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Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

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Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

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- COVID-19盛行的時期, 住院病童出現發燒與多系統發炎(multisystem inflammation)的現象, 因時序上與SARS-CoV-2感染有關(temporally associated), 故簡稱**PIMS-TS**
- 本研究中58位PIMS-TS病童, 其臨床症狀表現非常廣泛, 包括發燒, 腸胃道症狀, 皮膚疹; 嚴重時也可能演變成**心肌受損**, **休克**, **冠狀動脈血管瘤**等等
- 與川崎症 (KD)或川崎休克症候群 (KD shock syndrome)相比, PIMS-TS應該是不同的疾病, 因為**PIMS-TS病童年紀更大, 發炎反應更強, 心肌損傷的情況更嚴重**, 而且WBC count, neutrophil count, CRP, fibrinogen, troponin 比較高, 但是Hb, lymphocyte count以及platelet count 比較低
- 部分PIMS-TS病童會有冠狀動脈血管瘤, 如果**NT-proBNP跟troponin 數值升高**, 則建議**需要做心臟超音波檢查**以提早發現是否有冠狀動脈血管瘤
- PIMS-TS患者大部分都是**接受IVIG或是類固醇的治療**, 少數患者接受免疫調節劑治療

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前言

- 從2020年3月到5月, 在英國的兒科醫師們就有注意到在COVID-19疫情盛行的時期, 住院病童出現發燒與多系統發炎(multisystem inflammation)的現象, 這些孩子大部分都有休克或是多重器官衰竭的情況, 也需要住進加護病房
- 有些病童的症狀類似川崎氏症(Kawasaki disease)或是川崎氏症休克症候群(KD shock syndrome)
- 目前的臨床證據顯示這些兒童多系統發炎症候群(pediatric inflammatory multisystem syndrome) 在時序上跟SARS-CoV-2病毒感染有關(temporally associated), 故簡稱PIMS-TS
- 本研究描述這群符合PIMS-TS診斷標準的兒童之臨床症狀與實驗室檢驗特徵

方法

- 有關PIMS-TS兒童的研究獲得英國當地臨床研究辦公室之許可, 病患的病歷經由Great Ormond Street Hospital 的審核, 同時匿名收集病患的資料, 並未經由告知後同意的程序
- 川崎症(KD)或是川崎症休克症候群 (KD shock syndrome)的病童則是經由聖地牙哥大學(University of San Diego)的倫理委員會許可, 並獲得病童家屬或監護人的告知後同意(informed consent)才招募
- 毒性休克症候群(toxic shock syndrome)的病童則是由EUCLIDS及PERFORM研究中收集, 同樣經過英國研究倫理委員會的同意, 並取得家長或監護人的告知後同意

方法

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教學研究部

個案調查 (case ascertainment)

經由英國的警示, 世界衛生組織(WHO), 美國CDC以及歐盟CDC共同定義了與COVID-19相關的兒童發炎疾患(childhood inflammatory disorder)

Table 1. Case Definitions for Emerging Inflammatory Condition During COVID-19 Pandemic From the World Health Organization, Royal College of Paediatrics and Child Health, and Centers for Disease Control and Prevention

World Health Organization[8]	Royal College of Paediatrics and Child Health (United Kingdom)[7]	Centers for Disease Control and Prevention (United States)[9]
Children and adolescents 0-19 y of age with fever >3 d AND 2 of the following: 1. Rash or bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, or feet) 2. Hypotension or shock 3. Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO findings or elevated troponin/NT-proBNP) 4. Evidence of coagulopathy (by PT, APTT, elevated D-dimers) 5. Acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain) AND Elevated markers of inflammation such as ESR, CRP, or procalcitonin. AND No other obvious microbial cause of inflammation, including bacterial sepsis, staphylococcal or streptococcal shock syndromes. AND Evidence of COVID-19 (RT-PCR, antigen test, or serology positive), or likely contact with patients with COVID-19 Consider this syndrome in children with features of typical or atypical Kawasaki disease or toxic shock syndrome	A child presenting with persistent fever, inflammation (neutrophilia, elevated CRP, and lymphopenia) and evidence of single or multiorgan dysfunction (shock, cardiac, respiratory, kidney, gastrointestinal, or neurological disorder) with additional features (see listed in eAppendix in Supplement 2). This may include children fulfilling full or partial criteria for Kawasaki disease[a] Exclusion of any other microbial cause, including bacterial sepsis, staphylococcal or streptococcal shock syndromes, infections associated with myocarditis such as enterovirus (waiting for results of these investigations should not delay seeking expert advice) SARS-CoV-2 PCR test results may be positive or negative	An individual aged <21 y presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, kidney, respiratory, hematologic, gastrointestinal, dermatologic, or neurological) Fever >38.0 °C for ≥24 h or report of subjective fever lasting ≥24 h Laboratory evidence including, but not limited to, ≥1 of the following: an elevated CRP level, ESR, fibrinogen, procalcitonin, D-dimer, ferritin, lactic acid dehydrogenase, or IL-6; elevated neutrophils; reduced lymphocytes; and low albumin AND No alternative plausible diagnoses AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 wk prior to the onset of symptoms Additional comments Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection

方法

- CDC與WHO對於PIMS-TS的定義中, 都包含有SARS-CoV-2的實驗室檢驗證據或是有接觸史
- 但是本研究中所招募的兒童只要符合英國, 美國CDC或是WHO的定義即可, 不需要一定要有SARS-CoV-2感染的證據
- 研究資料來自電子病歷或是紙本病歷, 病程中的皮膚黏膜(mucocutaneous)表現皆被詳細記錄, 種族的分類則由親屬報告決定
- 美國心臟協會對於川崎氏症的診斷標準如下:

