Autoimmunity Reviews 18 (2019) 369–381

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Juvenile polyautoimmunity in a rheumatology setting

Clara Malagón[a,b,*], Maria del Pilar Gomez[b,c], Catalina Mosquera[a,b], Camilo Vargas[b,d,e], Tatiana Gonzalez[b,f], Cristine Arango[b,g], Lorena Martin[b,h], Pilar Perez[b,i], Laura Amaya-Uribe[j], Nicolas Molano-Gonzalez[j], Juan-Manuel Anaya[j,**]

[a] Postgraduate Pediatric Rheumatology Program, Universidad El Bosque, Bogota, Colombia
[b] Grupo de Reumatología e Inmunología Pediátrica (GRIP), Colombia
[c] Faculty of Medicine, Universidad Libre, Cali, Colombia
[d] Faculty of Medicine, Universidad del Valle, Cali, Colombia
[e] Inflammation and Autoimmunity Unit, Hospital Universitario del Valle, Cali, Colombia
[f] Faculty of Medicine, Universidad de Cartagena, Cartagena, Colombia
[g] Faculty of Medicine, Universidad Tecnológica de Pereira, Pereira, Colombia
[h] Faculty of Medicine, Pontificia Universidad Javeriana, Bogota, Colombia
[i] Faculty of Medicine, Universidad Surcolombiana, Neiva, Colombia
[j] Center for Autoimmune Diseases Research (CREA), School of Medicine and Health Sciences, Universidad del Rosario, Bogota, Colombia.

ARTICLE INFO

Keywords:
Autoimmune diseases
Polyautoimmunity
Juvenile patients
Autoimmune tautology
Systemic lupus erythematous
Juvenile idiopathic arthritis

ABSTRACT

Overt polyautoimmunity (PolyA) corresponds to the presence of more than one well-defined autoimmune disease (AD) manifested clinically in a single patient. The current study aimed to describe the main characteristics of juvenile PolyA in a pediatric rheumatology setting and analyze the chronological aspects, index cases, familial autoimmunity, and clustering pattern. This was a cross-sectional and multicenter study in which 313 children with overt PolyA were included. Patients were systematically interviewed and their medical records reviewed using a questionnaire that sought information about demographic, clinical, immunological, and familial characteristics. A hierarchical cluster analysis was done to determine similarities between autoimmune diseases based on PolyA. PolyA occurred simultaneously in 138 (44%) patients. Multiple autoimmune syndrome was observed in 62 (19.8%) patients. There were 25 index diseases of which, systemic lupus erythematosus (SLE, n = 134, 42.8%), juvenile idiopathic arthritis (JIA, n = 40, 12.7%), Hashimoto's thyroiditis (HT, n = 24, 7.66%), immune thrombocytopenic purpura (ITP n = 20, 6.39%), antiphospholipid syndrome (APS, n = 15, 4.79%), and vitiligo (VIT, n = 15, 4.79%) were the most frequent and represented 79.23% of the total number of patients. Familial autoimmunity influenced PolyA. A high aggregation of autoimmunity was observed (λ_r = 3.5). Three main clusters were identified, of which SLE and APS were the most similar pair of diseases (based on the Jaccard index) followed by HT and JIA, which were related to ITP and Sjögren's syndrome. The third cluster was composed of localized scleroderma and VIT. Our findings may assist physicians to make an early diagnosis of this frequent condition. Pediatric patients with ADs should be systematically assessed for PolyA.

Abbreviations: AAD, autoimmune Addison's disease; ADs, autoimmune diseases; AE, autoimmune encephalitis; AHP, autoimmune hypoparathyroidism; AIH, autoimmune hepatitis; AIHA, autoimmune hemolytic anemia; AIL, autoimmune leukopenia; AIP, autoimmune pancreatitis; AIT, autoimmune thrombocytopenia; AITD, autoimmune thyroid disease; APES, autoimmune polyendocrine syndrome; APS, antiphospholipid syndrome; AS, ankylosing spondylitis; AU, alopecia universalis; CD, celiac disease; CLT, chronic lymphocytic Thyroiditis; DL, discoid lupus; FDR, first-degree relatives; GD, Graves' disease; GN, glomerulonephritis; HT, Hashimoto's thyroiditis; IBD, inflammatory bowel disease; ITP, immune thrombocytopenic purpura; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; KFD, Kikuchi-Fujimoto disease; LoS, localized scleroderma; MAS, multiple autoimmune syndrome; MG, myasthenia gravis; PBC, primary biliary cholangitis; PSO, psoriasis; PolyA, polyautoimmunity; RA, rheumatoid arthritis; RP, Raynaud's phenomenon; SCL, scleritis; SD, standard deviation; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSc, systemic sclerosis; T1D, type 1 diabetes; U, uveitis; UC, ulcerative colitis; UV, urticarial vasculitis; VIT, vitiligo

* Correspondence to: C. Malagón: Postgraduate Pediatric Rheumatology Program, Universidad El Bosque, Bogota, Colombia.
** Correspondence to: J. M. Anaya: Center for Autoimmune Diseases Research (CREA), Cra. 26-63-B-51, Bogota, Colombia.
E-mail addresses: claramalagonmd@gmail.com (C. Malagón), juan.anaya@urosario.edu.co (J.-M. Anaya).

https://doi.org/10.1016/j.autrev.2018.11.006
Received 6 November 2018; Accepted 10 November 2018
Available online 14 February 2019
1568-9972/

1. Introduction

Autoimmune diseases (ADs) include a wide range of organ specific and systemic conditions that share several clinical signs and symptoms as well as pathogenic mechanisms (i.e., the autoimmune tautology) [1,2]. Characteristically, ADs tend to cluster within patients (i.e., polyautoimmunity, PolyA) and families. Two types of PolyA have been described: overt PolyA, which corresponds to the presence of more than one well-defined AD manifested clinically in a single patient, and latent PolyA which corresponds to the presence of autoantibodies not directly related to the underlying AD but with predictive value for an additional AD (e.g., the presence of anti-citrullinated protein antibodies in Sjögren's syndrome (SS), or the presence of anti-thyroperoxidase antibodies in euthyroid patients with ADs) [3–5].

There are differences in the epidemiology and clinical course of ADs among pediatric, adult, and senile groups [6–21]. The most prevalent ADs in adults are rheumatoid arthritis (RA), Hashimoto's thyroiditis (HT), systemic lupus erythematosus (SLE), and SS while in pediatric populations, the most frequent ADs are juvenile idiopathic arthritis (JIA), SLE, autoimmune myopathies, and scleroderma [7,14,15]. For instance, juvenile SLE corresponds to about 20% of SLE cases. The sex ratio is different from what is observed in adults and senile patients. Systemic manifestations including nephritis, neuro-psychiatric disease, and cytopenias are more common in juvenile SLE at presentation than in adults. Despite the fact that the immunosuppressive treatment has improved the survival rate, the organ damage index is higher for juvenile patients compared to adults. Ethnicity can also differentially influence adults and children. Juvenile SLE may have a more severe course in African-American, Hispanics, and Asian patients than in Caucasians [16,17]. Juvenile HT may frequently be asymptomatic or transient. The prevalence of Grave's disease (GD) in children is much lower than HT just as is the case in the adult population [18]. Autoimmune cytopenias are common in children [19]. As the first cause of chronic arthritis in children, JIA is a very heterogeneous disease and may precede or be followed by another AD [20].

The most common organ specific ADs that affect endocrine glands and the most common endocrinopathies in children are HT and Type 1 diabetes mellitus (T1D). Both are reported in association with systemic and organ-specific ADs [9].

