Annals of Pediatric Research

Research Artile
Published: 31 Aug, 2020

Do Severe Complications Like Aneurysms from Kawasaki and Kawasaki-Like Infections Arise in Children with Underlying Articulo-Autonomic Dysplasia/Ehlers-Danlos Syndrome?

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Abstract

A hypothesis is presented that some patients with severe Kawasaki or Kawasaki-like disease from COVID-19 may have underlying Ehlers-Danlos syndrome or related diseases in the arthritis-adrenaline disorder category. Sign and symptom frequencies from 710 patients having standard evaluations for Ehlers-Danlos syndrome are compared to those cited in reviews of Kawasaki disease with parallels in eye complaints, rashes and reactive skin, swallowing and gastrointestinal difficulties, pulmonary disease, and joint pain or arthritis. Mast cell mediators including complement factors, interleukin, and immune factors like cluster of differentiation 40 that may show chronic changes in arthritis-adrenaline disorder/Ehlers-Danlos syndrome are elevated in Kawasaki along with the Von Willebrand Factor that shows mutation by genomic analysis in some Ehlers-Danlos patients. Outlined procedures for hypothesis support or refutation include clinical observation for finding of tissue laxity (hyper mobility-clumsiness, skin elasticity, and skeletal change) and those of reciprocal dysautonomia (gastrointestinal problems from irritable bowel/mast cell activation disorder) in Kawasaki-like patients. Genomic analyses of gene structure and epigenetic regulation focused on molecules mediating ED's predispositions and Kawasaki inflammatory responses can provide additional testimony. The approach highlights new abilities to detect genetic and epigenetic factors that determine susceptibility to infection and, from their modulation by inflammation, promises new avenues of molecular therapy.

Keywords: Arthritis-Adrenaline disorder; Ehlers-Danlos syndrome; Kawasaki disease; Dysautonomia; Mast cell activation disorder; Aneurysms; Irritable bowel disease

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Received Date: *13 Jul 2020*
Accepted Date: *28 Aug 2020*
Published Date: *31 Aug 2020*

Citation:
Wilson GN, Tonk VS. Do Severe Complications Like Aneurysms from Kawasaki and Kawasaki-Like Infections Arise in Children with Underlying Articulo-Autonomic Dysplasia/Ehlers-Danlos Syndrome?. Ann Pediatr Res. 2020; 4(3): 1042.

Introduction

Ehlers-Danlos Syndrome (EDS) and related connective tissue dysplasias have lax tissue that results in joint, skin, and blood vessel laxity [1-3]. The tissue and joint laxity results in wear-and-tear osteoarthritis frequent joint injuries, and a more deformable skeleton that leads to scoliosis, flat feet, and toeing-in or -out with clumsiness and additional injury susceptibility. Most emphasized by the dermatologists Ehlers and Danlos were the skin elasticity and fragility that lead to atypical scars and even to rupture with trauma. Underappreciated by prior examiners and present diagnostic criteria is the autonomic reaction to lax and distensible vessels in EDS, the lower body blood pooling eliciting periodic adrenergic, "fight-or flight" increases in heart rate and blood pressure to restore cerebral circulation [4,5]. This sympathetic activation or dysautonomia ramps up inflammatory and immune responses including mast cell activation disorder while producing the dizziness, panic-anxiety, and fatigue of Postural Orthostatic Tachycardia Syndrome and the suppression of parasympathetic bowel motility that presents as irritable bowel syndrome [6-8]. The reciprocal tissue laxity and dysautonomia in EDS and related disorders is optimally described as an arthritis-adrenaline disorder category due to an underlying Articulo-Autonomic Dysplasia process (both AAD), a Nosology that facilitates diagnosis and leads directly to powerful preventive and therapeutic strategies [5,9].

Because the dramatic patients of Ehlers and Danlos cast EDS as a rare and extreme disorder, because children are naturally hyper mobile, and because the more severe complications of injury

Table 1: Finding frequencies in arthritis-adrenaline disorder/EDS and Kawasaki disease.