  持續發燒, 並合併下列5種皮膚黏膜特徵的其中4種

  (1)雙眼結膜充血，無分泌液。

  (2)嘴唇發紅乾裂、草莓舌、咽喉發炎、紅腫。

  (3)四肢末梢紅腫、手掌及腳掌脫皮。

  (4)軀幹多形性、無水泡性的紅斑或皮疹。

  (5)頸部淋巴結腫大。

方法

- 臨床類型的建立包括

(1) 一群休克 (shock) 的病人(需要使用強心劑或是輸液>20ml/kg)

(2) 一群符合川崎症診斷標準的病人

(3) 一群有發燒及發炎的病人, 但沒有休克或是不符合川崎症診斷標準

- SARS-CoV-2 IgG的測量是使用EDI novel Coronavirus COVID-19 IgG ELISA kit

與川崎症(KD), 川崎症休克症候群(KD shock syndrome), 毒性休克症候群(toxic shock syndrome)的比較

- 因為PIMS-TS兒童的特徵與川崎症或是川崎症休克症候群相似, 所以本研究與2002~2019年在Rady 兒童醫院的KD及KD shock syndrome 的個案, 以及在2012~2020年於EUCLIDS及PERFORM研究中所收集之toxic shock syndrome的個案做比較

方法

資料處理 (data management)

- 符合PIMS-TS診斷的兒童, 與罹患KD, KD shock syndrome, toxic shock syndrome的兒童, 以描述性的方式比較其臨床症狀與檢驗結果
- 因為個案數量都很少, 所以大數據的比較以及正式的統計都並未被執行
- 本研究的發現只能被解讀為是描述性與試探性的結果

結果

在2020年3月23日到5月16日, 共有58位分別住在英格蘭8間醫院的兒童符合PIMS-TS的診斷

臨床特徵

- 平均年紀為9歲 (3個月~17歲), 其中33位是女孩 (57%), 40位 (69%) 是非洲裔或是亞裔
- 58位兒童中有7位有其他的共病症, 包括氣喘 (3位), 神經障礙 (1位), 癲癇 (1位), 鐮刀型紅血球疾病(1位), 圓禿型落髮 (1位)
- 所有的病童都有高燒, 至少3~19天, 部分病童合併喉嚨痛 (n=6, 10%), 頭痛(n=15, 26%), 以及腹痛 (n=31, 53%); 紅疹 (n=30, 52%), 結膜炎 (n=26, 45%), 淋巴結腫大 (n=9, 16%), 嘴唇發紅乾裂(n=17, 29%), 手腳腫脹 (n=9, 16%)
- 29位(50%) 需要住在PICU (50%), 13位(22%)有急性腎功能損傷, 27位(47%)有休克且需要強心劑, 25位 (43%)需要呼吸器輔助通氣

Table 2. Demographics and Clinical Features of the PIMS-TS Cohort

Characteristic	No. (%)[a]											
			Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Age, median (IQR), y	9 (5.7-14)	10 (5.5-14)	10.5 (7-14)	10 (3-14)	8 (5-11)	10.5 (5.7-14)	6 (2-8)	10 (6-14)	9.5 (8-12.3)	9 (5-11)	10 (6-14)	7 (2.5-14)
Sex												
Male	25 (43)	17 (74)	16 (55)	22 (76)	10 (77)	28 (62)	6 (86)	32 (63)	6 (75)	32 (64)	19 (43)	8 (61)
Female	33 (57)	6 (26)	13 (45)	7 (24)	3 (23)	17 (38)	1 (14)	18 (37)	2 (25)	19 (36)	26 (57)	5 (39)
Race/ethnicity												
Black	22 (38)	7 (30)	14 (48)	8 (28)	8 (62)	14 (31)	2 (29)	20 (39)	7 (87.5)	15 (30)	18 (40)	4 (31)
Asian	18 (31)	6 (26)	6 (21)	6 (21)	0	12 (27)	0	12 (24)	0	12 (24)	11 (24)	1 (8)
White	12 (21)	8 (35)	6 (21)	12 (42)	4 (31)	14 (31)	4 (57)	14 (27)	1 (12.5)	17 (34)	13 (29)	5 (38)
Other[h]	6 (10)	2 (9)	3 (10)	3 (10)	1 (8)	5 (11)	1 (14)	5 (10)	0	6 (12)	3 (7)	3 (23)
Clinical features at presentation[i]												
Abdominal pain	31 (53)	13 (57)	18 (62)	13 (45)	2 (15)	29 (64)	1 (14)	30 (59)	2 (33)	29 (58)	24 (55)	7 (50)
Diarrhea	30 (52)	10 (44)	19 (66)	11 (38)	7 (54)	23 (51)	2 (29)	28 (55)	6 (75)	24 (48)	25 (75)	5 (36)
Rash	30 (52)	9 (39)	15 (50)	15 (50)	10 (77)	20 (44)	7 (100)	23 (45)	4 (63)	25 (50)	21 (48)	9 (64)
Shock[d]	29 (50)	0	29 (100)	0	6 (46)	23 (51)	1 (14)	28 (55)	6 (75)	23 (46)	25 (56)	4 (31)
Vomiting	26 (45)	10 (44)	15 (52)	11 (38)	5 (38)	21 (47)	2 (29)	23 (45)	5 (63)	21 (42)	20 (45)	6 (43)
Conjunctival injection	26 (45)	9 (39)	11 (38)	15 (52)	11 (85)	15 (33)	7 (100)	19 (37)	5 (63)	21 (42)	20 (45)	6 (43)
Mucous membrane changes	17 (29)	5 (22)	6 (21)	11 (38)	6 (46)	11 (24)	6 (86)	11 (22)	1 (17)	11 (22)	11 (25)	6 (43)
Headache	15 (26)	4 (17)	11 (38)	4 (14)	4 (31)	11 (24)	1 (14)	14 (27)	4 (50)	11 (22)	13 (30)	2 (14)
Respiratory symptoms	12 (21)	2 (13)	9 (31)	3 (10)	3 (23)	9 (20)	1 (14)	11 (22)	3 (38)	9 (18)	9 (20)	3 (21)
Lymphadenopathy	9 (16)	3 (13)	2 (7)	7 (24)	5 (38)	4 (9)	4 (57)	5 (10)	2 (33)	7 (14)	8 (18)	1 (7)
Swollen hands and feet	9 (16)	2 (13)	4 (14)	5 (17)	4 (31)	5 (11)	4 (57)	5 (10)	1 (17)	7 (14)	7 (16)	2 (14)
Sore throat	6 (10)	1 (4)	5 (17)	1 (3)	0	6 (13)	0	6 (12)	1 (17)	5 (10)	6 (14)	0
Confusion	5 (9)	0	5 (17)	0	1 (8)	4 (9)	0	5 (10)	1 (17)	4 (8)	5 (11)	0

