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High intelligence may exacerbate paediatric inflammatory response to SARS-CoV-2 infection

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ABSTRACT

The body's innate and acquired immune systems are critical in responses to a wide spectrum of assaults, including SARS-CoV-2 infection. We identify studies of autoimmunity to support our hypothesis that a high intelligence quotient (IQ) may put children at increased risk for severe COVID-19 sequelae; especially those whose viral load is high and/or who develop multisystem inflammatory syndrome in children (MIS-C). MIS-C is associated with a higher risk of COVID-19 morbidity and death, even in otherwise healthy children. As information and evidence about SARS-CoV-2 infection continue to expand, our hypothesis suggests adding a potentially intriguing piece to the pandemic puzzle for further investigation. Drawing on a select review of published research and case reports, we discuss immune dysregulation in paediatric patients with a high IQ, including post-infection cytokine expression in the myocardium. Further, we provide a review of 27 paediatric (≤19 years; median age 16) cases of severe COVID-19 outcomes, drawn from media sources published between March and September 2020, in which we identify possible evidence of a 'hyper brain, hyper body' response to infection. We aver these cases are noteworthy given that paediatric death with COVID-19 disease is remarkably rare, and the estimated prevalence of a high IQ (or giftedness) is only 2% in the general population. These observations warrant prospective and retrospective studies of autoinflammatory markers and mechanisms to elucidate any special psychoneuroimmunological vulnerability in children with a high IQ, as such studies may raise implications for how and when prophylactic medical care is provided to children.

Introduction

As global deaths due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and coronavirus disease 2019 (COVID-19) surpass 2 million [1], epidemiological analyses indicate that severe paediatric morbidity and mortality outcomes from COVID-19 are rare compared to such outcomes among (especially older) adults [2]. Yet once hospitalized, the percentage of ICU admission is similar for children and adults (33.2% and 32%, respectively) [3]. For researchers, an "essential question is why MIS-C develops in some paediatric patients in this age group and not in others" [4]. The reopening of schools [5] heightened efforts to identify contributory factors in the experience of children most seriously affected by COVID-19. Using evidence of inflammatory responses to SARS-CoV-2 infection (including research on autoimmune dysregulation and post-infection cytokines) to guide a review of reports of individual paediatric cases, we hypothesize that conducting prospective and retrospective studies of one potentially vulnerable paediatric cohort is warranted; namely, children with a high intelligence quotient (IQ), defined as being in the 98th percentile (or above) of the general population.

Early in the pandemic, there was consensus that the innate-immune system has a critical role in the inflammatory response to SARS-CoV-2 infection [6]. Patients who develop cytokine storm syndrome (when their body overreacts in attempting to fight viral infection, and attacks its own cells and tissues instead; "an immune system gone wild" [7]) have greater disease severity and poorer outcomes [8]. In April 2020, multisystem inflammatory syndrome in children (MIS-C) (also called paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS)) [9], presenting with some similar features to those of Kawasaki disease [10], was first reported. Researchers subsequently advised that controlling the host's inflammatory response "may be as important as targeting the virus" [11].

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Specifically, "immune dysregulation" was implicated in MIS-C [5] and described as one of "the hallmarks of COVID-19" [12]. A dysregulated immune response has also been implicated in acute myocarditis, which is particularly challenging to diagnose and treat [13]. Cytokine expression in the myocardium following viral infection can lead to a dysregulated inflammatory process and sudden cardiac death [14], and this is a notable feature of many otherwise healthy children who develop MIS-C [15]. Evidence in scholarly publications and national government datasets suggest children with severe COVID-19 outcomes (including death) often present with MIS-C 1–4 weeks after infection [4,10], and there is also research [16] to support the theory that once infected, and even though asymptomatic and without pain, their immune responses may be overreacting during this pre-clinical period of delay.