Localized scleroderma (LoS) is 5–7 times more common than systemic sclerosis (SSc) in children [10]. Antiphospholipid syndrome (APS) has been reported in juvenile patients with an increasing frequency and also as part of different patterns of PolyA [11]. In contrast, SS, multiple sclerosis, and some organ specific ADs are more frequent in adults than in children [12,13].

The natural history of ADs also shows differences between adult and juvenile patients. For instance, autoimmune thrombocytopenia (AIT) may be a transient and benign entity in pediatric patients while, in adults, the course tends to be chronic and frequently evolves towards SLE [22].

Most of the research on overt PolyA has been done on adults while the same research in the juvenile population mainly corresponds to case reports and some series of patients [11,23–42]. Nevertheless, and as mentioned above, the coexistence of some ADs in juvenile patients including SLE and APS [43], vitiligo (VIT) and HT [8], and T1D and HT [9,30,44] is well-known. However, since the analysis of the general characteristics, chronologic aspects, and clustering patterns of juvenile PolyA have been not fully evaluated, a study of a large series of juvenile patients with overt PolyA was undertaken in an attempt to address such topics.

2. Patients and methods

2.1. Patients

This was a cross-sectional and multicenter study in which 313 children with PolyA were included. Patients were assessed at 15 pediatric rheumatology clinics in five different Colombian cities by researchers/pediatric rheumatologists belonging to the “Grupo de Reumatología e Inmunología Pediátrica” (GRIP). The period of the study was from June 2015 to June 2018. Juvenile patients (i.e., under 18 years) with juvenile onset ADs (i.e., before the 16th birthday) meeting international criteria for ADs were included. Patients with undifferentiated conditions were excluded. Each patient was evaluated by a pediatric rheumatologist at each participating center. The information on patient demographics and cumulative clinical and laboratory data was obtained by physical examination, interview, and chart review.

All data were collected in an electronic and secure database. Patients having two ADs were classified as having overt PolyA. When three or more ADs coexisted, patients were classified as having multiple autoimmune syndrome (MAS) [45]. The first identified AD was considered the index disease [46]. Concerning the sequence in which ADs appeared, those diagnosed at the same time or within a lag period of 6 months were considered “simultaneous” (i.e., synchronous). When this interval was longer than 6 months, diseases were classified as “sequential”. The additional ADs were nominated as second, third, and even fourth disease.

The following ADs were studied and patients were classified based on internationally validated criteria for diseases including SLE [47], JIA [48,49], HT [50], GD [51], idiopathic thrombocytopenic purpura (ITP) [52], APS [53,54], VIT [55], juvenile dermatomyositis (JDM) [56], LoS [57], glomerulonephritis (GN) other than lupus nephritis (e.g., IgA GN, membranoproliferative GN, mesangial GN) [58–60], autoimmune leukopenia (AIL) [61,62], discoid lupus (DL) [63], SS [64] (although these criteria are for adult patients, they were also considered in this study); urticarial vasculitis (UV) [65], T1D [66], uveitis (U) [67], autoimmune hemolytic anemia (AIHA) [68], alopecia universalis (AU) [69], psoriasis (PSO) [70], Raynaud's phenomenon (RP) [71], inflammatory bowel disease (IBD) [72], autoimmune encephalitis (AE) [73], scleritis (SCL) [74], autoimmune hepatitis (AIH) [75], autoimmune hypoparathyroidism (AHP) [76], SSc [77], autoimmune Addison's disease (AAD) [78], Kikuchi-Fujimoto disease (KFD) [79], myasthenia gravis (MG) [80], and autoimmune pancreatitis (AIP) [81].

The presence of familial autoimmunity and familial autoimmune disease [82] was assessed by interviewing the patients and, in most of the cases, by clinical evaluation of the affected family members as previously reported [83]. First-degree relatives (FDR) included parents and siblings. Extended family included grandparents, aunts, uncles and cousins.

2.2. Statistical methods

Categorical variables are described with absolute and relative frequencies while continuous variables are described with mean and standard deviations. Bivariate analysis was done to evaluate associations between pairs of variables. Chi Square test and Kruskall-Wallis test were used accordingly.

In order to determine similarities between diseases based on their co-occurrence (i.e., PolyA), a hierarchical cluster analysis was done using the ward agglomeration method and the Jaccard index as the similarity measure. This is an asymmetric distance that takes into account the co-occurrence of diseases regardless of the time of appearance while omitting simultaneous absences in patients in order to calculate the index [84]. Statistical analysis was done in R version 3.4.4 [85].

3. Results

3.1. General characteristics

A total of 313 patients were included. The general characteristics of the patients are presented in Table 1.

Table 1
General characteristics of 313 pediatric patients with polyautoimmunity.

Characteristic	N	Mean	SD
Sex (Female)	269 (86%)		
Age at onset AD1 (years)	313	10.45	3.67
Follow-up (months)	312[a]	55.90	43.73
Simultaneity[b]	138 (44)		
ANAs (%)	248/307 (80.7)		
ENAs (%)[c]	171/255 (67.05)		
ACA (%)	125/211 (59.24)		
LAC (%)	103/204 (50.04)		
Anti-thyroid antibodies (%)[d]	118/234 (50.42)		
Rheumatoid factor (%)	21/85 (24.70)		
Anti-DNA antibodies (%)	157/220 (71.36)		

Abbreviations: AD: autoimmune disease; ANAs: antinuclear antibodies; ENAs; anti-extractable nuclear antigen antibodies; ACA: anti-cardiolipin antibodies; LAC: lupus anticoagulant.

[a] One patient died soon thereafter the diagnosis.

[b] Corresponds to ADs diagnosed at the same time (i.e., synchronous), or during a period no longer than 6 months.

[c] At least one of the following: anti-Ro, anti-La, anti-Sm, anti-RNP.

[d] At least one of the following: anti-TPO or anti-Tg antibodies. Since "in early stages of HT, TSH may be normal and anti-thyroid antibodies may be positive with or without goiter" [18], HT as PolyA, not as index disease, was considered in the presence of such autoantibodies. Thyroid ultrasound was not routinely done.

Of the 313 patients, 138 (44%) developed two ADs simultaneously. With respect to the rest, the mean interval period for the second AD was 23.45 ± 32.88 months, and the mean age at onset of the second AD was 12.41 ± 3.37 years. MAS was documented in 62 (19.8%) patients of whom 55 developed three ADs and seven developed four ADs. The male-female ratio of MAS was 1:7.8 (Fig. 1).

Out of 62 patients with MAS, six presented with autoimmune polyendocrine syndrome (abbreviated APES, instead of APS). In six patients, the index disease was JIA. For five of the six patients, the onset of the index disease occurred during the first decade of life. Three patients developed HT and T1D; two patients had HT and AAD, one presented with hypoparathyroidism and T1D. Three of them had a non-endocrine AD as the index disease (JIA (n = 1), RP (n = 1), and AIL (n = 1)). A patient with VIT, HT, and recurrent candida infections carried the P326L mutation at *AIRE*. However, no additional endocrine involvement was observed as seen in "autoimmune polyendocrinopathy candidiasis ectodermal dystrophy" (APECED, also known as APES1) patients.

A family history of AD in the nuclear or extended families was reported in 107 (34.18%) patients of whom 55 (17.57%) had familial autoimmunity (i.e., diverse ADs in the nuclear family). The most common ADs reported for parents were HT, SLE, and RA and the most common ADs in siblings were HT, SLE, and T1D.