Table 3. Clinical Outcomes and Management

Characteristic	No. (%)[a]											
			Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Cardiac/circulatory/kidney												
Acute kidney injury[h]	13 (22)	2 (9)	11 (38)	2 (7)	3 (23)	10 (22)	0	13 (25)	3 (38)	10 (20)	11 (24)	2 (67)
Inotropic support	27 (47)	0	27 (93)	0	6 (46)	21 (47)	1 (14)	26 (51)	6 (75)	21 (42)	23 (52)	4 (29)
Extracorporeal membrane oxygenation	3 (5)	0	3 (10.3)	0	0	3 (7)	0	3 (60)	0	3 (6)	3 (7)	0
Respiratory												
Intubation	25 (43)	2 (9)	23 (79)	2 (7)	5 (38)	20 (44)	1 (14)	24 (47)	5 (63)	20 (40)	20 (45)	5 (36)
Pharmacotherapy												
Intravenous immunoglobulin	41 (71)	14 (61)	21 (72)	20 (69)	13 (100)	28 (62)	7 (100)	34 (68)	8 (100)	33 (66)	33 (75)	8 (57)
Corticosteroids	37 (64)	12 (52)	19 (66)	18 (62)	12 (92)	25 (56)	7 (100)	30 (59)	7 (88)	30 (60)	33 (75)	4 (29)
Anakinra (IL-1 receptor antagonist)	3 (5)	1 (4)	2 (7)	1 (3.4)	0	3 (7)	0	3 (6)	0	3 (6)	2 (5)	1 (8)
Infliximab (TNF-α antagonist)	8 (14)	4 (17)	2 (7)	6 (21)	4 (31)	4 (9)	3 (43)	5 (19)	3 (38)	5 (10)	7 (16)	1 (8)
No. of immunomodulatory agents												
2[i]	35 (60)	11 (48)	18 (62)	17 (59)	12 (92)	23 (51)	7 (100)	28 (55)	7 (88)	28 (56)	32 (71)	3 (23)
3[i]	9 (16)	4 (17)	3 (10)	6 (21)	4 (31)	5 (11)	3 (43)	6 (12)	3 (38)	6 (12)	8 (18)	1 (8)
Outcomes												
Coronary artery aneurysm (*z* score >2)	8 (14)	1 (4)	5 (17)	3 (10)	8 (62)	0	1 (14)	7 (14)	8 (100)	0	6 (13)	2 (15)
Death	1 (2)	0	1 (3)	0	0	1 (2)	0	1 (2)	0	1 (2)	1 (2)	0

結果

SARS-CoV-2檢驗結果 (SARS-CoV-2 test results)

- 有15位(26%)病童的PCR為陽性
- SARS-CoV-2 IgG在46位病童中有40位(87%)呈現陽性 (有12位病童未測IgG)
- 58位病童中, 有45位 (78%)有SARS-CoV-2感染或感染過的證據

實驗室檢查 (Laboratory investigations)

- 所有的病人都有明顯發炎的狀態 (inflammatory state)

➔CRP (中位數, 229mg/L, IQR: 156-338), 中性球數量 (13X10^9/L, IQR:10~19), 運鐵蛋白 (ferritin) (610μg/L, IQR:359~1280)