EDS [5]	Female[1] %	Male[2] %	Kawasaki children[3] [9-11]	All %
Finding frequencies/prevalences known in Kawasaki				
Male: female prevalence	1:4-5		Male: female prevalence	1.6:1
Dizygotic/monozygotic twin concordance	29/60[4]		Dizygotic/monozygotic twin concordance	13.3/14.1
Presence in sibling	25[4]		Presence in sibling	0.025
Transient rashes (primarily facial and truncal)	42	27	Polymorphous rash (primarily truncal)	>90
Eye complaints (dryness, inflammation)	35	23	Bilateral conjunctivitis	80-90
Reactive skin, mucosa (urticaria, lesions)	52	18	Oral mucoepithelial inflammation, fissured lips	80-90
Swallowing difficulty	29	8.9	Strawberry tongue, pharyngitis	80
Skin fragility (scarring, slow healing)	43	23	Extremity desquamation	80
Reactive airway disease, shortness of breath	43	29	Early cough, coryza, dyspnea	>50
Cervical lymphadenopathy	rare	rare	Cervical lymphadenopathy (1 node >1.5 cm)	50
Nausea, vomiting	52	27	Vomiting, inanition	37
Aneurysms-diffuse	0.56	0	Aneurysms-mostly coronary artery	20-255
Muscle weakness	37	17	Muscle weakness	19
Abdominal pain, bloating	70	47	Abdominal pain	18
Arthralgia/arthritis	89	63	Arthralgia/arthritis	7.5-15
Bladder issues (frequency, UTI)	46	13	Pyuria	?5
Gall bladder inflammation	18	5.9	Gall bladder hydrops	rare
Acute bowel obstruction	rare	rare	Acute bowel obstruction	rare
Findings frequencies to be ascertained in Kawasaki [10-12] and Kawasaki-like [13] patients				
Popping of joints	87	68		
Elastic skin	77	58		
Hyper mobility--Beighton score above 6-7 of 8-9	59	29		
Signs of lower body blood pooling	57	38		
Deformations like flat feet/toeing in-out	31/15	30/14		
Early colic-feeding problems as harbingers of IBS	30	31		
Clumsiness walking with frequent falls	22	14		
Altered mediators of inflammation in EDS			**Altered mediators of inflammation in Kawasaki**	
Complement component 1R [complement factor)			C3/C4 activation products (complement factors)	
Mast cell mediators-- interleukins 1, 4, 6, 37; fibrillin-1; transforming growth factor-beta; tumor necrosis factor α; tryptase; histamine			Cluster of differentia 40; Tumor necrosis factor α Interleukin 18	
von Willebrand factor gene altered in 12 patients[4]			von Willebrand factor antigen	

[1]Usually under age 5 but adult cases reported; [2]in 596 females; [3]in 114 males; [4]from reference [9]; [5]similar to population prevalence in Western countries [11]

and autonomic imbalance present most obviously in the teenage or adult years, affected children who would benefit greatly from joint protection are rarely diagnosed. The many (60%) who have arthralgia are usually told they have "growing pains" while the few (<1%) with cardiac issues like aortic dilation are not evaluated unless they have more obvious and severe disorders like Marfan syndrome [2]. The under-recognition of affected children, frequent exacerbation of connective tissue and dysautonomia symptoms by streptococcal or mononucleosis infections, more severe and persistent course of these infections, and their slow healing in patients with EDS raises the question of whether some children with more severe Kawasaki disease [10-12] and Kawasaki-like infections [13] might have underlying EDS [1-5]. We outline procedures for clinical and genomic evaluation that could support or reject this hypothesis.