Familial autoimmunity was more common in boys than in girls (Fig. 2). Patients in whom PolyA was diagnosed simultaneously were older than patients in whom PolyA was diagnosed sequentially (Fig. 3). In addition, patients who had siblings with autoimmunity had an earlier age at onset of the index AD than those whose siblings did not have autoimmunity (Fig. 4A). Moreover, patients who had siblings with ADs had a longer time span between the first and the second AD (Fig. 4B).

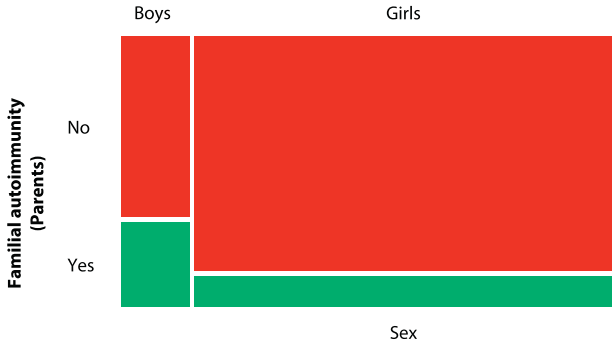

Fig. 2. Familial autoimmunity and gender. Mosaic plot showing conditional distribution of familial autoimmunity in parents for each gender. The area of the tiles (i.e., the bin size), corresponds to the number of observations within each category (i.e., there were 44 boys and 269 girls). Boys disclosed a higher familial autoimmunity (14/44; 31.82%) than girls (31/269; 11.52%), OR: 3.58; 95% CI: 1.71–7.48; p = .001 (by Fisher's exact test).

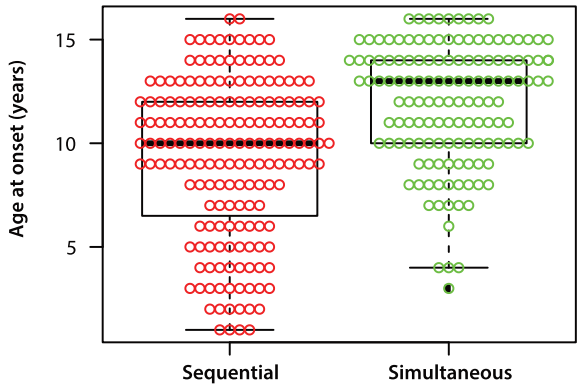

Fig. 3. Age at onset and diagnosis of PolyA. Boxplot of age at onset and status of simultaneity. Patients in whom PolyA was diagnosed simultaneously were older than patients in whom PolyA was diagnosed sequentially (11.94 ± 2.91 vs. 9.29 ± 3.8 years, p = 5.35e−10).

3.2. Index autoimmune diseases

There were 25 index diseases. Their number, percentage, and sex ratio are described in Table 2. Although the sex ratio showed variations among diseases, a female predominance was observed in all of them. Some ADs such as ITP, GD, JDM, and SS were documented exclusively in girls.

A total of 37 diseases coexisted with the 25 index diseases thus generating the PolyA phenomenon. The most common index diseases and their respective PolyA are shown in Fig. 5. SLE (n = 134), JIA

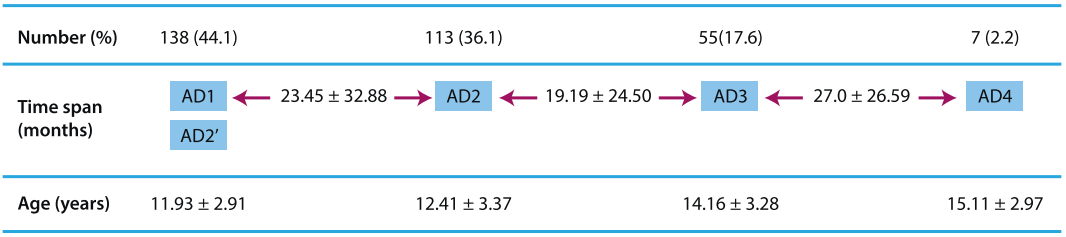

Fig. 1. Chronologic aspects of 313 patients with juvenile PolyA. The mean follow-up of patients was 55.90 ± 43.73 months. There were 138 patients who developed PolyA simultaneously (AD1/AD2'). AD: autoimmune disease.

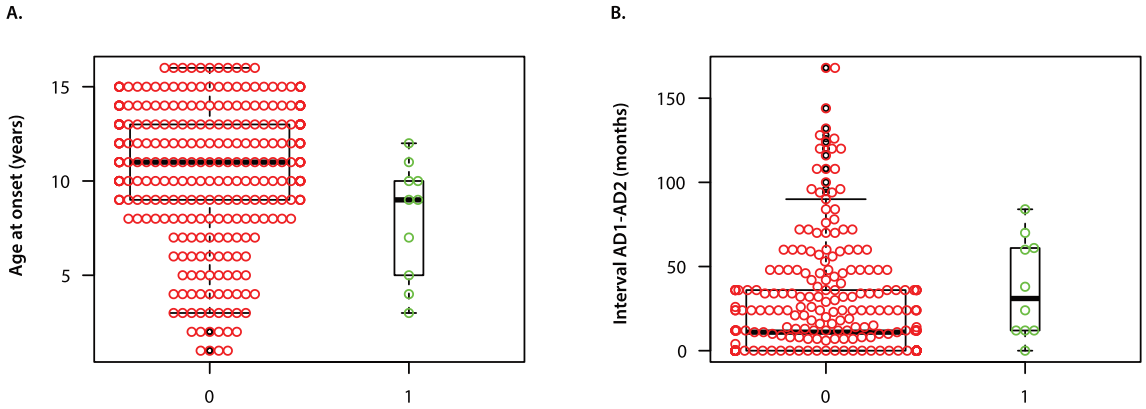

Fig. 4. Associations of familial autoimmunity in siblings. A. Boxplot of age at onset and familial autoimmunity in siblings. Patients with polyautoimmunity having siblings with autoimmunity (1) had an earlier age at onset of the first AD than those with no autoimmunity in siblings (0) (8 ± 3.1 vs. 10.54 ± 3.67 years, p = .019). B. Boxplot of time span between the first and the second AD and familial autoimmunity in siblings. The time span between the first and the second AD was longer in those patients presenting with familial autoimmunity in siblings (1) as compared with those negative for familial autoimmunity (0) (37.3 ± 29.47 vs. 23 ± 32.93 months, p = .031).

Table 2
Index autoimmune diseases in 313 pediatric patients with polyautoimmunity.

Autoimmune disease	Abbreviation	N	%	Sex ratio (F/M)
Systemic lupus erythematosus	SLE	134	42.8	7.9:1
Juvenile idiopathic arthritis	JIA	40	12.8	4.7:1
Hashimoto's thyroiditis	HT	24	7.7	23: 1
Idiopathic thrombocytopenic purpura	ITP	20	6.4	20:0
Antiphospholipid syndrome	APS	15	4.8	14:1
Vitiligo	VIT	15	4.8	1.1:1
Juvenile dermatomyositis	JDM	10	3.2	10:0
Localized scleroderma	LoS	9	2.8	3.5:1
Glomerulonephritis	GN	6	1.9	6:0
Graves' disease	GD	4	1.3	4:0
Autoimmune leukopenia	AIL	4	1.3	1:1
Discoid lupus	DL	4	1.3	1:1
Sjögren's syndrome	SS	4	1.3	4:0
Urticarial vasculitis	UV	4	1.3	3:1
Type 1 diabetes	T1D	3	0.9	2:1
Uveitis	U	3	0.9	2:1
Autoimmune hemolytic anemia	AIHA	2	0.6	2:0
Alopecia universalis	AU	2	0.6	1:1
Psoriasis	PSO	2	0.6	2:0
Raynaud's phenomenon	RP	2	0.6	1.1
Inflammatory bowel disease	IBD	1	0.3	1:0
Autoimmune encephalitis	AE	1	0.3	0:1
Scleritis	SCL	1	0.3	1:0
Autoimmune hepatitis	AIH	1	0.3	1:0
Autoimmune hypoparathyroidism	AHP	1	0.3	0:1
Systemic sclerosis	SSc	1	0.3	1:0

(n = 40), HT (n = 24), ITP (n = 20), APS (n = 15), and VIT (n = 15) represented 79.23% of the total number of patients (Fig. 5). The index AD appeared before the eleventh birthday in 47.9% of the cases. The most prevalent index diseases that appeared during the first decade of life were JIA, ITP, JDM, and VIT while during the second decade of life, SLE and APS were the most frequent (Fig. 6).