➔68% (34/50)有Troponin 上升, 83% (24/29) 有NT-proBNP上升, 包含2位因嚴重心肌功能失常而需要使用ECMO的病童

Table 4. Laboratory Results

	Reference range	Median (IQR)[a]											
				Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
		All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Kawasaki criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Virology, No. (%)													
SARS-CoV-2 respiratory PCR positive		15 (26)	5/23 (22)	10 (35)	5 (17)	0	15 (33)	0	15 (29)	0	15 (30)	15 (33)	
SARS-CoV-2 IgG antibody		40/46 (83)	15/18 (83)	22/25 (88)	18/23 (78)	8/12 (67)	32/36 (89)	4/6 (67)	36/42 (86)	6 (75)	34/40 (75)	40/42 (95)	
Any SARS-CoV-2 PCR or IgG positive		45/58 (78)	17 (74)	25 (86)	20 (69)	8 (62)	37 (82)	4 (57)	41 (80)	6 (75)	39 (78)	45 (100)	
No positive test result		13 (22)	6 (26)	4 (14)	9 (31)	5 (39)	8 (18)	3 (43)	10 (20)	2 (25)	11 (22)	0	13/13 (100)
Laboratory values													
Hematology													
Total white blood cell count, $\times 10^9$/L	4-13.5	17 (12-22) [n = 58]	16 (11.2-19) [n = 23]	18 (14-28) [n = 29]	17 (11.3-18.8) [n = 29]	17 (13.5-26.4) [n = 13]	17 (12.15-22.6) [n = 45]	17 (11-17) [n = 7]	17.4 (12.5-22.4) [n = 51]	20 (15-29) [n = 8]	17 (11.6-21.7) [n = 50]	17 (12-23) [n = 45]	17 (13-21) [n = 13]
Neutrophil count, $\times 10^9$/L	1.5-7	13 (10-19) [n = 58]	10.7 (7.4-16) [n = 23]	16 (11-25) [n = 29]	10.8 (6.8-16) [n = 29]	13.2 (10.2-16.4) [n = 13]	12.5 (8.5-19.5) [n = 45]	12.5 (6-14) [n = 7]	14 (10.1-19.2) [n = 51]	16 (13-26) [n = 8]	12 (7.9-18.9) [n = 50]	14 (9-20) [n = 45]	13 (8-18) [n = 13]
Lymphocyte count, $\times 10^9$/L	1.5-4	0.8 (0.5-1.5) [n = 58]	1.2 (0.7-2.9) [n = 23]	0.7 (0.4-0.9) [n = 29]	1.3 (0.7-2.8) [n = 29]	1.2 (0.5-1.6) [n = 13]	0.8 (0.6-1.5) [n = 45]	1.3 (0.5-1.8) [n = 7]	0.8 (0.5-1.4) [n = 51]	0.6 (0.4-1.3) [n = 8]	0.8 (0.6-1.6) [n = 50]	0.8 (0.4-1.4) [n = 45]	0.8 (0.5-2.9) [n = 13]
Hemoglobin, g/L	111-147	92 (83-103) [n = 51]	97 (87-108) [n = 19]	85 (74-100) [n = 27]	99.5 (88-109) [n = 24]	88.5 (72-109) [n = 12]	92.5 (83-102) [n = 39]	109 (84-110) [n = 6]	91 (83-101.5) [n = 45]	80 (70-95) [n = 8]	93 (83-106) [n = 43]	93 (83-103) [n = 42]	88 (79-106) [n = 9]
Platelet count, $\times 10^9$/L	200-450	151 (104-210) [n = 55]	175.5 (101-209) [n = 22]	136 (75-214) [n = 28]	176 (118-210) [n = 27]	176 (125-262) [n = 12]	147.5 (93-195) [n = 43]	176 (106-302) [n = 6]	150 (101-210) [n = 49]	173 (123-230) [n = 8]	151 (97-209) [n = 47]	142 (91-201) [n = 42]	180 (129-332) [n = 13]
Inflammatory markers													
C-reactive protein, mg/L	0-5	229 (156-338) [n = 58]	176 (82-192) [n = 23]	321 (223-371) [n = 29]	176 (83-229) [n = 29]	295 (173-357) [n = 13]	206 (151-331) [n = 45]	238 (106-339) [n = 7]	220 (156-338) [n = 51]	301 (205-361) [n = 8]	191 (132-330.5) [n = 50]	251 (158-342) [n = 45]	220 (131-323) [n = 13]
Ferritin, µg/L	7-140	610 (359-1280) [n = 52]	379.5 (195-831) [n = 20]	888 (556-1530) [n = 28]	378 (180-907) [n = 25]	620 (306.3-1254) [n = 12]	592 (373-1443) [n = 41]	357 (146-1078) [n = 6]	631 (381-1342) [n = 47]	637 (376-1076) [n = 8]	574 (355-1378) [n = 45]	679 (374-1249) [n = 42]	495 (190-1627) [n = 11]

Table 4. Laboratory Results (continued)

		Median (IQR)[a]											
				Stratification by shock[d]		Stratification by Kawasaki disease[e]		Stratification by Kawasaki clinical criteria[e]		Stratification by coronary artery aneurysm[f]		Stratification by evidence of SARS-CoV-2 infection[g]	
	Reference range	All PIMS-TS cases (n = 58)[b]	Febrile and inflammatory (n = 23)[c]	Shock present (n = 29)	Shock absent (n = 29)	Kawasaki disease (n = 13)	Not Kawasaki disease (n = 45)	Criteria met (n = 7)	Kawasaki criteria not met (n = 51)	Present (n = 8)	Absent (n = 50)	Positive (n = 45)	Negative (n = 13)
Biochemistry													
Lactate dehydrogenase, U/L	125-243	419 (319-887) [n = 41]	327 (274-463) [n = 15]	764 (291-989) [n = 23]	327 (273.5-451.8) [n = 18]	373 (309-828) [n = 9]	448 (319-912.5) [n = 32]	359 (246-373) [n = 3]	434 (323-906) [n = 38]	615 (371-905) [n = 6]	408 (311-900) [n = 35]	414 (310-915) [n = 34]	1104 (327-1209) [n = 7]
ALT, U/L	0-34	42 (26-95) [n = 56]	40 (21-79) [n = 23]	47 (30-107) [n = 28]	31.5 (20-77) [n = 28]	36.5 (18.75-117.8) [n = 12]	42 (27-97) [n = 44]	26 (12-141) [n = 6]	43 (28-96) [n = 50]	86 (34-129) [n = 8]	40 (25-77) [n = 48]	42 (30-95) [n = 43]	28 (22-273) [n = 13]
Albumin, g/L	35-54	24 (21-27) [n = 51]	27 (24-33) [n = 19]	22 (20-24) [n = 27]	27 (25-32) [n = 24]	24 (20-27) [n = 12]	24 (21-29) [n = 39]	27 (23-28) [n = 6]	24 (21-28) [n = 45]	21 (18-26) [n = 8]	25 (21-29) [n = 43]	24 (21-27) [n = 41]	27 (21-31) [n = 10]
Creatinine, μmol/L	30-80 (varies with age)	71 (43-108) [n = 48]	62 (42-93) [n = 19]	78 (42-104) [n = 32]	61 (45-92) [n = 20]	72 (46-123) [n = 8]	71 (41-102) [n = 33]	42 (40-46) [n = 3]	76 (40-118) [n = 25]	72 (46-122) [n = 8]	71 (40-101) [n = 33]	67 (44-116) [n = 30]	76 (40-96) [n = 11]
Cardiac markers													
Troponin, ng/L	0-15	45 (8-294) [n = 56]	8 (5-45) [n = 17]	124 (45-497) [n = 26]	8 (5-45) [n = 22]	19.3 (7-153) [n = 12]	45.1 (8-355) [n = 38]	10 (5-38) [n = 6]	47.5 (11-353) [n = 44]	100 (25-379) [n = 7]	45 (7-278) [n = 43]	45 (8-202) [n = 41]	256 (9-598) [n = 9]
NT-proBNP, pg/mL	<100	788 (174-10 548) [n = 29]	310.5 (106-1354) [n = 17]	14 017 (7004-35 000) [n = 11]	212.5 (70-876) [n = 18]	788 (56-32 169) [n = 7]	921.5 (180-9962) [n = 22]	118 (23-636) [n = 4]	1833 (213-12 868) [n = 25]	32 169 (1994-35 000) [n = 3]	629 (155-7597) [n = 26]	1140 (184-11 719) [n = 27]	11 (10-12) [n = 2]
Coagulation													
Fibrinogen, g/L	1.99-4.09	5.7 (4.4-7) [n = 51]	4.8 (3.5-5.8) [n = 18]	6.1 (5-7.3) [n = 27]	4.9 (3.9-6.7) [n = 24]	7.1 (4.8-7.6) [n = 13]	5.7 (4.3-6.8) [n = 38]	6 (4.7-7.4) [n = 7]	5.7 (4.3-6.9) [n = 44]	6.9 (5.7-7.8) [n = 8]	5.5 (4.3-6.8) [n = 43]	5.8 (4.4-7.1) [n = 42]	5.5 (3.8-7.6) [n = 9]
D-dimer, ng/mL	100-560	3578 (2085-8235) [n = 53]	2402 (1336-4248) [n = 20]	5935 (3548-12 842) [n = 28]	2383 (1357-4360) [n = 25]	3238 (969-6262) [n = 11]	3578 (2205-10 000) [n = 42]	3494 (1733-6650) [n = 6]	3578 (2205-8729) [n = 47]	4375 (2662-6906) [n = 6]	3564 (1964-10 000) [n = 47]	3910 (2563-10 000) [n = 27]	2094 (1379-5815) [n = 10]

