed with MIS-C. Two patients (patients 1 and 2) had several significant thrombotic risk factors. Patients 3 and 4 did not have any previous personal or family risk factors for thrombosis. However, in patient 3, after thrombosis diagnosis,

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Table 1 Characteristics of children with SARS-CoV-2 infection and thrombosis from EPICO-AEP cohort (cases 1–4) and from literature review (cases 5–13)

N	Age	Sex	Medical background/ risk factors	Other thrombotic risk factors	Family thrombotic history	Thrombotic complication	Other signs/symptoms	SARS-CoV-2 RT-PCR	SARS-CoV-2 Abs	D-dimer (µg/L)	Thrombo-prophylaxis*	Anticoagulation treatment	Thrombophilia work-up	Outcome†
1	4 years	Female	Systemic juvenile idiopathic arthritis on treatment with steroids and canakinumab	Central venous catheter	No	Right iliac vein thrombosis	Fever, cough and rhinorrhoea	Positive	Negative	5953‡	No	LWH	NA	Discharged without sequelae
2	12 years	Female	B cell acute lymphoblastic leukaemia on induction chemotherapy and obesity	Central venous catheter and asparaginase treatment	No	Thrombosis of the right upper limb	Dyspnoea and thoracic pain (pulmonary embolism was ruled out)	Positive	IgG positive	232‡	LWH	LWH	Decreased protein C activity (58%)	Discharged without sequelae
3	13 years	Female	No	No	No	Left common and superficial femoral vein thrombosis	Fever, hyporexia, headache, asthenia, rash, abdominal pain and vomiting	Positive	NA	1194‡	No	LWH and cava filter	Lupus anticoagulant positive (remained positive 5 months later)	Discharged without sequelae
4	13 years	Female	No	No	No	Thrombosis of the transverse sinuses and of the jugular vein, pulmonary embolism and femoral thrombosis	Fever and odynophagia	Positive	NA	35 420‡	No	Continuous unfractionated heparin followed by LWH	Normal	Discharged without sequelae
5	16 years	Female	Homozygous sickle cell disease	No	ND	Bilateral pulmonary embolism	Fever, cough, anosmia, acute chest syndrome	Positive	ND	23 611	No	Yes (not fully described)	ND	Discharged
6	5 years	Male	No	ECMO	ND	Right middle cerebral artery infarction, cerebral oedema and diffuse contralateral subarachnoid haemorrhage§	Fever, cough, and abdominal pain; cardiogenic shock with cardiopulmonary failure	ND	Positive	15 000	Yes	ND	ND	Brain dead
7	2 months	Male	Tracheomalacia requiring tracheostomy	ECMO	ND	Bilateral middle cerebral artery and posterior cerebral artery territory infarction with haemorrhagic transformation§	Respiratory failure, pneumomediastinum, and bilateral pneumothoraces	ND	Negative	ND	ND	ND	ND	Admitted
8	12 years	Female	No	No	No	Popliteal-to-common iliac vein thrombosis and massive pulmonary embolism	No	Negative	IgM positive	1953	No	Percutaneous mechanical venous thrombectomy, thrombolysis and infrahepatic venous filter	Antiphospholipid antibodies	Discharged without neurological deficits
9	16 years	Male	ND	Sphenoid sinusitis	ND	Cavernous sinus thrombosis and left middle cerebral artery stroke	Aseptic meningitis associated with stupor	Positive	ND	ND	No	Yes (not fully described)	ND	Died
10	16 years	Male	ND	ND	ND	Deep venous thrombosis of the lower limbs with pulmonary emboli	ND	Positive	ND	ND	ND	ND	ND	ND
11	6 years	Male	ND	ND	ND	Small segmental pulmonary emboli	MIS-C (fever, hypoxic respiratory failure, abdominal pain)	Positive	ND	ND	ND	ND	ND	ND
12	5 years	Male	No	ECMO	ND	Right anterior and middle cerebral artery ischaemic infarction§	MIS-C (fever, vomiting, cough, abdominal pain)	Negative	Positive	18 300	Heparin	ND	ND	Brain dead
13	2 years	Female	No	Miliary tuberculosis	ND	Thrombosis of the superior sagittal sinus and the transverse sinuses and cerebral infarction involving the anterior limb of the right internal capsule, lentiform nucleus and thalamus	Weakness, lethargy and cervical lymphadenopathy	Positive	ND	14 800	No	Aspirin	ND	Discharged with residual left haemiparesis

*Thromboprophylaxis before thrombosis diagnosis.
†Outcome when this article or the reviewed articles were published.
‡Highest value during the episode.
§These cases were supposed to be hypercoagulable manifestations of COVID-19/MIS-C.
Abs, antibodies; ECMO, extracorporeal membrane oxygenation; LWH, low-weight heparin; MIS-C, multi-inflammatory syndrome related to SARS-CoV-2 in children; NA, not available; ND, not described; RT-PCR, real-time PCR.

a thrombophilia work-up was performed, which revealed a positive lupus anticoagulant, remaining positive 5 months later.