SLE was the index disease for 134 patients in whom 16 different ADs coexisted. In 110 (82%) patients, the second AD occurred simultaneously with SLE. The most common coexistent ADs with SLE were APS (59.7%), HT (14.9%), and SS (7.5%) (Fig. 5). Sequential PolyA was seen with VIT and LoS. MAS was seen in 18 (13.4%) patients for whom SLE was the index disease. Three of them developed a fourth AD: SS in two cases and SSc in one case. Familial autoimmunity was registered in 8.9% of the patients with SLE as the index disease.

For patients with JIA as the index disease, 14 additional ADs were registered (Fig. 5). The most common were HT (30%), SS (20%), VIT (10%), and LoS (10%). MAS was observed in 7 (17.5%), and one of them developed JDM as a fourth AD. Familial autoimmunity was registered for 20% of these patients.

HT, the third most common index disease, was observed in 24 patients in whom 10 different ADs coexisted, mainly SLE (25%), JIA (25%), and VIT (12.5%). MAS was registered in 25% of those cases, and familial autoimmunity in 8.3%.

ITP was an index disease for 20 patients. The diseases most frequently coexisting with ITP as the index disease were SLE, HT, and APS. MAS was documented in 8 (40%) patients (Fig. 5) and familial autoimmunity in 25%. All patients with ITP were female.

APS was an index disease for 15 patients. The most common coexistent ADs were SLE (73.3%) and HT (6.66%). MAS was documented in 3 (20%) patients, and just one patient had familial autoimmunity.

For patients with VIT as the index AD, the most frequent coexistent diseases were HT (40%), U (13.3%), and JIA (13.3%) (Fig. 5). MAS was documented in two patients (13.3%). None of them had a familial autoimmunity.

JDM was the index disease for 10 patients in whom seven different ADs coexisted. All patients were female. Two patients had familial autoimmunity. The most common ADs coexistent with JDM were HT (30%) and SS (20%). One JDM patient developed MAS.

LoS was the index disease for 9 patients with VIT, SS, psoriasis (PSO), and HT as coexistent diseases. Familial autoimmunity was observed in 20% of these patients. As second AD, LoS coexisted with JIA (n = 4) and SLE (n = 2). Two patients developed LoS as the third AD.

Some peculiarities in our patients were documented. SS was confirmed by minor salivary gland biopsy in 36 (11.5%) patients with sicca symptoms (i.e., xerophthalmia and/or xerostomia) and enlarged salivary glands. Out of 4 patients for whom SS was the index AD, three developed SLE after a mean interval of 17.5 months.

In addition to VIT, other dermatologic ADs that are part of PolyA were UV, PSO, DL, and alopecia universalis (AU). One girl developed discoid lupus and facial lupus panniculitis. Two years later, she developed primary central nervous system vasculitis. She did not develop SLE during follow up and recovered after high dose pulse intravenous steroids.

There were only four patients with GD as the index AD (Table 2). Two patients developed GD as a third AD following APS (Fig. 5). One girl with GD treated with tapazole developed drug-induced SLE.

AIH was the index disease for a girl who developed primary biliary cholangitis years later. Another girl developed JDM and AIH simultaneously, the latter having been confirmed by liver biopsy. AIH was also documented in two cases of SLE.

Juvenile IBD includes CRD, UC, and unclassified IBD. One boy

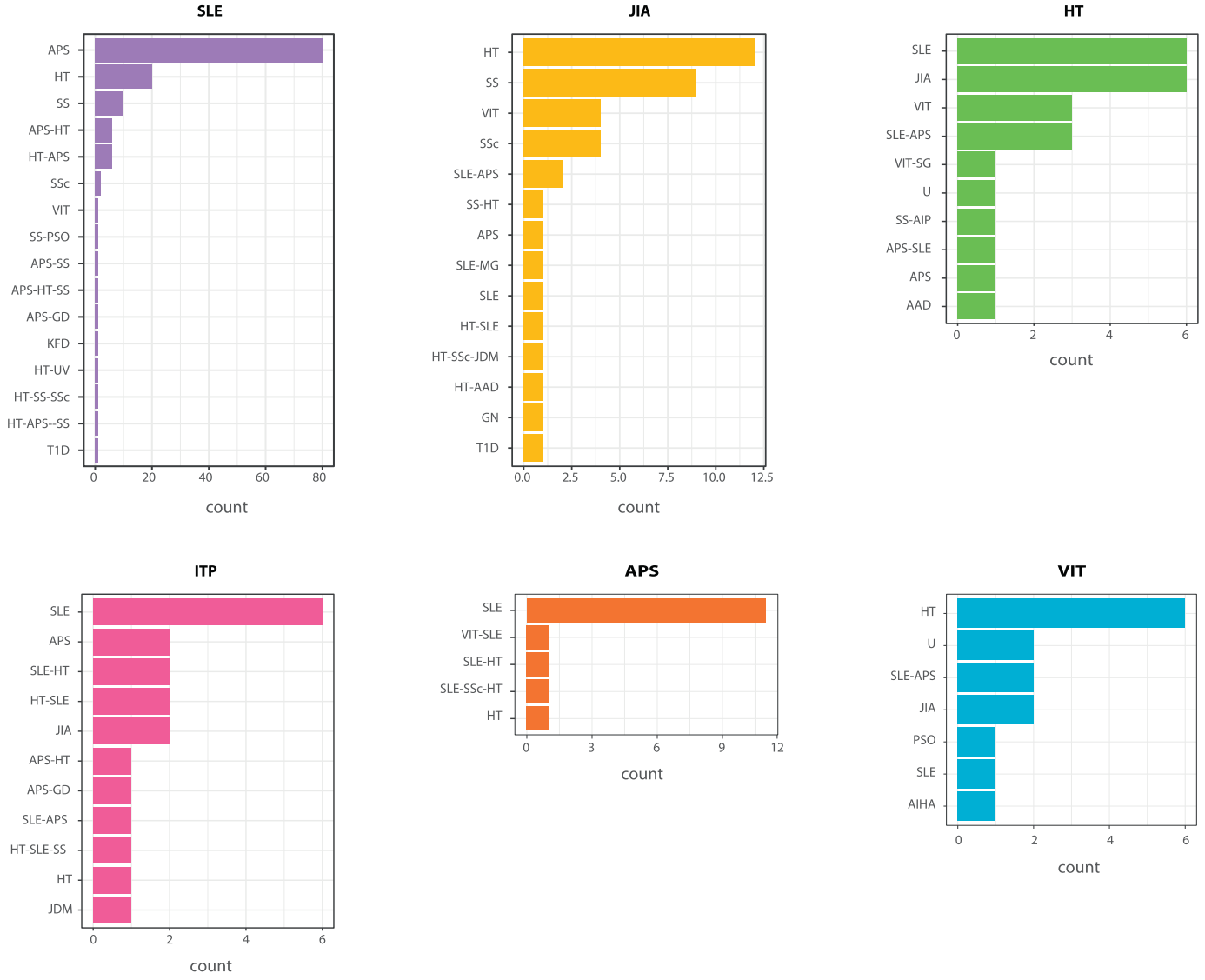

Fig. 5. Polyautoimmunity in the six most frequent index autoimmune diseases. SLE: Systemic lupus erythematosus, JIA: Juvenile idiopathic arthritis, HT: Hashimoto's thyroiditis, ITP: Immune thrombocytopenic purpura, APS: Antiphospholipid syndrome, VIT: Vitiligo. HT as PolyA, not as index disease, was considered in the presence of anti-thyroid antibodies (i.e., latent PolyA). Bars represent the number of patients (i.e., count).