結果

微生物與病毒檢測(microbiological and virological investigations)

- 針對staphylococci及streptococci的血液培養, 皮膚表現培養或是其他地方的細菌培養全都呈現陰性
- 使用多病毒篩檢片(multiplex panel) 做呼吸道病毒篩檢, 發現只有一位病人同時有腺病毒(adenovirus)及腸病毒 (enterovirus)
- 有一位病人有明顯的EBV病毒血症 (viremia), 但是檢測familial hemophagocytic lymphocytic histiocytosis則是陰性

結果

住院後的臨床病程 (Clinical course following admission)

- 檢視病童的臨床病程可區分為3種臨床類型 (clinical patterns)

➔第一類: 23個病童有持續發燒與發炎指標(inflammatory markers)上升的情況, 但是沒有器官衰竭或皮膚黏膜類似川崎症或毒性休克症候群的表現

➔第二類: 29個病童有休克, 大多是因為左心室功能失常 (62%; 18/29), 合併troponin(66%, 19/29) 上升及NT-proBNP 上升(100%, 11/11), 有4個病人出現心律不整, 1位有first degree AV block, 1位有心搏過速(tachycardia), 1位有心房震顫(atrial fibrillation), 1位有second degree AV block

➔第三類: 7個病童符合美國心臟協會有關川崎症的診斷標準, 其中1位有休克, 如果將冠狀動脈血管瘤納入診斷標準, 則有13位病童符合川崎症的診斷

結果

- 總共有55位病童接受心臟超音波檢查以探查是否有冠狀動脈血管瘤, 其中8位病童有冠狀動脈擴張的現象(z score>2), 包括7位z scores 超過2.5, 有2位有巨大冠狀動脈血管瘤(z score>10)
- 有8位病童發展出冠狀動脈瘤, 包括1位有發燒及發炎, 5位有休克, 1位有川崎症的皮膚黏膜症狀, 1位有休克合併川崎症的皮膚黏膜症狀

比較同時有休克及冠狀動脈血管瘤的病人之實驗室檢驗結果

- 符合PIMS-TS診斷的病童中, 有29位出現過休克,跟沒有休克的病童相比, 這些有過休克的病童有CRP升高, neutrophil counts升高, albumin降低, lymphocyte counts降低, troponin升高, NT-proBNP升高的情況
- 有冠狀動脈擴張或是冠狀動脈血管瘤的病童, 跟沒有冠狀動脈異常的病童相比, 其實驗室檢驗結果並無明顯差異

結果

治療(treatment)