Evidence of an association between a high IQ and immune dysregulation in children was reported some decades prior to the SARS-CoV-2 pandemic [17]. While no large paediatric studies on this have been conducted since, Karpinski et al. published a study in 2018 of nearly 4000 adult Mensa participants, and concluded that a high IQ is associated with a higher risk of physiological diseases "related to immune dysregulation" [18]. Citing studies that investigated interleukin levels, cytokines and immune cells, they theorized that "If these individuals take in their world in such an overexcitable manner intellectually (hyper brain), then the potential exists for an intense level of physiological processing as well (hyper body)." They explained how the idea of 'hyper brain, hyper body' connections is rooted in the work of the Polish psychiatrist and psychologist Kazimierz Dabrowski, who described a tendency for "hyper-reactions and intensities to occur with greater frequency and of greater strength in the intellectually gifted compared to those with a normal or lower IQ"; these children have "overexcitabilities". In particular, "bright individuals tended to be "neurotically allergic or nervous," a condition which he observed to be relatively absent in the intellectually delayed." Importantly, individuals with a high IQ demonstrated a "uniquely heightened way of experiencing and responding to their environment within five domains: psychomotor, sensory, intellectual, imaginational, and emotional." These domains encompass psychologist Howard Gardner's theory of "multiple intelligences": linguistic, logical-mathematical, spatial, musical, bodily-kinesthetic, interpersonal, intrapersonal, naturalist, and existential [19]. Also described as visual/spatial [20], psychomotoric [21] and sensorimotor [22], they include artistic and athletic giftedness.

Evidence to support our hypothesis

Sparked by media reports of severe COVID-19 outcomes in children where a high IQ was indicated, we investigated further evidence for potential SARS-CoV-2 vulnerabilities in paediatric (age 19 years or younger) patients with a high IQ by conducting a search of the National Center for Biotechnology Information (NCBI) developed PubMed database, from the National Library of Medicine (NLM). A scanning search [23] using the terms 'high IQ' or 'gifted' and 'COVID-19′, 'SARS-CoV-2′ or 'coronavirus' yielded no results, so we turned our attention to a detailed review of published news and social media reports. In addition to tracking national and international reports of severe paediatric outcomes with COVID-19, we conducted weekly online Google searches, between March 15 and September 30, 2020, using search term combinations that included 'child', 'children', 'youth', 'death', 'died', 'COVID-19′ and 'coronavirus', in conjunction with the names of countries or US states. Only news and social media reports of cases of individuals aged ≤19 years, with no reported pre-existing conditions other than autoimmune disorders, were included. We then screened for evidence of a high IQ using proxy terms such as "bright", "talented" or "intelligent". We also treated terms that denoted athletic intelligence (psychomotor [18], bodily-kinesthetic [19]), such as "star athlete", as evidence indicative of a high IQ. When reports of severe paediatric outcomes did not provide evidence indicative of a high IQ but included identifying information (notably the child's name), we conducted further Google and social media searches (via Facebook, Twitter and Instagram, including personal correspondence via these platforms) to investigate evidence of a high IQ. In total, we found news and social media reports of 27 children and adolescents with evidence indicative of a high IQ who experienced severe COVID-19 outcomes (including 20 deaths) during the pandemic, as presented in Table 1. These reports originated from four countries, with 24 of the 27 from the United States of America. They include 15 females and 12 males aged 3–19 years (median 16). A positive test result for COVID-19 was reported in 22 of the 27 cases (three post-mortem), two tested negative, one child was not tested, and two were not reported.

Support for our hypothesis

Information and evidence about SARS-CoV-2 infection continue to expand, and our observations are intended to support our hypothesis and add a potentially intriguing piece to the pandemic puzzle: that for some children, a high IQ may be associated with an increased risk for severe COVID-19 sequelae, especially if their viral load is high [12]. The studies we review below illuminate the critical problem with overproduction of interleukin-6 (IL-6); similarities between MIS-C and paedatric Kawasaki disease; and the autoimmune association between Parkinson's disease, high IQ, and other features of immune dysregulation. These studies explain the role of IL-6 in promoting effective cell-mediated immune responses and facilitating successful virus clearance, and the risk of myocarditis in exceptional young athletes. The most relevant studies are summarized in Table 2, and our hypothesis about a potential association between high IQ and severe paediatric outcomes with COVID-19, as supported by the studies cited in Table 2, is represented in Fig. 1.