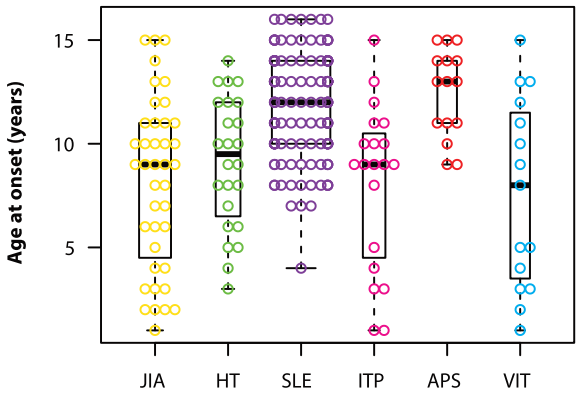

Fig. 6. Age at onset of index ADs. Boxplot of the most frequent index diseases in a series of 313 juvenile patients with PolyA ($p = 1.27e-10$). JIA: juvenile idiopathic arthritis; HT: Hashimoto's thyroiditis; SLE: systemic lupus erythematosus; ITP: immune thrombocytopenic purpura; APS: antiphospholipid syndrome; VIT: vitiligo.

developed autoimmune hypoparathyroidism (AHP), diabetes insipidus, and chronic colitis. Another patient with UC presented with HT. A teenager who had chronic uveitis developed UC and central venous thrombosis secondary to APS one year later.

PolyA in CD has been reported frequently (Table 3). However, CD was not observed as an index AD in this study. Although three patients with APES had symptoms suggesting CD, all were negative for specific CD autoantibodies. However, there was an improvement in gastrointestinal symptoms for two of them when a gluten-free diet was started.

Although uncommon, a patient presenting SLE and KFD was identified (Fig. 5). Of the four patients with UV as the index disease three developed SLE and one developed JIA. Another peculiarity of this series was one patient with autoimmune encephalitis who simultaneously developed T1D.

3.3. PolyA clustering

Three clusters of PolyA were obtained (Fig. 7). Nodes of the tree are present at different heights thus representing the dissimilarity index values at which each branch merges with others. The Jaccard index

Table 3
Polyautoimmunity in children (review of literature).

Index AD	N	Sex	Age[a]	Reported PolyA (number of cases)	Intervals(months)	Ref.
SLE	1	F	16	SS	AD1-AD2 (0)	Sobel JD et al. [92]
SLE	1	F	16	TA	AD1-AD2 (48)	Saxe PA et al. [93]
SLE	1	F	12	HT, UV	AD1-AD2 (3)	DeAmicis T et al. [94]
SLE	1	M	11	WG	AD1-AD2 (1.7)	Erdogan O et al. [95]
SLE	1	F	12	AIH	AD1-AD2 (0)	Usta Y et al. [96]
SLE	1	F	11	AIH	AD1-AD2 (0)	Deen MEJ et al. [97]
SLE	1	M	13	APS	AD1-AD2 (0)	Patel A et al. [98]
SLE	1	M	6	CD	AD1-AD2 (0)	Criscov GI et al. [99]
SLE	1	F	16	APS	AD1-AD2 (0)	Hirakawa E et al. [100]
SLE	1	F	11	APS	AD1-AD2 (0)	Patra S et al. [101]
SLE	49	F 5:M1	Mean 11.5	AIHA	AD1-AD2 (0)	Gormezano NWS et al. [28]
SLE	11	F10:M1	ND	ES	AD1-AD2 (0) 9/11 AD1-AD2 (3) AIHA – ITP AD1-AD2 (30) ITP-AIHA	Lube GE et al. [102]
SLE	1	F	12	CRD	AD1-AD2 (36)	Nagata M et al. [103]
SLE	8	F 3:M 1	Mean 10.2	APS	AD1-AD2 (37.7)	Campos LMA et al. [104]
SLE	144	F 6.5:M1	Mean 13	HT (42),APS (42), AIHA(26), T1D (23), VIT (4), CD (3), SS (1), AG (1), PSC (1), MG (1)	Evaluation made at onset	Setoue DN et al. [31]
SLE	1	M	9	UC	AD1-AD2 (12)	Stevens HP et al. [105]
SLE	1	F	10	SS	AD1-AD2 (24)	Fraga A et al. [106]
SLE	1	F	14	APS	AD1-AD2 (0)	Paudyal B et al. [107]
SLE	2	F2:M0	2.7 13	HT HT	AD1-AD2 (0)1/2 AD1-AD2 (171)1/2	Álvarez Madrid C et al. [108]
SLE	1	F	M	CAPS	ND	Falcini F et al. [109]
SLE	1	M	10	DMP	AD1-AD2 (0)	Wollina U et al. [110]
JIA	41	F:3.2:M1 F9: M1	Mean 7.4 Mean 9.1	HT (31), CD (10)	ND	Stagi S et al. [24]
JIA	1	F	20 months	T1D, CD and AIHA	AD1-AD2 (2) AD2-AD3 (3) AD3-AD4 (5)	Mroczkowska-Juchkiewicz A et al. [111]
JIA	1	F	12	SLE	AD1-AD2 (120)	Bazso A et al. [112]
JIA	1 1	F F	8 2.5	HT GD	AD1-AD2 (24) AD2-AD3 (178)	Álvarez Madrid C et al. [108]
JIA	15	F2:M 1	Mean 10.7	AITD (7), GD (1), CD (3), PSO(3),T1D (1)	ND	Tronconi E et al. [113]
JIA	2	F/M	ND	SLE	ND	Saulsbury FT et al. [114]
JIA	2	F	Mean 6	T1D	AD1-AD2 (Mean 36)	Rudolf MC et al. [115]
JIA	4	F 3:M 1	Mean 9	CD	ND	Lepore L et al. [116]
JIA	1	F	5	SLE	AD1-AD2 (60)	Martini A et al. [117]
JIA	5	F/M	Mean 7	T1D (3), CD (1),HT (1)	ND	Pohjankoski H et al. [118]
JIA	20	F/M	Mean 7.3	T1D	AD1-AD2 (Mean 40)	Schenck S et al. [119]
SoJIA	1	F	10	CD	AD1-AD2 (0)	Michelin CM et al. [120]
HT	16	F/M	Mean 9.7	CD (6) AA (4), VIT (2), JIA (2), APS (1) and DL (1).	ND	Larizza D et al. [121]
HT	28	F/M	Mean 8.5	CD	ND	Ansaldi N et al. [34]
HT	1	M	12	VIT	AD1-AD2 (1)	Kuzmanovska DB et al. [122]
HT	1	F	5	PA	AD1-AD2 (48)	Suzuki N et al. [123]
HT	1	F	11	CD SLE	AD1-AD2 (1.2) AD2-AD3 (0)	Latif S et al. [124]
HT	1	F	2	ITP,CD	AD1-AD2 (0)	Dogan M et al. [125]
HT	1	F	5	T1D	AD1-AD2 (0)	Maschio M et al. [126]
HT	1	M	18 months	MG	AD1-AD2 (0)	Tsao CY et al. [127]
HT	1	M	14	VIT,AIH	AD1-AD2 (0)	Keskin M et al. [128]
HT	2	F/M	Mean 7	JIA	ND	Pohjankoski H et al. [118]
HT	2	F	Mean 10	SLE	AD1-AD2 (18)	Alves C et al. [129]
HT	1	F	8	SLE	AD1-AD2 (36)	Álvarez Madrid C et al. [108]
HT	1	F	15	CD	AD1-AD2 (0)	Bank I et al. [130]
HT	2	F/M	Mean 14.6	CD	ND	Sahin Y et al. [131]
HT	55	F/M	Mean 9.3	T1D	AD1-AD2 (0)	Piatkowska E et al. [132]
HT	5	F:2 M:3	Mean 13.5	VIT	ND	Prindaville B et al. [133]
HT	12	F2:M1	Mean 14.2	CD	ND	Sattar N et al. [134]
GD	2	M	11	AAD	AD1-AD2 (0)	Russell GA et al. [135]
GD	1	F	13	AIHA,MG	AD1-AD2-AD3 (0)	Sarkhy A et al. [136]
GD	1	F	3	JIA	AD1-AD2 (48)	Marques VLS et al. [137]
GD	1	F	8	CD	AD1-AD2 (2)	Gora-Gebka M et al. [138]
GD	1	F	8	ITP	AD1-AD2 (0)	Chintu C et al. [139]
GD	1	M	13	AIHA	AD1-AD2 (0)	O'Brien D et al. [140]
GD	1	F	17	CD,T1D	AD1-AD2 (0) AD2-AD3 (6)	Ruch W et al. [141]
GD	4	F/M	Mean 8.5	CD	ND	Ansaldi N et al. [34]
GD	1	F/M	9.7	CD	ND	Larizza D et al. [121]
GD	1	M	4	VIT	AD1-AD2 (6)	Prindaville B et al. [133]
GD	2	F	13.9	CD	ND	Sattar N et al. [134]
ITP	1	F	12	GD	AD1-AD2 (108)	Chintu C et al. [139]
ITP	1	F	10	GD	AD1-AD2 (6)	Lee ACW et al. [142]
ITP	1	F	5	SLE	AD1-AD2 (228)	Jayabose et al. [143]
ITP	2	F/M	ND	SLE	AD1-AD2 (22)	Caggiani et al. [144]