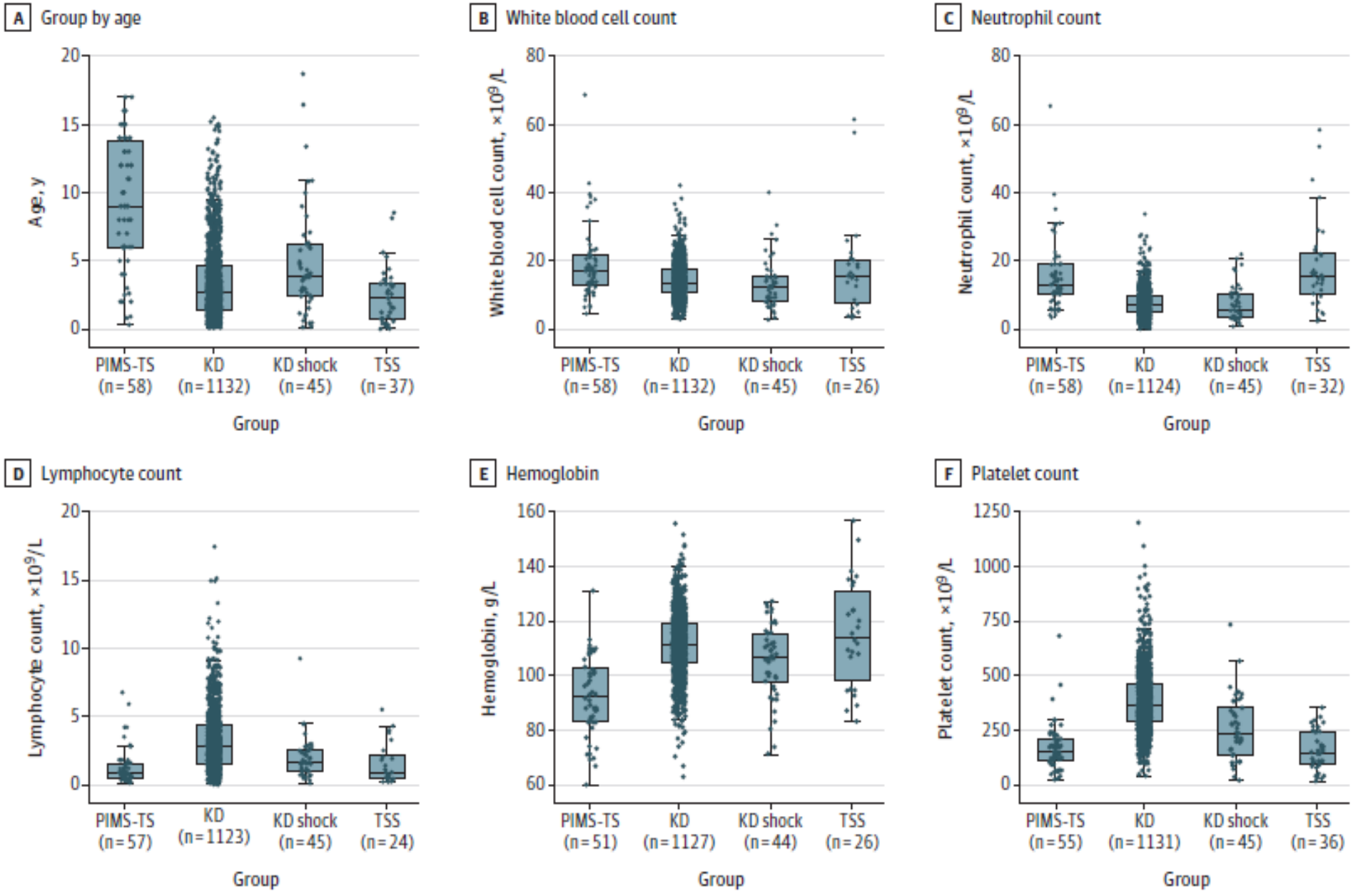
- 47%的病童需要使用強心劑, 71%需要使用IVIG, 64%需要使用類固醇
- 有3位病人接受anakinra (IL-1 receptor antagonist) 治療, 有8位接受infliximab (anti-TNF monoclonal antibody) 治療
- 22%的病人僅接受支持療法即康復

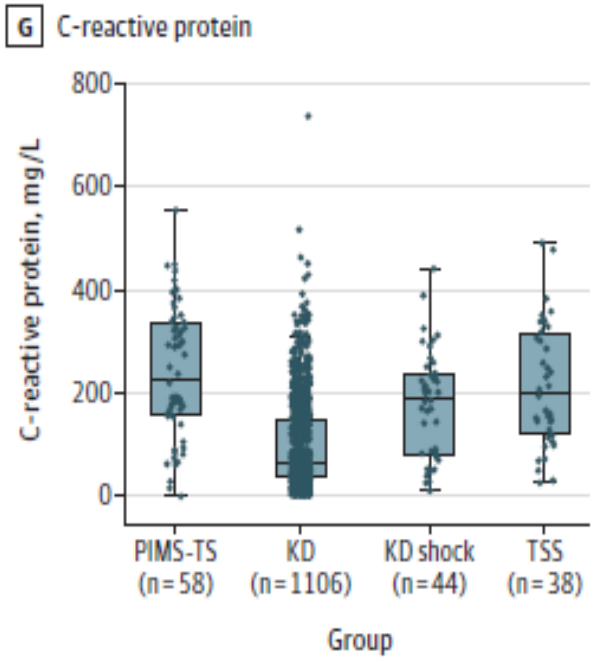
結果

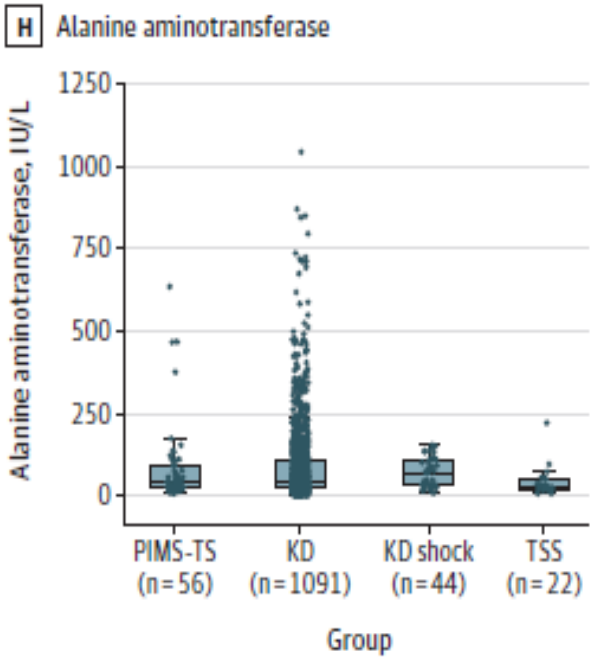
與其他兒童發炎性疾病(childhood inflammatory diseases)做比較