The role of interleukin-6 overproduction in SARS-CoV-2 infection

Interleukin-6 (IL-6) is a pleotropic cytokine with a key role in regulating the body's immune response to viruses, and its overexpression is associated with immune system dysregulation [27]. Macrophage activation syndrome (MAS), which is related to hemophagocytic lymphohistiocytosis (HLH), is a rare complication of systemic juvenile idiopathic arthritis (SJIA), an autoimmune paediatric disease where increased levels of IL-6 correlate with disease activity [28]. Increased levels of IL-6 are noted with juvenile systemic lupus erythematosus (jSLE) [29,30], and have been used as a potential biomarker in the treatment of paediatric patients with non-juvenile idiopathic arthritis [31]. Elevated IL-6 levels have also been associated with increased disease severity in influenza virus infections; H1N1 influenza A [32], SARS-CoV-1 [27], and numerous paediatric cases with SARS-CoV-2 [33], including MIS-C [9,34,35]. A recent study to investigate an association between IL-6 levels and IQ (albeit in older adults; mean age 74 years) reported an association with *low* levels of IL-6 and a high IQ [36], unlike the high IL-6 levels reported with MIS-C. However, the properties of IL-6 depend on its transduction pathway in the body (anti-inflammatory or pro-inflammatory) [27], and in this regard, the relevance of the vital role played by T cells in regulating the body's immune response to viral infections like COVID-19 is important to understand [37].

In the first week of infection, SARS-CoV-2 activates T cells, including virus-specific memory CD4+ cells that peak within two weeks, and remain detectable for a longer period in up to 100% of COVID-19 patients [38]. Long-lived memory T and B cells are a key feature of autoimmune diseases such as jSLE and lupus nephritis (LN), to name two, and in jSLE, an association with pro-inflammatory cytokines is evident [39,40]. Of relevance, given the evidence linking IL-6 and a high IQ, recent reports indicate that "SARS-CoV-2-specific T cells" and "long-lasting memory T cells" may have a protective effect in patients recovering from COVID-19, and those who have never contracted the disease [41]. A 2008 study of H17 influenza virus in rodents reported that the activity of CD4+ T cells "diminished in the absence of IL-6", thereby

Table 1
News and social media reports of severe paediatric COVID-19 outcomes from March 15 to September 30 2020.