(*continued on next page*)

Table 3 (*continued*)

Index AD	N	Sex	Age[a]	Reported PolyA (number of cases)	Intervals(months)	Ref.
APS	2	F/M	5.3	SLE	AD1-AD2 (9) AD2-AD3 (14)	Gattorno M et al. [145]
APS	40	F/M	ND	SLE	ND	Avcin T et al. [11]
APS	4	F/M	Mean 11.5	SLE	ND	Zamora-Ustaran A et al. [146]
APS	1	F	10	SLE	AD1-AD2 (0)	Bhadauria D et al. [147]
VIT	13	F1.6:M1	Mean 10.2	HT	AD1-AD2 (57)	Kakourou T et al. [36]
VIT	11	F1.7:M1	Mean 8.46	HT	AD1-AD2 (0) 5/11	Prcic S et al. [148]
					AD1-AD2 (49,5) 6/11	
VIT	28	F/M	Mean 9.5	HT(21) AA(3) T1D(3) and PSO (1)	ND	Yang Y et al. [25]
VIT	1	M	8	PA,HT	AD1-AD2 (48) AD2-AD3 (48)	Stagi S et al. [24]
VIT	1	M	5	HT	AD1-AD2 (108)	Madden BP et al. [149]
VIT	4	F	Mean 7.5	HT	AD1-AD2 (72)	Uncu S et al. [150]
VIT	3	F3:M0	Mean 8.6	PSO	AD1-AD2 (mean 6.6)	Bakar-Dertlioğlu S et al. [151]
VIT	1	M	9	ITP,AIHA	AD1-AD2 (12) AD2-AD3 (24)	Walters TR et al. [152]
VIT	6	F/M	Mean 12.1	HT (4)	AD1-AD2 (0)	Cho SB et al. [153]
				GD (2)	AD1-AD2 (Mean 21.6)	
VIT	16	F/M	Mean 7	HT	ND	Kroon MW et al. [37]
VIT	9	F/M	Mean 9.5	HT (6),GD(1),AA(1) and T1D(1)	AD1-AD2 (5.5)	Iacovelli P et al. [154]
VIT	3	F2:M1	Mean 4	GD	ND	Prindaville B et al. [133]
DPM	1	F	12	HT	AD1-AD2 (0)	Go T et al. [155]
DPM[1]	1	F	14	MG	AD1-AD2 (24)	Tsao CY et al. [127]
DPM	1	M	15	SS	AD1-AD2 (0)	Holmes M.V et al. [156]
LoS	11	F/M	Mean 7.1	JIA (4), HT(2),VIT(1), PSO (1), SS (1), T1D (1) and SLE(1).	ND	Arango C et al. [33]
MG	1	F	14	GD	AD1-AD2 (72)	Kobayashi T et al. [157]
				DPM	AD1-AD2 (348)	
MG	1	M	10	GD	AD1-AD2 (0)	Koves IH et al. [158]
MG	1	F	7	HT	AD1-AD2 (0)	Kitthaweesin K et al. [159]
SS	1	F	9	SLE	AD1-AD2 (24)	Palcoux JB et al. [160]
SS	1	F	13	JIA	AD1-AD2 (24)	Franklin D et al. [161]
	1	F	12	SLE	AD1-AD2 (ND)	
SS	1	F	16	SLE	AD1-AD2 (72)	Tasdemir M et al. [162]
CD	1	F	Mean 7	JIA	ND	Pohjankoski H et al. [118]
CD	1	M	12	AAD	AD1-AD2 (0)	Miconi F et al. [163]
CD	1	F	1	SLE	AD1:AD2 ND	Mukamel M et al. [164]
T1D	1	F	6	SLE, SSc and CD	AD1:AD2 (108)	Zeglaoui H et al. [165]
T1D	106	F: 70	Mean 8.3	AIJ	AD1:AD2 (Mean 57.6)	Hermann G et al. [29]
		M: 36			AD1:AD2 (Mean 50.4)	
T1D	1	F	6	HT	AD1:AD2 (36)	Fisher et al. [166]
				JIA	AD1:AD2 (36)	
T1D	5	M1,5:F1	Mean 9.4	JIA	AD1:AD2 (Mean 83)	Rudolf MC et al. [115]
T1D	5	F:4	Mean 12.8	AITD	AD1:AD2 (ND)	Hansen D et al. [167]
		M:1				
T1D	1	F	5	SLE	AD1:AD2 (48)	Tulpar S et al. [168]
T1D	3	F	Mean 9.4	CD	AD1:AD2 (ND)	Ergur AT et al. [27]
	20	F/M		HT		
T1D	1	F2: M0	2	HT	AD1:AD2 (108); AD1:AD2 (48)	Nagy KH et al. [169]
				JIA		
T1D	55	F4.5:M:1	Mean 9.6	HT	AD1:AD2 (Mean 44.4)	Radetti G et al. [170]
T1D	26	F1.9: M 1	Mean 11.5	CD	AD1:AD2 (Mean 84).	Nasir AM et al. [171]
	65			HT	AD1:AD2 (ND)	
T1D	7	F1,1:M 1	Mean 8.5	GD	AD1:AD2 (0) 1/7	Lombardo F et al. [39]
					AD1:AD2(Mean 75) 6/7	
T1D	49	F2.5:M1	Mean 7.7	HT	AD1:AD2 (Mean 44.4).	Riquetto ADC et al. [40]
T1D	21	M2:F1	Mean 11.3	HT	AD1:AD2 (27.6)	Joseph J et al. [172]
				GD	AD1:AD2 (ND)	
T1D	17	F/M	Mean 8.1	CD	AD1:AD2 (24)	Singh P et al. [42]
				CD and HT	AD1:AD2 (24)	
T1D	19	F/M	Mean 8.3	HT	AD1:AD2 (ND)	Jung ES et al. [173]
T1D	6	F/M	Mean 9.18	HT	AD1:AD2 (ND)	Nowier SR et al. [174]
T1D	7	F/M	Mean 7	JIA	AD1:AD2 (ND)	Pohjankoski H et al. [118]
T1D	1	F	14	JIA	AD1:AD2 (6)	Agrawal S et al. [175]
T1D	17	F/M	ND	HT 14	AD1:AD2 (ND)	Burek CL et al. [26]
				GD 3		
T1D	34	F/M	Mean 6.7	JIA	AD1:AD2 (56.4)	Schenck S et al. [119]
T1D[2]	3287	F/M	ND	HT,GD,VIT,PSO,AAD	AD1:AD2 (ND)	Hughes JW et al. [9]
AIH	2	F	12	SLE	AD1:AD2 (Mean 55)	Deen MEJ et al. [97]
AA	22	M1.2: F 1	Mean 6,7	HT	AD1:AD2 (0) 3/22.	Kurtev A et al. [38]
					AD1:AD2 (Mean 46,5)	
UC	1	M	23 months	AIH,T1D,HT	AD1:AD2:AD3 (0)	Najafi M et al. [176]
UC	4	F	2	AIH	AD1:AD2 (0)	Giraldo Escobar LM et al. [178]
IBD	28	M1.1:F1	11.5	PSC,AIH,CD	AD1:AD2,AD2:AD3,AD3:AD4 (ND)	Ordonez F et al. [177]
SSc	1	M	12	SLE	AD1:AD2 (36)	Lin H–K et al. [179]
ES	1	F	2	AIH	AD1:AD2 (12)	Jarasvaraparn C et al. [180]
KFD	1	M	16	SLE	AD1:AD2 (0)	Kinouchi R et al. [181]