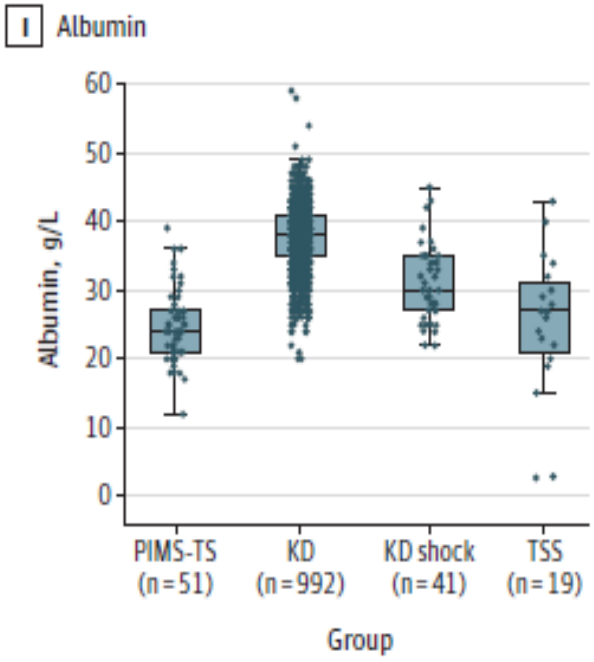
- 可與PIMS-TS比較之兒童發炎性疾病族群包括: 1132位川崎症(KD) (平均2.7歲, IQR: 1.4-4.7), 45位川崎症休克症候群(KD shock syndrome) (平均3.8歲, IQR: 0.2~18), 37位毒性休克症候群(toxic shock syndrome) (平均7.4歲, IQR: 2.4-15.4)
- PIMS-TS的病童大多比KD或KD shock syndrome的病童年紀大, 而且WBC count, neutrophil count, CRP也比較高, 反之也有比較嚴重的lymphopenia及貧血
- PIMS-TS的病童通常platelet counts較低, 但是fibrinogen及troponin升高
- 不過肝功能指數 (ALT), D-dimer 則跟KD或是KD shock syndrome的病童類似
- PIMS-TS病童跟toxic shock syndrome的病童相比, 年紀較大, 血色素 (Hb)較低, CRP及肝功能指數(ALT)較高

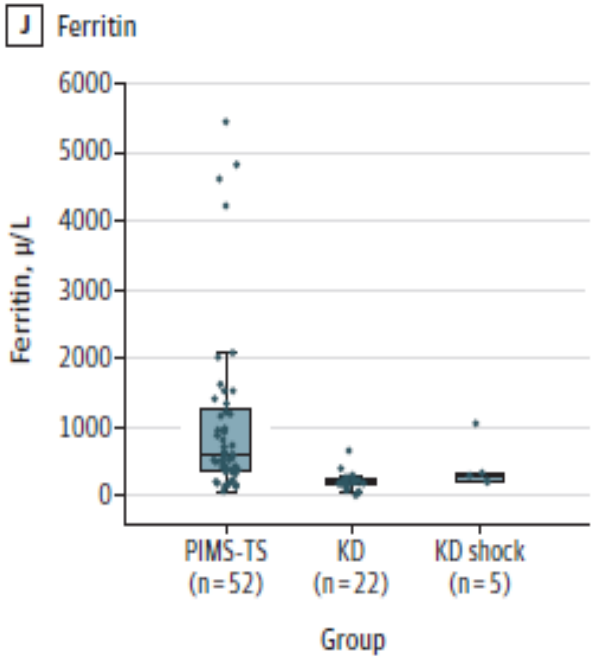
Figure. Comparison of Age and Laboratory Results in 4 Different Patient Groups

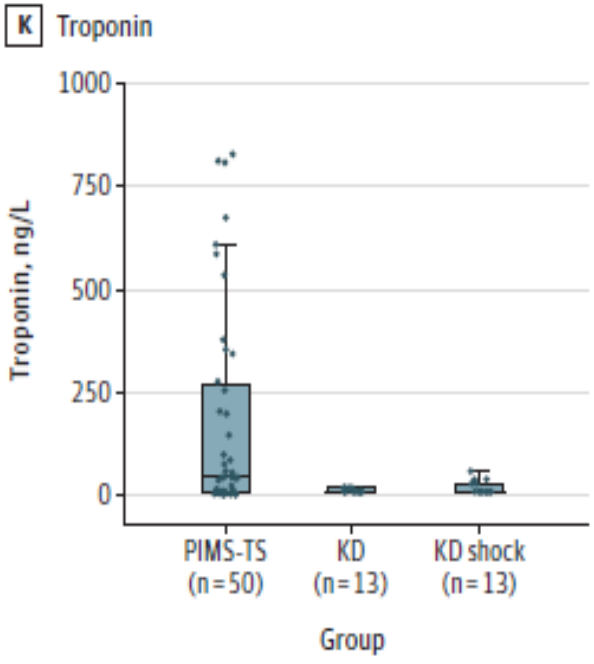


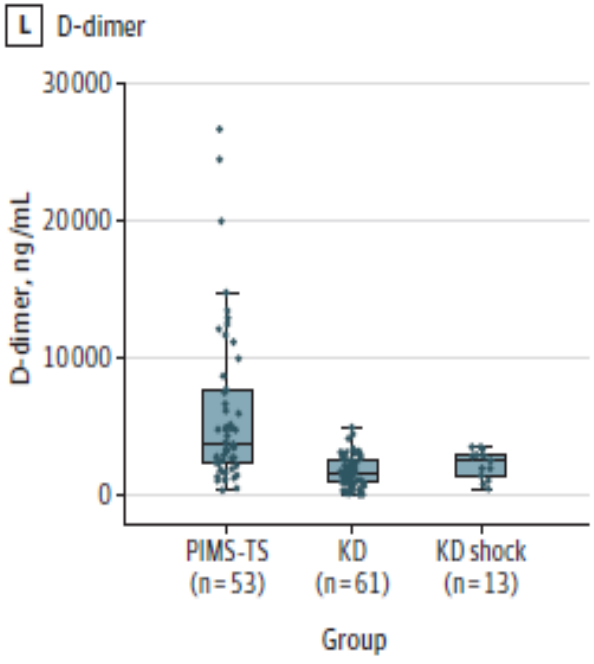

G
C-reactive protein
C-reactive protein, mg/L
800
600
400
200
0
PIMS-TS (n=58)
KD (n=1106)
KD shock (n=44)
TSS (n=38)
Group


H
Alanine aminotransferase
Alanine aminotransferase, IU/L
1250
1000
750
500
250
0
PIMS-TS (n=56)
KD (n=1091)
KD shock (n=44)
TSS (n=22)
Group


