Maternal Autoimmune Disorders and Risk of Kawasaki Disease in Offspring

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We assessed the association between maternal autoimmune disorders and offspring risk of Kawasaki disease in a longitudinal cohort of 792 108 newborns. We found that maternal autoimmune disorders, especially autoimmune thyroiditis, may be risk factors for Kawasaki disease in children, particularly young children. *(J Pediatr 2020;222:240-3).*

Kawasaki disease, an acute pediatric vasculitis frequently involving the coronary arteries, is the leading cause of acquired heart disease among children in developed countries.[1] The incidence peaks between 1 and 4 years of age.[2] Evidence places Kawasaki disease on the spectrum between an infectious disease and an autoimmune disease,[2] but risk factors are poorly understood.[1] Given the early age of onset, researchers have questioned whether prenatal or perinatal exposures may be risk factors, including maternal autoimmune disorders that may share immune pathways with Kawasaki disease.[3,4] Published evidence of a possible association between maternal autoimmune disorders and Kawasaki disease in children stems from a case-control study that was potentially underpowered.[4] In the present study, we examined the association between maternal autoimmune disorders and risk of Kawasaki disease in a longitudinal cohort of children with data from birth up to 12 years of age.

Methods

We conducted a retrospective cohort study of infants born in hospitals in Quebec, Canada between 2006 and 2016. We followed the infants over time from birth until the end of the study on March 31, 2018, to identify hospitalizations for Kawasaki disease. Infants who died at birth were excluded. We extracted data for each child from the Maintenance and Use of Data for the Study of Hospital Clientele Registry, which contains discharge summaries for all hospitalizations in Quebec. Each discharge summary contains diagnoses coded using the *International Classification of Diseases, Ninth Revision* and *Tenth Revision*. Maternal discharge summaries are linked with the infant, allowing us to identify maternal exposures.

The main exposure measure was any maternal autoimmune disorder (yes, no). We used a wide definition of autoimmunity that included rheumatologic disorders, vasculitis, and traditional autoimmune diseases (**Table I**; available at www.jpeds.com).[5] We analyzed autoimmune thyroiditis separately, because this disorder was sufficiently frequent in the data. We identified maternal autoimmune disorders from the delivery discharge summary, as well as from any other hospitalization of the mother between 1989 and 2018. As a secondary exposure measure, we considered the number of maternal autoimmune disorders (0, 1, 2, or more).

The main outcome measure was hospitalization for Kawasaki disease between 0 and 12 years of age. We identified potential confounders, including maternal age at delivery (<25, 25-34, ≥35 years), parity (0, 1, ≥2 previous deliveries), multiple birth (yes, no), preterm birth before 37 weeks gestation (yes, no), infant sex (male, female), socioeconomic deprivation (low, low-moderate, moderate, moderate-high, high, unknown), and time period at birth (2006-2008, 2009-2012, 2013-2016). Socioeconomic deprivation was determined using neighborhood-level census data on income, employment, and education.[6]

We calculated the incidence of Kawasaki disease per 100 000 person-years. Using Cox proportional hazards regression, we estimated hazard ratios and 95% CIs for the association between maternal autoimmune disorders and the risk of Kawasaki disease. We used the number of days since birth as the time scale and censored children who were never hospitalized for Kawasaki disease by the study end. We considered death to be a competing event using the Fine and Gray method. We accounted for siblings in the same family using robust sandwich estimators and verified that hazards were proportional using log (-log survival) curves.