(*continued on next page*)

Table 3 (*continued*)

Index AD	N	Sex	Age[a]	Reported PolyA (number of cases)	Intervals(months)	Ref.
KFD	1	F	12	SLE	AD1:AD2 (0)	Martins S et al. [182]

Abbreviations: AA: alopecia areata; AAD: Addison's disease; AG: autoimmune gastritis; AIH: autoimmune hepatitis; AIHA: autoimmune hemolytic anemia; APS: antiphospholipid syndrome; CAPS: catastrophic antiphospholipid syndrome; CD: celiac disease; CRD: crohn's disease, DL: discoid lupus; DPM: dermatopolymyositis; ES: evans syndrome, GD: Graves' disease, HT: Hashimoto's thyroiditis; IBD: inflammatory bowel disease; ITP: immune thrombocytopenic purpura; JIA: juvenile idiopathic arthritis, KFD: kikuchi-Fujimoto disease; LoS: localized scleroderma, MG: myasthenia gravis; ND: No data, PA: pernicious anemia; PSC: primary sclerosing cholangitis; PSO: psoriasis, SLE: systemic lupus erythematosus; SS: sjögren's syndrome; SoJIA: systemic-onset juvenile idiopathic arthritis; SSc: systemic sclerosis; TA: Takayasu's arteritis; T1D: type 1 diabetes; UC: ulcerative colitis; UV: urticarial vasculitis; VIT: vitiligo; WG: wegener granulomatosis.

[a] Age at onset of the first AD. Otherwise, signaled data correspond to years.

[1] This patient presented polymyositis without dermatological manifestations.

[2] This was a multiethnic registry of juvenile patients with T1D followed until adulthood.

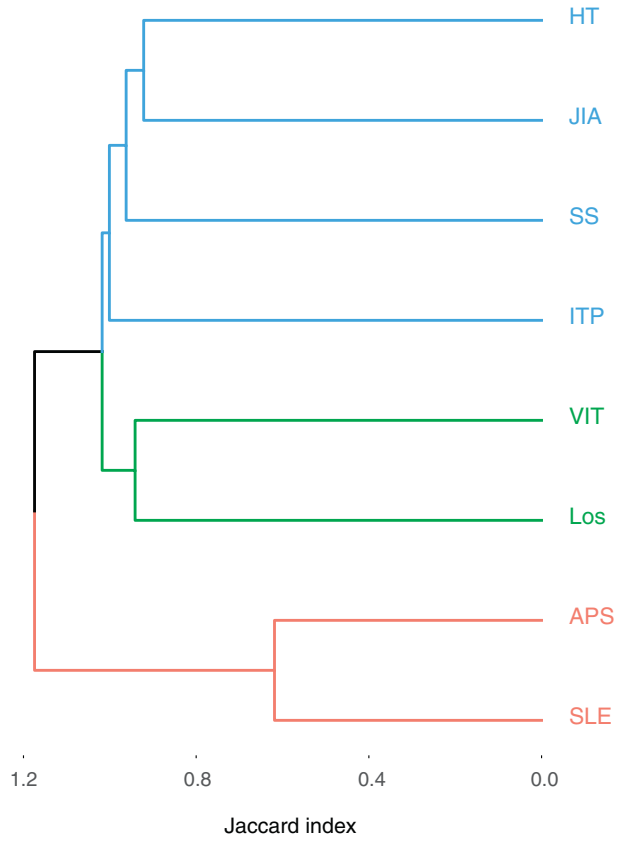

Fig. 7. Polyautoimmunity cluster dendogram. Three main clusters were obtained based on the combinations of PolyA registered in the current series (see colors). The Jaccard index, or dissimilarity coefficient, indicated that APS and SLE were the more similar, followed by JIA and HT, both of which were close to SS and/or ITP; and finally between VIT and LoS (see text for details).

takes simultaneous appearance (rather than simultaneous absence) into account as a criterion for similarity. Values near zero represent high similarity (i.e., low dissimilarity). For example, SLE and APS merged in the lowest node which implies that they were the most similar pair of diseases (i.e. coexisted most frequently). The next most similar pair of diseases were HT and JIA. SS was observed frequently in patients with HT and/or JIA. ITP was related to patients presenting with HT, JIA, and/or SS. The last branch of the tree indicated that LoS and VIT were similar. However, these diseases were more related to the HT-JIA-SS-ITP group than to the SLE-APS cluster (Fig. 7).

4. Discussion

We describe an extensive series of patients with juvenile PolyA from a rheumatology setting, and report novel findings concerning the clinical characteristics, chronology, familial autoimmunity, index cases, and grouping patterns. Preliminary reports on the current registry have been published [35].

PolyA presented simultaneously in 44% of the cases with the rest appearing over a span of 2 years on average between the index and the following AD (Fig. 1). The importance of PolyA relies on the relationship of diverse phenotypes with a single genotype and similar environmental exposures which supports the autoimmune tautology hypothesis (i.e., the common mechanisms of ADs) [2,45].