I
Albumin
Albumin, g/L
60
50
40
30
20
10
0
PIMS-TS (n=51)
KD (n=992)
KD shock (n=41)
TSS (n=19)
Group


J
Ferritin
Ferritin, μ/L
6000
5000
4000
3000
2000
1000
0
PIMS-TS (n=52)
KD (n=22)
KD shock (n=5)
Group


K
Troponin
Troponin, ng/L
1000
750
500
250
0
PIMS-TS (n=50)
KD (n=13)
KD shock (n=13)
Group


L
D-dimer
D-dimer, ng/mL
30000
20000
10000
0
PIMS-TS (n=53)
KD (n=61)
KD shock (n=13)
Group

討論

- 本研究中58位Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) 的病童, 其臨床症狀表現非常廣泛, 包括發燒, 腸胃道症狀, 皮膚疹; 疾病的嚴重度也有各種情況, 包括心肌受損, 休克, 冠狀動脈血管瘤等等
- 與KD, KD shock syndrome, toxic shock syndrome相比, PIMS-TS應該是不同的疾病
- 這些不尋常的發炎疾病都是在COVID-19疫情開始發生之後數個月才出現, 一開始因為都找不到病因, 所以不同的專業群體在網路上討論, 並且很快速地出現個案報告, 就時序上來說, 這些個案應該與SARS-CoV-2有關連

討論

- 這些符合PIMS-TS診斷標準的病童, 可以初步區分為三種臨床類型

(1) 第一類: 有持續發燒, 且發炎指標(inflammatory markers)升高, 但沒有川崎症, 休克或是器官衰竭的情況

(2) 第二類: 同時符合川崎症的診斷

(3) 第三類: 有休克過, 且在臨床上, 心電圖上, 實驗室檢驗上都有心肌損傷的證據

- 本研究也發現, PIMS-TS的病童年紀通常比KD或是KD shock syndrome的患者年長, 而且實驗室檢驗數值也不同
- PIMS-TS病童跟COVID-19疫情發生前的川崎症患者相比, 年紀更大, 有更強的發炎現象, 與更嚴重的心肌損傷的情況, 這代表這兩者是不同的疾病, 而且所需的治療方式也不同
- CRP, ferritin, troponin, NT-proBNP 的數值可以用來預測PIMS-TS的疾病病程

討論

- 但是在PIMS-TS病童中, 有冠狀動脈擴張或血管瘤的出現的病童跟沒有冠狀動脈異常的病童相比, 不論是在臨床症狀或是實驗室檢查上, 都沒有明顯差異
- 在PIMS-TS的三種臨床類型中, 只有一小部分的病童會有冠狀動脈血管瘤, 而且與各種發炎指標的量或是心肌損傷的情況無相關性, 這表示冠狀動脈的異常並不是嚴重發炎的後遺症, 但如果病童的NT-proBNP跟troponin 的量升高, 則就建議需要做心臟超音波檢查以提早發現是否有冠狀動脈血管瘤
- 本研究的病童使用各種免疫調節劑治療, 因為並非隨機分組的研究, 所以無法提供有效治療方式的證據, 至於在川崎症中可用來減少冠狀動脈血管瘤發生的藥物對於PIMS-TS是否有效, 也需要進一步的研究
- 本研究也無法提出PIMS-TS的致病機轉, 但是這群病人大部分沒有其他病毒感染的證據, 卻都有SARS-CoV-2的抗體, 表示這疾病與後天免疫的異常發展有關

討論

- 過去的研究發現SARS-CoV-1的抗體會經由形成免疫複合體(immune complexes) 或是直接活化免疫細胞造成宿主的發炎反應
- SARS-CoV-1的抗棘蛋白抗體 (antispike antibodies) 也能強化靈長類及人類巨噬細胞(macrophage)的發炎反應, 因此推測SARS-CoV-2的抗體可能也會誘發相似的發炎反應
- PIMS-TS的致病機轉可能與SARS-CoV-2所引發之不尋常的後天免疫反應 (抗體或是T細胞)有關, 這也是研發疫苗所需著重的地方
- PIMST-TS與川崎症在某些臨床症狀相似, 在川崎症的免疫複合體(immune complexes)可以經由Fc gamma receptor 或是活化neutrophil 而產生發炎反應, 而本研究中的PIMS-TS患者大部分都是接受IVIG或是類固醇的治療, 少數患者接受免疫調節劑治療
- PIMS-TS患者的CPR會升高, IL-6也跟心肌功能缺損有關, 但是anti-IL-6 agents的效用還需要更多研究去認證

限制

- 第一: 這是病歷回溯性研究, 所以病患的評估與處理跟不同的醫師或是醫院有關, 並非依據標準作業流程
- 第二: 在疫情盛行期間, PCR檢測並非例行性的執行, 所以只有一小部分的病童有接受檢查, 有可能病毒是在腸胃道, 內皮細胞, 心肌組織裡複製, 但因為無法取的檢體, 所以無法得知
- 第三: 英國的兒童的血清盛行率 (seroprevalence) 目前不得而知, 所以目前不清楚群體中SARS-CoV-2 IgG陽性率有多高
- 第四: 因為川崎症並沒有診斷工具, 所以本研究無法排除其實是川崎症而非SARS-CoV-2感染的患者, 本研究只是嘗試去區分哪些兒童符合川崎症的診斷, 而哪些不符合川崎症的診斷
- 第五: 因為英格蘭並沒有全國統一的川崎症或是毒性休克症候群的登記資料庫, 所以無法比較PIMS-TS與川崎症的盛行率

結論

- 本研究主要是收集符合PIMS-TS診斷的兒童住院病患, 所以臨床表現與疾病嚴重度表現不一, 從發燒及發炎反應到心肌損傷, 休克, 以及冠狀動脈血管瘤都有
- 與川崎症及川崎症休克症候群的比較提供了探索PIMS-TS的洞察觀點, 也代表PIMS-TS與其他發炎性疾病的不同