Evidence of a high IQ	Age(sex)	Country	Outcome	COVID-19 test	Information source(s)
"a bright little girl"	3 (female)	USA	*Death (COVID-19)*	Positive (post-mortem)	New York Daily News [1]
"very bright" "smart little cookie"	5 (female)	USA	*Death (COVID-19; developed rare form of meningitis and brain swelling; died <2 weeks after on ventilator)*	Positive	ABC News [2]
"a very intelligent and mature girl for her age" "learning English at lightning speed"	6 (female)	USA	*Death (COVID-19)*	Positive	Tampa Bay Times [3]
"intelligent" "bright"	8 (female)	USA	*Death (COVID-19; anosmial, died 4 days after testing positive)*	Positive	News Observer [4]
"A smart child" "phenomenal"	9 (female)	USA	*Death (COVID-19)*	Positive (post-mortem)	CNN [5], Obituary [6]]
"a curious student" "what you want every student to be" "lover of books… always sneaking in extra reading time during classes, even during math" "leader"	9 (female)	USA	*Death (COVID-19; paralysis in her arms and legs; brain inflammation)*	Positive	WLWT [7], The Highland County Press [8], Spectrum News 1 [9]
"a straight A student" "cares a lot about school" "when she woke up, she was so concerned about the assignments she had missed" "overly worried about it"	12 (female)	USA	*Recovered (COVID-19 and adenovirus infection; fulminant myocarditis; heart attack required CPR)*	Positive	The Detroit News [10], Personal correspondence
"athletic, intelligent, funny, and mature" "voted Class President" "passion for swimming, competitive speaking on the Speech and Debate team" "playing viola in the orchestra"	13 (male)	USA	*Death (initially reported as COVID-19; autopsy noted cardiac tamponade**)*	Negative	ABC News [11], GoFundMe [12], Los Angeles County Medical Examiner-Courier [13], Claremont Courier [14]
"Imagination unbounded" "danced instead of walked most times" "had dreams, big ones and would've accomplished them"	13 (female)	USA	*Death (COVID-19; comorbidity scleroderma)*	Positive (post-mortem)	Stars and Stripes [15], The Lawton Constitution [16]
"a precocious talent" "a talented futsal player"	14 (male)	Portugal	*Death (COVID-19; comorbidity psoriasis)*	Positive	New Zealand Herald [17]
Attends a high school with an admissions exam, requirements for academic excellence, and 100% graduation rate	14 (male)	USA	*Recovered (COVID-19 and heart failure, hand rash, abdominal pain, high fever one week later, sore throat; swollen neck, nausea, cough,* dysgeusia*)*	Positive	New York Times [18], Author research
"beyond her years" "might've been 15, but you would've thought she was about to graduate" "a leader" "had a bright future ahead of her"	15 (female)	USA	*Death (COVID-19; MIS-C)*	Negative	The Baltimore Sun [19]
"an avid learner" "very bright" "high honors" "unique" "super imaginative" "an amazing student" "a leader" "she was 'that student.'"	15 (female)	USA	*Death (COVID-19 not tested for; died overnight; cause of death "cardiac arrhythmia of undetermined etiology")*	Not tested	Press Herald [20], Office of Chief Medical Examiner correspondence
"bright" "ambitious"	16 (female)	France	*Death (COVID-19; intensive care; complained "my heart hurts"; initial negative test then positive)*	Negative and Positive	Daily Mail [21]
"on all the sports teams" Selected for regional math team competition (5th place out of 53 schools).	16 (male)	USA	*Recovered (COVID-19; critically ill in hospital for one month; on ECMO and life support)*	Positive	The Washington Post [22], Alexandria Times [23], Author research
"football player who dreamed of turning pro" "wanted to… get to the NFL"	17 (male)	USA	*Death (COVID-19 leading to heart failure; had lymphohistiocytic and eosinophilic myocarditis, severe cadiomegaly)*	Positive	New York Post [24], The New Orleans Advocate [25]
"exceptional" "National Honors Society inductee" "had so much going on for her,… future was bright"	17 (female)	USA	*Death (COVID-19; died two weeks after testing positive; found unresponsive in home)*	Positive	BuzzFeed [26], NBCDFW [27]
"extremely bright" "schedule was vigorous – top academic courses, including organic chemistry" "She picked up things so fast"	18 (female)	USA	*Death (COVID-19)*	Not reported	The Citizens' Voice [28]
"excelled in math and science"	18 (female)	USA	*Death (COVID-19; born with genetic immune deficiency)*	Positive	Daily Mail [29]
"artistic talents in abundance" "She danced, she drew, she sang, she sculpted" "so sensitive" "so talented" "so much potential"	18 (female)	USA	*Death (COVID-19; comorbidity systemic lupus, eczema; initially experienced chest pain, cough, fever; on ventilator)*	Positive	Education Week [30], CBS News [31]
"phenomenal ability" "DEAN'S LIST (3.5–3.99)" "Offensive Player of the Year"	18/19 (male)	USA	*Recovered (COVID-19 (diagnosed with heart condition after testing positive)*	Positive	Spartanburg Herald-Journal [32], Georgia State Sports [33], Spartanburg Herald-Journal [34]
"earned a weighted GPA well above a 4.0" "school's scholar athlete of the year" "a killer trumpet player" "honors student" "completed high school early"	18/19 (male)	USA	*Recovered (COVID-19 (virus hit "very hard compared to most of his teammates", ER with breathing issues, 14 days battling, one of worst cases, now possible heart disease and additional sequelae)*	Positive	Sports Illustrated [35], The Huddle [36]
"star athlete"	19 (male)	USA	*Death (COVID-19)*	Not reported	K5 News [37]
"a talented basketball player" "all-time leading scorer" "member of the 2018 USSSA National Championship team"	19 (male)	USA	*Death (COVID-19; "incredibly tired for two weeks… it was secretly attacking his body in a way they have never seen before")*	Positive	WFRB [38], New York Times [39]
		Canada	*Death (COVID-19)*	Positive	CBC [40]

(*continued on next page*)

Table 1 (*continued*)