The only patient receiving thromboprophylaxis (low-weight heparin) before thrombosis was patient 2. D-dimer levels were severely increased in patients 1 (5953 µg/L) and 4 (35 420 µg/L) but were only slightly increased in the other cases (1194 and 232 µg/L, respectively). All cases except patient 3 had SARS-CoV-2 RT-PCR confirmation coinciding with thrombosis diagnosis. In patient 3, COVID-19 was initially suspected but not microbiologically confirmed until 3 weeks after thrombosis. All cases had thrombosis affecting the limbs, with cerebral venous sinus thrombosis and pulmonary embolism in one of them. All patients were treated with heparin and discharged without sequelae.

DISCUSSION

To the best of our knowledge, this is the first study that describes thrombotic complications in children with SARS-CoV-2 infection in a large cohort. Only four patients developed a thrombotic complication (1.2% of hospitalised children with non-MIS-C SARS-CoV-2 infection). Although this prevalence is not as high as in hospitalised adults with COVID-19,[1] it is slightly higher than that previously described in hospitalised children without COVID-19 (0.13%–0.55%). Among the factors associated with a lower incidence of thromboembolic complications in children with COVID-19, a different balance in coagulation homeostasis, with a higher concentration of antithrombotic serum factors (eg, alpha-2-macroglobulin) in children compared with adults, a protective 'healthy' endothelium or fewer comorbidities have been proposed.

Only two of our four cases had significant thrombotic risk factors (central venous catheter, obesity, malignancy or asparaginase treatment), highlighting the difficulty of predicting thrombotic complications in children with COVID-19 to initiate anticoagulant prophylaxis. Thrombosis is very uncommon in patients under 18 years old, and systemic anticoagulant prophylaxis may have adverse events that outweigh its benefit. Of note, one patient was diagnosed with antiphospholipid syndrome, showing lupus anticoagulant persistently elevated. Transient lupus anticoagulant has been described in patients with COVID-19, but its significance is unclear.

We conducted a systematic search in order to review reported paediatric patients diagnosed with SARS-CoV-2 infections with any thrombotic complication (search strategy in online supplemental material). Ten cases were found (full references in online supplemental material); one of them included in our series (case 4). Table 1 (cases 5–13) shows the main characteristics of the reported cases. Additionally, three (3.8%) and four (2.2%) cases diagnosed with MIS-C from two other national cohorts developed a venous thrombosis, but their full clinical information was not available.[4]

The central nervous system was the most commonly affected site (six cases), followed by the lung (five cases) and lower limbs (three cases). Similar to our data, most of the patients were adolescents. This age distribution is also seen in patients with MIS-C, in which the prevalence of thrombosis increases with the age of the patients: 0 of 66 (0%), 1 of 75 (1.3%) and 3 of 45 (6.7%) in patients aged <5 years, 5–12 years and 13–20 years, respectively.[4] This peak of cases with thrombosis affecting adolescents is similar to what is seen in hospitalised children without COVID-19.

Markedly elevated plasma D-dimer levels (eg, ≥5 times the upper limit of normal values) has been proposed as an indication for anticoagulant prophylaxis in children hospitalised with SARS-CoV-2-related illness.[3] In our cohort, 68 of 169 (40.2%) had a value >1500 µg/L. However, only 2 of 68 (2.9%) cases developed a thrombotic complication. Therefore, the use of the D-dimer value is not specific enough to make decisions regarding anticoagulant prophylaxis in children. In our opinion, other factors, such as the age (considering adolescents especially vulnerable), coexistence of risk factors (eg, malignancy, indwelling central venous catheter, obesity, immobility, etc),[5] or MIS-C diagnosis, should be considered when initiating anticoagulant prophylaxis in children with COVID-19. Of note, a clinical trial is currently evaluating the safety and efficacy of thromboprophylaxis in children hospitalised with signs and/or symptoms of SARS-CoV-2 infection (ClinicalTrials.gov NCT04354155).

Our study has some limitations, such as the variability of tests that were used to diagnose infection, not only the gold standard PCR, which could make false results. Additionally, since ultrasound was not routinely performed in all patients, subclinical thrombosis may not have been diagnosed.

In conclusion, except in the MIS-C, unlike adults, thrombotic complications seem very uncommon in children with SARS-CoV-2. Adolescence and previous thrombotic risk factors may be considered when initiating thromboprophylaxis in children with COVID-19. Further studies are needed to clarify risk factors among children with COVID-19 in order to develop specific recommendations.

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Correction notice This paper has been updated since it was published online. There has been a change to an author's first name in the EPICO-AEP Working Group.

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Contributors DA-A, CC, CM and AT designed the study. SM, AM-d-A, AS-A, MP and EO did the follow-up of patients with COVID-19 and thrombosis. DA-A and CC drafted the initial manuscript. CM, AT, SM, AM-d-A, AS-A, MP and EO reviewed and edited the manuscript. All authors approved the final version of the manuscript.

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