We adjusted regression models for confounders using inverse probability weighting of the propensity score.[7]

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Table II. Incidence of Kawasaki disease according to maternal and infant characteristics

Characteristics	Total children, n	Children with Kawasaki disease, n	Person-years	Incidence per 100 000 person-years (95% CI)
Maternal autoimmune disorder				
Any	13 239	20	91 716	21.8 (14.1-33.8)
Rheumatologic*	3991	7	28 026	25.0 (11.9-52.4)
Vasculitis†	1031	<5	6408	31.2 (7.8-124.8)
Traditional autoimmune disease‡	8567	15	59 789	25.1 (15.1-41.6)
Autoimmune thyroiditis	1240	6	9321	64.4 (28.9-143.3)
No	778 869	759	5 396 414	14.1 (13.1-15.1)
Number of maternal autoimmune disorders				
≥2	809	<5	5787	51.8 (16.7-160.7)
1	12 430	17	85 929	19.8 (12.3-31.8)
0	778 869	759	5 396 414	14.1 (13.1-15.1)
Maternal age at delivery, y				
<25	127 212	122	906 160	13.5 (11.3-16.1)
25-34	529 186	507	3 685 126	13.8 (12.6-15.0)
≥35	135 710	150	896 845	16.7 (14.3-19.6)
Parity				
0	387 582	399	2 696 079	14.8 (13.4-16.3)
1	277 058	262	1 920 419	13.6 (12.1-15.4)
≥2	127 468	118	871 632	13.5 (11.3-16.2)
Multiple birth				
Yes	12 515	16	83 313	19.2 (11.8-31.3)
No	779 593	763	5 404 817	14.1 (13.2-15.2)
Preterm birth				
Yes	50 853	51	352 859	14.5 (11.0-19.0)
No	741 255	728	5 135 271	14.2 (13.2-15.2)
Infant sex				
Male	406 453	468	2 816 688	16.6 (15.2-18.2)
Female	385 655	311	2 671 442	11.6 (10.4-13.0)
Socioeconomic deprivation				
Low	140 087	143	984 900	14.5 (12.3-17.1)
Low-moderate	156 199	128	1 092 126	11.7 (9.9-13.9)
Moderate	154 764	151	1 077 082	14.0 (12.0-16.4)
Moderate-high	153 886	156	1 067 514	14.6 (12.5-17.1)
High	156 597	172	1 082 929	15.9 (13.7-18.4)
Time period				
2006-2008	206 868	225	2 190 548	10.3 (9.0-11.7)
2009-2012	325 730	334	2 354 412	14.2 (12.7-15.8)
2013-2016	259 510	220	943 171	23.3 (20.4-26.6)
Total	792 108	779	5 488 130	14.2 (13.2-15.2)

*Ankylosing spondylitis, psoriatic arthritis/psoriasis, rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, systemic sclerosis.
†Anti-glomerular basement membrane antibody disease, Behçet syndrome, Cogan syndrome, cryoglobulinemic vasculitis, eosinophilic granulomatosis with polyangiitis, giant cell arteritis, granulomatosis with polyangiitis, hypocomplementemic urticarial vasculitis, IgA vasculitis, Kawasaki disease, microscopic polyangiitis, polyarteritis nodosa, Takayasu arteritis.
‡Antiphospholipid syndrome, celiac disease, Graves disease, Guillain-Barré syndrome, autoimmune thyroiditis, myasthenia gravis, type 1 diabetes mellitus, ulcerative colitis, unspecified.

The propensity score is the probability of maternal autoimmune disease given maternal and infant characteristics, computed from logistic regression models with maternal age, parity, multiple birth, preterm birth, infant sex, socioeconomic deprivation, and time period as predictors.

We used a quadratic time interaction term to estimate hazard ratios at age 1, 2, and 5 years and calculated CIs with the delta method. We performed analyses in SAS version 9.4 (SAS Institute, Cary, North Carolina) and obtained an ethics waiver from the Institutional Review Board of the University of Montreal Hospital Centre because the data were anonymized.

Results

In this cohort of 792 108 newborns, 13 239 (1.7%) had a mother with an autoimmune disorder and 779 (0.1%) were hospitalized for Kawasaki disease during the follow-up period (Table II). The incidence of Kawasaki disease was greater in the presence of maternal autoimmune disorder compared with no autoimmune disorder. The incidence of Kawasaki disease was substantially higher in the presence of 2 or more autoimmune disorders. Among the mothers of children with Kawasaki disease, 95% of those with autoimmune disease were diagnosed in the period before delivery.