Evidence of a high IQ	Age(sex)	Country	Outcome	COVID-19 test	Information source(s)
"Star athlete" "demonstrated academic and athletic perseverance"	19 (male)				
"Great student. Great athlete" "played football, baseball and track" "named the homecoming king his senior year"	19 (male)	USA	*Recovered (COVID-19 (mild symptoms for about a week, then chills, body aches, high fever, open-heart surgery, existing heart malformation found and valves on verge of failure)*	Positive, Negative and Positive	GoFundMe [41], The Fresno Bee [42]
"graduated early" "[football] scholarship"	19/20 (male)	USA	*Recovered. COVID-19 (harrowing experience, battled virus for 3 weeks, lost 14 lb)*	Positive	Twitter [43], Sports Naut [44]

*One paediatric MIS-C study reported that almost a third of 186 patients tested negative for SARS-CoV-2 but had detectable antibodies [4].
**There is cause for questioning whether the autopsy and negative COVID-19 test confirms no SARS-CoV-2 infection. The child died 12 days after becoming ill [16]; other cardiac tamponade cases [24], including a negative test result [25], have been reported during the pandemic; and TGFBR1 gene mutation (noted in the child's autopsy as 'Other Significant Condition') is increased with Il-6 [26].

Table 2
Most relevant studies cited that support a potential association between a high IQ and severe paediatric COVID-19 outcomes.

Reference	Author(s)	Year	Study Title	Journal
11	Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP	2020	The trinity of COVID-19: immunity, inflammation and intervention	Nature Reviews Immunology
15	Jain S, Nolan SM, Singh AR, et al.	2020	Myocarditis in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with Coronavirus Disease 2019 (COVID-19)	Cardiology in Review
17	Benbow CP	1985	Intellectually gifted students also suffer from immune disorders	Behavioral and Brain Sciences
18	Karpinski RI, Kinase Kolb AM, Tetreault NA, Borowski TB	2018	High intelligence: A risk factor for psychological and physiological overexcitabilities	Intelligence
36	Segerstrom SC, Reed RG, Scott AB	2017	Intelligence and Interleukin-6 in Older Adults: The Role of Repetitive Thought	Psychosomatic Medicine
44	Carlsson E, Frostell A, Ludvigsson J, Faresjö M	2014	Psychological Stress in Children May Alter the Immune Response	Journal of Immunology
46	Eren F, Ömerelli Çete A, Avcil S, Baykara B	2018	Emotional and Behavioral Characteristics of Gifted Children and their Families	Archives of Neuropsychiatry
50	Yıldız S, Altay N, Kılıcarslan-Toruner E	2017	Health, Care and Family Problems in Gifted Children: A Literature Review	Journal for the Education of Gifted Young Scientists
51	Morey JN, Boggero IA, Scott AB, Segerstrom SC	2015	Current Directions in Stress and Human Immune Function	Current Opinion in Psychology
52	Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD	2016	Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness	Psychopharmacology (Berl)
54	Hughes HK, Mills Ko E, Rose D, Ashwood P	2018	Immune Dysfunction and Autoimmunity as Pathological Mechanisms in Autism Spectrum Disorders	Frontiers in Cellular Neuroscience
56	Crespi BJ	2016	Autism As a Disorder of High Intelligence	Frontiers in Neuroscience
57	Leitner Y	2014	The Co-Occurrence of Autism and Attention Deficit Hyperactivity Disorder in Children - What Do We Know?	Frontiers in Human Neuroscience
58	Cordeiro ML, Farias AC, Cunha A, et al.	2011	Co-Occurrence of ADHD and High IQ: A Case Series Empirical Study	Journal of Attention Disorders
59	Pfeiffer SI	2015	Gifted students with a coexisting disability: The twice exceptional	Estudos de Psicologia
76	Fardell C, Torén K, Schiöler L, Nissbrandt H, Åberg M	2020	High IQ in Early Adulthood Is Associated with Parkinson's Disease	Journal of Parkinson's Disease
79	Schneider W, Niklas F, Schmiedeler S	2014	Intellectual development from early childhood to early adulthood: The impact of early IQ differences on stability and change over time	Learning and Individual Differences
80	Nazarenko LD	2013	The Role of Intelligence in Sport	Teorija i praktika fiziceskoj kul'tury
85	Deary IJ, Batty GD	2007	Cognitive epidemiology	Journal of Epidemiology and Community Health
86	Louveau A, Smirnov I, Keyes TJ, et al.	2015	Structural and functional features of central nervous system lymphatic vessels	Nature