Methods

Frequent historical and physical findings in EDS were noted in 956 patients, their frequencies calculated in a subsequent 710 patients (596 females and 114 males) using standard forms [5]. Whole exome sequencing was performed mainly through the GeneDx© Company after ascertaining insurance coverage. Consent for testing, for report of results of secondary findings not necessarily related to EDS, and for de-identified publication of results was obtained by a GeneDx genetic counselor, the nature of testing and consent for de-identified publication also discussed by the ordering physician. GeneDx© performance of whole exome sequencing was by standard methods [14], yielding DNA variants qualified as of uncertain significance, likely pathogenic or pathogenic. Benign or likely benign DNA variants like the single nucleotide polymorphisms used for ancestry or disease association are not reported in whole exome sequencing that yields an average 30,000 DNA changes per individual. Only exonic or exon-intron junctional DNA sequence changes that significantly alter protein amino acid sequence or RNA splicing are reported and qualified as to their significance, use of the genetic code a considerable

advantage of looking at gene regions (exons) rather than at the entire genome with its 99.5% of intragenic DNA [15].

Among 727 of the 1656 patients who had adequate insurance coverage of the whole exome sequencing (almost 50% having zero out-of-pocket costs), 440 (61%) had a DNA reported with only 16 (4.4%) scored as related to the EDS-dysautonomia symptoms (likely pathogenic or pathogenic). However, recognition of the reciprocal tissue laxity-dysautonomia or articulo-autonomic dysplasia process facilitated a novel approach to DNA variant interpretation, qualifying 148 or 20% of the 727 patients tested to have variants of likely relevance to (strong or evident diagnostic utility for) and another 227 or 32% to have variants of possible relevance to (uncertain or conditional diagnostic utility for) EDS. These results added many novel genes from that for mitochondrial polymerase G [16] to those like collagen type V genes that can cause EDS, the former typical of those causing autonomic imbalance with reciprocal joint laxity [9], the latter typical of connective tissue/vessel laxity that produce dysautonomia [5]. Among the newly associated genes with EDS as part of the arthritis-adrenaline disorder category were nine patients with mutations in the Von Willebrand Factor (VWF) gene that interacts with the collagen type III gene that is associated with vascular EDS [9,17]. These results emphasize the ability to objectively measure genetic predisposition to EDS-dysautonomia that might exacerbate symptoms in those patients who contract Kawasaki-like disease.

Results

Table 1 compares prevalences and finding frequencies in the 710 patients with standard ED's evaluations with those known and worth looking for in Kawasaki-like diseases [5,10-12]. It is of course expected that complications of a chronic disease that accrue over time would be very different from those appearing acutely in an infectious disease, but we point out signs and symptoms typical of EDS predisposition that might be exacerbated to produce a subset of Kawasaki patients who have more severe findings. Compromising this comparison are the greater female affliction in EDS and the fact that children under 12 comprise only 15% of the indicated EDS patients. However, the finding frequencies to be ascertained in Kawasaki (Table 1, lower rows) are similar or increased in EDS children compared to those given for adults.

Findings of skin, mucosal, and pulmonary inflammation in Kawasaki that occur in 50% to 90% of patients have parallels in the rashes and reactive skin that arise from mast cell activation disorder in EDS, as do gastrointestinal symptoms like vomiting or nausea. As many as 21% of females and 25% of males with EDS are underweight (BMI less than 19) due to the gastrointestinal symptoms of IBS and the food-medication intolerances (68% of females, 29% of males) from MCAD. Muscle weakness, abdominal pain, and joint pain-inflammation are shared by the two patient groups, while gall bladder and bladder inflammation, relatively rare in Kawasaki, have potential precedents in the EDS population. Bowel obstruction and perforation or aneurysms are only common in the rare vascular type of EDS, none of these patients having typical facial or skin findings of that disorder. Also, the majority of the 351 of 710 (50%) who had whole exome sequencing excluded pathogenic changes in the associated collagen type III gene (5 of them did have DNA variants in the collagen type III gene but these were not qualified as having diagnostic utility for vascular EDS).