The presence of a maternal autoimmune disorder was associated with the risk of Kawasaki disease before age 12 years (Table III). Compared with no maternal autoimmune disorder, the risk of Kawasaki disease was 1.84-fold greater in the presence of a rheumatologic disorder, 1.5-fold greater in the presence of vasculitis, and 1.81-fold greater in the presence of a traditional autoimmune disorder. The magnitude of most associations was stronger early in childhood. At age 1 year, the risk of Kawasaki disease was 2.21-fold greater with maternal vasculitis, 2.57-fold greater with a maternal traditional autoimmune disease, 10.98-fold greater with maternal autoimmune thyroiditis, and 3.63-fold greater with multiple maternal autoimmune disorders.

Table III. Associations between maternal autoimmune disorders and risk of Kawasaki disease by age 12 years

Disorders	Hazard ratio (95% CI)*			
	1 year	2 years	5 years	All ages
Maternal autoimmune disorder				
Any	1.75 (1.51-2.03)	1.69 (1.47-1.94)	1.32 (1.10-1.58)	1.58 (1.39-1.79)
Rheumatologic	1.65 (1.42-1.91)	1.70 (1.48-1.95)	2.06 (1.77-2.41)	1.84 (1.63-2.09)
Vasculitis	2.21 (1.86-2.62)	1.87 (1.61-2.16)	0.57 (0.42-0.79)	1.50 (1.32-1.71)
Traditional autoimmune disease	2.57 (2.19-3.00)	2.20 (1.91-2.52)	0.73 (0.56-0.96)	1.81 (1.59-2.04)
Autoimmune thyroiditis	10.98 (9.42-12.81)	8.11 (7.15-9.21)	0.97 (0.72-1.31)	6.10 (5.48-6.80)
None	Reference	Reference	Reference	Reference
Number of autoimmune disorders				
≥2	3.63 (1.14-11.54)	3.45 (1.07-11.10)	2.42 (0.51-11.49)	3.69 (1.16-11.73)
1	1.69 (0.96-2.97)	1.60 (0.97-2.66)	1.12 (0.49-2.60)	1.46 (0.91-2.34)
0	Reference	Reference	Reference	Reference

*Hazard ratio for maternal autoimmune disorder vs no disorder, adjusted for maternal age at delivery, parity, multiple birth, preterm birth, infant sex, socioeconomic deprivation, and time period.

Discussion

In this study of 792 108 infants with 5.4 million person-years of follow-up, maternal autoimmune disorders were associated with an increased risk of Kawasaki disease in children up to 12 years of age. The associations were more prominent for Kawasaki disease occurring early in childhood, especially at age 1 year. Maternal rheumatologic disorders, vasculitis, and traditional autoimmune diseases, such as autoimmune thyroiditis, all tended to be associated with the risk of Kawasaki disease.

Few previous studies have assessed whether maternal autoimmune disorders increase the risk of Kawasaki disease in offspring. A case-control study of 1019 children with Kawasaki disease in the US found a nonsignificant association with maternal autoimmune disorders during pregnancy, but asthma was included in the definition of autoimmunity.[4] The American Autoimmune Related Diseases Association does not consider asthma an autoimmune disease.[5] A study of 240 children found that a family history of autoimmune thyroiditis was associated with Kawasaki disease among children with celiac disease.[8] Newborns whose mothers have autoimmune thyroiditis have abnormal levels of inflammatory cytokines and lymphocyte subsets in cord blood,[9] factors implicated in the pathogenesis of Kawasaki disease.[2] In our data, maternal autoimmune thyroiditis was strongly associated with the risk of Kawasaki disease in offspring, a notable finding in light of the tendency for autoimmune thyroiditis to cluster with other autoimmune diseases.[10]