compromising protective anti-viral immunity. When the virus activated dendritic cells (which process and present antigen to T cells), high levels of IL-6 were produced [42]. Essentially, too little IL-6 prior to infection could increase susceptibility and risk of complications, with a rebound or overshoot of increased IL-6 and other pro-inflammatory cytokines resulting in the autoinflammatory phase of the disease (COVID-19 cytokine storm; MIS-C). This serves as an explanation of why low levels of IL-6, and therefore a high IQ, may *increase* the risk of COVID-19 and/or MIS-C, making high IQ, alongside the established role of elevated IL-6 [43], a potential socio-demographic marker for poor outcomes.

Paediatric evidence of immune dysregulation with high IQ, stress and autism spectrum disorder

Acting as a pro-inflammatory cytokine, IL-6 is also elevated by psychological stressors, such as depression, with "an increased secretion" found in "high-stressed children" [44]. The SARS-CoV-2 pandemic has been reported as posing significant psychological health risks to all children [45], but evidence suggests that a high IQ may increase those risks [46,47]. Dabrowski included "imaginational, and emotional domains" in his description of multiple intelligences in individuals with a high IQ [18], and other researchers have suggested these individuals are "more sensitive to existential issues" [48]. One report on suicide in children with a high IQ described them as "understanding adult situations and world events but being powerless to affect their outcomes" [49]. Some perceived "problems that the world created" as "catastrophic", and their "solution was to remove all the problems, all at once". Correspondingly, a recent literature review exploring health, care and family problems in gifted children found "emotional problems" were most common (a rate of 81%) [50], which implies a heightened level of stress associated with a high IQ. The review found "no signs of physical health and care problems" (though notably, its search terms

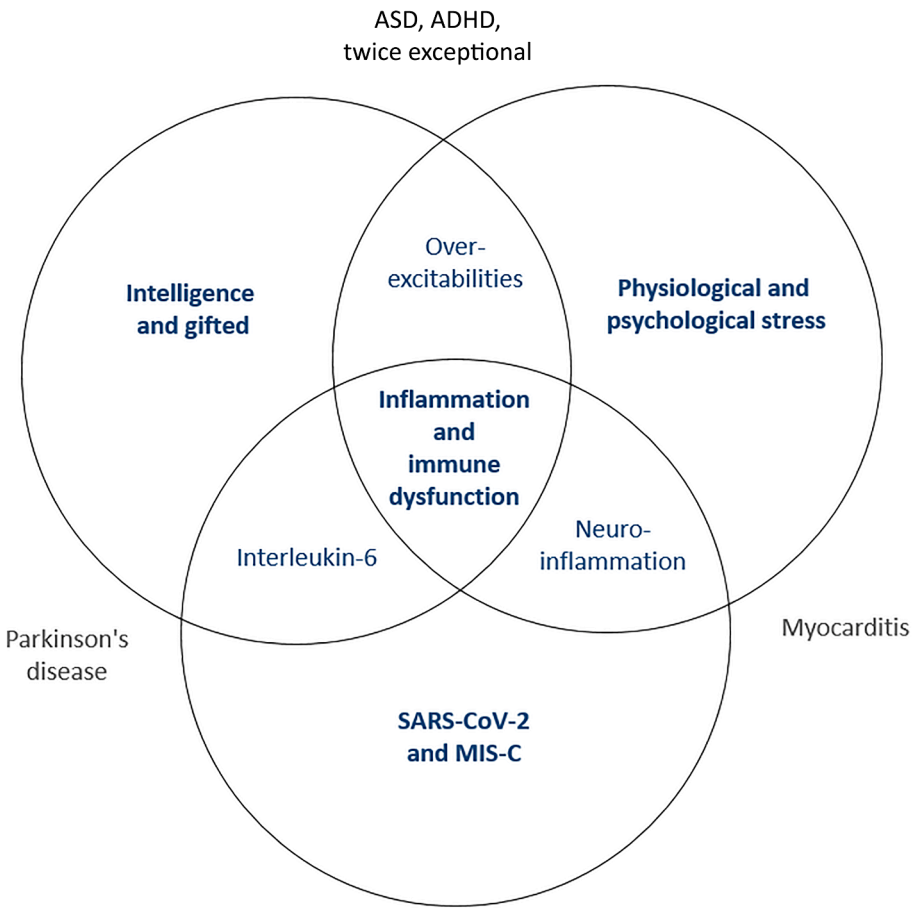

Fig. 1. Intersections of studies cited that support a potential association between a high IQ and severe paediatric COVID-19 outcomes.