The findings to be ascertained in Kawasaki or Kawasaki-like patients (lower rows, Table 1) are very obvious in children. The four bilateral manoeuvres of the Beighton scale (bending the fifth finger back beyond 90 degrees, bringing thumb to touch forearm with bent wrist, assessing extension of elbows and knees 10 to 15 degrees beyond the horizontal) that comprise 8 of the 9 points would be performed passively in young children; the ninth maneuver of touching palms to floor without knee flexion can be used only in those old enough to cooperate [1-3,5]. Elastic skin can be assessed by stretching the skin around jaw or on forearm to see if it forms a thin (epidermal) fold of over an inch or so, while blood pooling can manifest as leg-foot discolor or venous dissention when standing or held upright. Most parents will recall severe colic, feeding problems, or clumsiness; children older than a year or so can be watched for clumsiness, flat feet, or toe-deviations when walking.

Additional measures of inflammatory and mast cell mediators are needed in both disorders, those in EDS extrapolated from mast cell research [6] or from whole exome sequencing results that showed the nine patients with mutations in the Von Willebrand Factor gene [9]. The correlation of complement factors, component 1R being mutated in the rare periodontal type of EDS that has up to a 16% rate of aneurysms and C3/C4 activation products being elevated but probably not specific for Kawasaki [18]. If the modulation of fibrillin-1 and transforming growth factor-beta mediators related to aortic dilation in Marfan syndrome and the tryptase released by mast cell activation play a role in aneurysms, then study of these pathways and those of interleukins (IL1, 3, 6, 37, 18 mentioned in Table 1, lower panel) could lead to new therapies in Kawasaki-like diseases [19].

Discussion

The ability to scan many genes for mutations and DNA methylation patterns using genomic approaches is providing new insights into epigenesis, the modification of gene expression by environmental factors, and the interaction of into genes and environment (multifactorial determination) that produces common diseases like arthritis-adrenaline disorder/EDS and diabetes [20]. Although it has long been appreciated that gene changes in disorders like sickle cell anemia confer specific infection risks [21], genetic and epigenetic factors that make infection lethal in one person and asymptomatic in their neighbor has mostly focused on immune deficiencies like the hyper-immunoglobulin M disease associated with Cluster of Differentiation 40 (CD40) implicated in the Kawasaki inflammatory response (Table 1, last row) [22]. The abnormal increase in immunoglobulin M illustrates that an overly aggressive and unbalanced inflammatory response to infection can cause more severe disease, as was postulated for the many young and healthy adults who succumbed to the 1918 influenza epidemic [23].

Patients with EDS as indicated by the underlying mechanism of articulo-autonomic dysplasia have enhanced inflammatory responses through their reciprocal adrenergic stimulation and mast cell activation, manifest as flushing, migratory erythematous rashes, urticaria and reactive skin, pruritis, angioedema, reactive airway disease, gastrointestinal disturbances, and a variety of food-medication intolerances as partially listed in Table 1. In addition, their lax and more easily distended vessels lead to lower body blood pooling and hypotension that leads to the orthostatic dizziness, syncope, and compensatory tachycardia of postural orthostatic tachycardia syndrome, predispositions that could make them more susceptible to septic shock. A last Genomic technology now allows definition of susceptibility factors in any infectious disease, whether looking at common infections in particular genetic diseases as with

sickle cell or looking for genetic disorders and epigenetic changes in severe infections as we propose here for Kawasaki-like diseases [21,10-12]. Looking for clinical signs of arthritis-adrenaline disorder and its component connective tissue dysplasias like EDS is readily done by measuring hyper mobility, skin elasticity, clumsiness and other signs in patients with Kawasaki (Table 1, lower rows). The complementary genomic approach can first define germ line predispositions by whole exome sequencing, and then pursue inflammatory mediators that add epigenetic insult to Kawasaki-like disease using the parallels in the last row of Table 1. These twin approaches can quickly determine whether the genetic factors in Kawasaki susceptibility suggested by the 13% to 14% twin concordance (Table 1, upper rows) include predisposition to the arthritis-adrenaline disorder category and its member diseases like EDS.

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