Although evidence that Kawasaki disease is a true autoimmune disease is weak,[2,11] the association with autoimmune maternal disorders reinforces the possibility of a genetically determined immune component. Kawasaki disease clusters in families,[12-14] and genome-wide association studies show that single nucleotide polymorphisms in the immune-related genes *BLK* and *CD40* are implicated in Kawasaki disease, as well as in lupus and rheumatoid arthritis.[15] Genome-wide association studies also indicate that immune loci for cytokines are inherited, and that maternal genes may influence neonatal levels of immune cytokines involved in early inflammatory responses owing to maternal–infant cross-genetic interaction.[16] Children with Kawasaki disease have elevated levels of B cell-activating factor found in lupus and rheumatoid arthritis[3] and high titers of anti-endothelial autoantibodies found in systematic vasculitis and other vascular diseases.[11]

Studies have implicated microchimerism, or transfer of maternal cells to the fetus, in the pathogenesis of inflammatory diseases in childhood.[17,18] Maternal cells have been found in myocardial tissue of infants, and it has been proposed that attempts to clear foreign maternal cells may result in a localized autoinflammatory response in young children.[17]

Our study has some limitations. We used administrative hospital data, and possible coding errors may have attenuated the associations. We included a range of autoimmune disorders but were limited to diseases that were sufficiently frequent in the data. As such, we could not analyze specific autoimmune disorders apart from autoimmune thyroiditis owing to low frequencies. We did not have information on ethnicity, paternal autoimmune disease, or immunosuppressive biological therapy. Future studies are needed to determine whether the associations in this study are generalizable to other settings.

This longitudinal cohort study of 792 108 children found that maternal autoimmune disorders may be associated with the risk of Kawasaki disease in young children. The associations raise the question of whether Kawasaki disease may be genetically determined, although more research is needed to explore this pathway. In the meantime, Kawasaki disease should be suspected in children with coronary vasculitis and a maternal history of autoimmune disorders. ■

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Table I. Diagnostic codes for maternal autoimmune disorders

Disorders*	*International Classification of Diseases Ninth revision/Tenth revision* codes
Rheumatologic	
Ankylosing spondylitis	720/M45
Psoriatic arthritis/psoriasis	696.0, 696.1/L40, M07.0, M07.1, M07.2, M07.3, M09.0
Rheumatoid arthritis	714/M06
Sjögren syndrome	710.2/M35.0
Systemic lupus erythematosus	710.0/M32
Systemic sclerosis	710.1/M34.9, M34.8, M34.0, M34.1
Vasculitis	
Antiglomerular basement membrane antibody disease (Goodpasture)	446.2/M31.0
Behçet syndrome	136.1, 711.2, 616.51/M35.2, N77.8
Cogan syndrome	370.52/H16.3
Cryoglobulinemic vasculitis	273.2/D89.1
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	-/M30.1
Giant cell arteritis	446.5/M31.5, M31.6
Granulomatosis with polyangiitis	446.4/M31.3
Hypocomplementemic urticarial vasculitis	581.2, 582.2, 583.2/M31.8
IgA vasculitis (Henoch-Schönlein purpura)	287.0/D69.0
Kawasaki disease	446.1/M30.3
Microscopic polyangiitis	-/M31.7
Polyarteritis nodosa	446.0/M30.0, M30.8
Takayasu arteritis	446.7/M31.4
Traditional autoimmune diseases	
Antiphospholipid syndrome	289.81/D68.6
Celiac disease	579.0/K90.0
Graves disease	242.0/E05.0
Guillain-Barré syndrome	357.0/G61.0
Autoimmune thyroiditis	245.2/E06.3
Myasthenia gravis	358.0/G70.0
Type 1 diabetes mellitus	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93/E10, 0245
Ulcerative colitis	556/K51
Unspecified	279.49/M35.9

*We did not include Addison disease, alopecia areata, autoimmune hemolytic anemia, autoimmune hemophilia, autoimmune hepatitis, autoimmune polyendocrinopathy, bullous pemphigoid, Duhring–Brocq disease, Evans syndrome, Lambert–Eaton myasthenic syndrome, multiple sclerosis, pemphigus, Schmidt syndrome, stiff-person syndrome, and vitiligo, because these disorders were rare.