included 'gifted/talented children' but not 'high IQ' or 'intelligence'), yet psychologists have argued that psychological stress *can* have a physical effect, by dysregulating the immune system [51]. Supporting our hypothesis, the role of acute stress in exacerbating pro-inflammatory cytokine induction [52] points to a potential special psychoneuroimmunological vulnerability in children with a high IQ.

Furthermore, based on the increased risk of inflammation and immune dysregulation reported in children with autism spectrum disorder (ASD) [53,54], researchers have been prompted to examine whether ASD could be a paediatric risk factor for SARS-CoV-2 [55]. This may be particularly relevant to our hypothesis given a recent synthesis report that proposed a genetic connection between ASD and a high IQ ("autism as a disorder of high intelligence" [56]). Offering "new insights and research questions into the nature and inter-relationships of intelligence, autism, and schizophrenia", the article cited genetic studies suggesting common alleles "for" autism "overlap substantially and significantly with alleles "for" high intelligence". Given these shared alleles, together with evidence of a high IQ co-occurrence in some children with attention deficit hyperactivity disorder (ADHD) [58] (a condition commonly co-existing in children with ASD [57]), it is plausible that children with a high IQ and ASD ("the twice exceptional" [59]) may also have shared, or overlapping, inflammatory vulnerability to SARS-CoV-2 infection.

Identifying similarities between autoimmune diseases and COVID-19

Based on reports of antiphospholipid syndrome, autoimmune cytopenia, Guillain-Barré syndrome and Kawasaki disease, a "crossroad" of autoimmunity and SARS-CoV2 infection has been a topic of considerable interest to researchers (reviewed by Rodríguez Y et al. [60]). Early connections between COVID-19 outcomes and MIS-C highlighted similarities with the acute multisystem inflammatory Kawasaki disease, one of the most common causes of acquired heart disease in children. Our review did not find an association between paediatric Kawasaki disease and a high IQ, other than noting a significantly higher incidence of the disease in South Asian countries (highest in Japan [61]), which rank top in international IQ lists [62]. Of relevance however, levels of IL-6 can be significantly higher when Kawasaki disease patients develop (even rarer) Kawasaki disease shock syndrome (KDSS) [63], such that treatment strategies stress the importance of "Ending powerful inflammation in the acute phase as early as possible" [64].

Kawasaki disease typically has long-term health repercussions. In research by King et al., 34% of families reported "a lasting effect", and described some affected children as "having significantly more attention difficulties" [65]. This is similar to reports of long-lasting COVID-19 symptoms of "prolonged fatigue" and "brain fog" [66], including reports in the form of anecdotal evidence of long-lasting COVID-19 symptoms occurring in children [67]. Reports of "Difficulty thinking" following SARS-CoV-2 infection have been cast in terms of concerns that the virus "may damage brain cells" [68]. King et al. also recommended lifetime cardiovascular management following Kawasaki disease [69], echoing concerns related to dysregulated immune response and acute myocarditis with COVID-19.

One more eponymous autoimmune disease to receive attention during the pandemic is Parkinson's disease [70,71], which can present with increased levels of pro-inflammatory cytokines in the brain, including IL-6 [72] and immune dysregulation [73]. Over the course of the 1918 Spanish flu pandemic, there was "a 2–3-fold-increased risk" of Parkinson's disease [74], and in October 2020, Israeli physicians

reported a single case of probable parkinsonism following SARS-CoV-2 infection [75]. Moreover, Swedish research published in the same month identified high IQ as a risk factor for Parkinson's disease [76], which reiterates previous findings reliant on occupational complexity measures [77,78]. Given that a high IQ is relatively stable from child to adulthood [79], this lends support to a potential association between high IQ and immune dysregulation following viral infection.

Evidence of myocarditis with high athletic intelligence

In several of the paediatric cases of severe COVID-19 outcomes that we present in Table 1, the children were described as exceptionally talented athletes who experienced severe cardiac complications after SARS-CoV-2 infection. In the context of our hypothesis, and the 'hyper brain, hyper body' paradigm, we treat these cases as reflecting a high physical IQ [80] or high psychomotor [18], bodily-kinesthetic [19] intelligence; they are "exceptionally gifted" athletes [22] with "high performance brains, as well as bodies" [81]. Between June and August 2020, a group of doctors in the USA performed cardiac magnetic resonance imaging on 26 competitive college athletes recovering from COVID-19 disease, and reported that 15% had "findings suggestive of myocarditis" [82]. None of the athletes tested required hospitalization when infected, but these results convinced the country's Pac-12 and Big Ten collegiate conferences to postpone games in the fall, and some top-flight collegiate players opted out entirely. Another US study of 54 student athletes recovering from asymptomatic, mild or moderate symptoms of COVID-19 reported a high prevalence of late pericardial enhancement [83]. Given doctors' warnings of exercise-induced accelerated viral replication and increased inflammation with COVID-19 [82], plus the unknown long-term effects after myocarditis [84], we encourage future research that considers high athletic intelligence as an independent variable.

Implications of the hypothesis

More thorough understandings of the relationship between intelligence and mortality and morbidity [85], and the connections between the brain and the immune system [86], remain relatively new fields of research. COVID-19 is a novel disease; therefore, researchers must examine paediatric risk factors with "very little evidence at our disposal" [87] and consider "other diseases with overlapping manifestations" [88]. We aver a potential special psychoneuroimmunological vulnerability may exist in children with a high IQ, and especially in those who develop MIS-C following SARS-CoV-2 infection. With the tendency for obituaries to celebrate life achievements, it may not be significant that the paediatric cases we present are indicative of a high IQ, though other published research demonstrates an association between high IQ and immune system health [14,17]. Certainly, IQ is challenging to identify as a clinical characteristic. Educational attainment is often used as a proxy [89], but this substitute is not entirely reliable, even in schools. A focus on "academic ability or achievement" may obscure other intelligences; plus these children are "not always high achievers" [90]. Of significant concern, children in lower socioeconomic groups are less likely to be identified, and during the pandemic, are less sheltered from the virus and more adversely affected by lockdowns [91,92]. Therefore, albeit limited by a lack of current clinical data on paediatric high IQ, testing our hypothesis through retrospective autoimmune analysis of paediatric MIS-C cases, using proxies where necessary, would provide valuable information. Furthermore, with IQ remaining relatively stable into adulthood [79], our hypothesis also warrants exploration among adult patient populations.

Numbers of severe paediatric COVID-19 outcomes worldwide are currently very small (a near zero mortality rate [93]; 0.07% children have died in the USA [94]) and an estimated 2% of the general population has a high IQ [15,85]. Via media reports alone, our review identified 27 cases where evidence of a high IQ was indicated (including 17 deaths in the USA, or 15% of the total 112 deaths reported there by October 1, 2020 [94]). Autoinflammatory evidence suggests IL-6 may amplify paediatric response to infections and contribute to a cytokine storm, and some researchers suggest, "Early detection of children with mild symptoms or an asymptomatic state, and early diagnosis of MIS-C are mandatory for the management of COVID-19 and the prevention of transmission and a severe inflammatory state" [95]. Similarly, Karpinski et al. argued the beneficial impact of understanding the relationship between high IQ and illness, and recent SJIA studies report a very low rate of MAS episodes (or milder disease) in children who were prescribed an IL-6 monoclonal antibody [28]. Therefore, in the context of SARS-CoV-2 infection, and the benefits of timely action, our hypothesis extends the challenge to increase awareness of high IQ as a potentially identifiable paediatric characteristic in immune dysregulation, exacerbated inflammatory response and COVID-19 disease susceptibility. It raises implications for how and when prophylactic medical care is provided to children. Further investigation should help clarify the evidence cited here, and may support efforts to save lives.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The datasets analyzed for this study can be found in Table 1.

Author contributions

PMH conceived of the study; PMH conducted the reviews and wrote the manuscript report drafts; MJF and BML provided study design advice and oversight; PMH, BML and MJF edited the manuscripts; all read and approved the final submission.

Consent statement/ethical approval

Not required.

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