At the time of writing, 62 (19.8%) patients have developed MAS. Of these, 6 (9.6%) had APES2, universally known as “Schmidt's syndrome” owing to a case reported by Schmidt in 1926 of two patients that presented AAD and chronic lymphocytic thyroiditis [86]. Afterward in 1964, Carpenter included the presence of T1D to the syndrome thus defining the classic triad for APES2 [87]. APES2 is diagnosed by the presence of at least two of the previously described conditions in one patient. Another polygenic form of APES is APES type 3, defined as the presence of AITD and another AD including T1D, but does not typically include adrenal gland malfunction. Other diseases such as pernicious anemia or CD may also be observed. Finally, APES type 4 has been described as the association of two or more organ-specific ADs coexisting with autoimmune endocrinopathies. There is, nevertheless, some controversy around this topic, and some authors argue that APES2, APES3, and APES4 are different manifestations of the same syndrome [88]. This disagreement has strong foundations since, as is documented herein (Fig. 5), there are several patients with organ-specific ADs, both endocrine and non-endocrine, that coexist with a systemic AD. As mentioned by Kahaly and Frommer, “early detection of specific autoantibodies and latent organ-specific dysfunction is advocated to alert physicians to take appropriate action in order to prevent full-blown APES disease” [88]. APES represents a florid type of PolyA.

Some familial characteristics influenced juvenile PolyA. First, familial autoimmunity was not rare among patients with PolyA (17.57%). Considering an AD prevalence of 5% [1], a high aggregation of autoimmunity was evident ($\lambda_r = 3.5$). Second, familial autoimmunity in parents was more frequent in the case of boys than in that of girls, and familial autoimmunity in siblings influences both the age at onset and the time span for the appearance of the second AD (Fig. 4). Our findings confirm previous reports in which the influence of familial autoimmunity on PolyA has been reported [89–91].

The most frequent AD encountered was SLE, followed by JIA, HT, ITP, APS, and VIT. Table 3 summarizes a review of literature on PolyA in children [11,24,25,27–29,31,33,34,36–38,40,42,92–182].

As previously reported and confirmed by this study, PolyA in patients with SLE is a common finding [183]. SLE may be the index, second, third and even fourth AD. These multiple associations may be documented at the onset of the index AD or during the follow up after a variable period of time.

A recent multicentric study of juvenile SLE determined the prevalence of PolyA at onset of the disease, and found APS, HT, AIH, and T1D in 29%, 29%, 18%, and 15% of patients respectively [31].

Cumulative reports have indicated that the prevalence of antiphospholipid antibodies in children with SLE ranges from 19% to 87% for anticardiolipin antibodies, and from 10% to 62% for lupus anticoagulant [184]. However, not all patients carrying these autoantibodies develop APS (i.e., thrombotic events). During the past two decades, numerous case reports and a few cohorts of "secondary APS syndrome" have been published (Table 3). This pattern of PolyA (i.e., SLE-APS) was the most common in our study.

As has been reported by others, patients with JIA as the index AD may develop other ADs. Tronconi et al. [113] screened JIA patients for an additional AD and determined that they present a high autoimmunity burden because of PolyA (Table 3). The coexistence of JIA and AITD has been confirmed by several authors but the prevalence is variable. Mihailova et al. [185] reported a prevalence of 44.4%. JIA patients usually present with subclinical hypothyroidism, AITD, and CD [24]. Alpigiani et al. [186] reported the presence of anti-thyroid antibodies in 14% of JIA patients although all of them were euthyroid. Five of our patients with JIA (12,5%) developed SLE as second or third AD and 80% developed MAS.

AITD is often reported in patients with PolyA. The thyroid functional status should be screened in patients with systemic and organ specific ADs on a regular basis because those patients may be asymptomatic or have euthyroid goiter or clinical hypothyroidism [187]. Patients with antithyroid autoantibodies may develop hypothyroidism after a highly variable period of time. Our results confirm the presence of AITD in multiple combinations of PolyA such as JIA, SLE, VIT, and AA.

Childhood ITP is considered to be a heterogeneous disease, and in the setting of PolyA, it can be seen coexisting with several ADs (Fig. 5). In a small cohort of patients with ITP who developed SLE, the following risk factors were identified: older age at onset, female gender, positive antinuclear antibodies, and chronic course of ITP [22].

APS was the fifth most frequent index disease in our series. Thrombotic and non-thrombotic hematological and neurological complications that negatively impact prognosis may appear. While hematologic involvement is the most common non-thrombotic manifestation in APS PolyA, thrombotic complications are the most common manifestations in patients with isolated APS as well as in the absence of SLE [188,189].

The coexistance of VIT with other ADs is well-known, especially HT, JIA, T1D, PSO, PA, SLE, and AAD. VIT was the index disease for 15 patients (Table 2, Fig. 5). Several PolyA in VIT has been described (Table 3) [8,190].

PolyA in T1D is not uncommon and may appear both at onset and during the course of the disease [30,191]. In a multiethnic registry of juvenile patients with T1D followed to adulthood, PolyA was documented in 27% of the cases [9]. The prevalence was higher in females, non-Hispanic girls, and in older patients. The most common ADs in PolyA were AITD, CD, AAD, SLE, and SSc [9]. PolyA had a negative impact on the control of T1D and increase morbidity. Among our patients, only 8 (2.55%) T1D patients were identified (partially due to recruitment bias). Of these, three (37.5%) presented T1D as the index disease (Table 2).

No patients with CD were observed in our series. CD is a rare condition in Colombians [192]. Reported cases of PolyA in CD are summarized in Table 3. In populations where the coexistence of T1D and CD is recognized, screening for CD (i.e., autoantibody profile) is recommended in T1D children at disease onset, annually during the first 4 years of the disease, and every 2 years over the following 6 years [193].

Three main clusters of PolyA were determined (Fig. 7). The first one involved SLE and APS. The second one was characterized by HT, JIA, SS, and ITP, and the third one by VIT and LoS. These clusters represent the most significant combinations of PolyA in our series, and may serve to guide the screening of patients for PolyA with any of the ADs present in the clusters. Those combinations depend upon the prevalence of ADs, and these may vary from one population to another due to genetic background, ancestry, and environmental factors.

We acknowledge the shortcomings of this cross-sectional and multicenter study, including confounding (e.g., other associated factors may be present that were not measured, heterogeneity in clinical practice among different centers spite of having a unified study protocol), personal and recruitment bias, heterogeneity and lack of laboratory standardization, and missing data. In most cases, the suspicion of an additional AD was an atypical clinical course. Biopsies of target organs helped us to confirm the presence of additional ADs. Nevertheless, this study gave us the opportunity to analyze the characteristics of juvenile PolyA, and to set up a now ongoing registry that will serve as a valuable resource for doing controlled prospective clinical and serological studies to look for PolyA in children.

5. Conclusions

A broad spectrum of PolyA was seen in juvenile patients, from classical and well known (e.g., SLE and APS, and HT and VIT) to rare PolyA (e.g., T1D and autoimmune encephalitis, or LoS, VIT, and PSO). APES should be considered as a classical PolyA in which several non-endocrine diseases may coexist. Some ADs such as CD and T1D were rarely observed in this study. As was mentioned, this could be due to recruitment bias but also to ancestry.

PolyA may be present at onset and also develop during the course of almost any AD, therefore it should be suspected in every patient with any AD in whom changes in either the clinical manifestations or autoantibody profile appear.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This research did not receive any specific grant from any funding agency in any public, commercial or not-for-profit sector.

Acknowledgments

We would like to thank all our colleagues including the pediatricians, endocrinologists, dermatologists and rheumatologists who assisted us with diagnoses and assessments of patients.

References

[1] Anaya J-M, Shoenfeld Y, Rojas-Villarraga A, Levy RA, Cervera R. Autoimmunity: From Bench to Bedside. Bogota (Colombia): Rosario University Press; 2013https://www.ncbi.nlm.nih.gov/pubmed/29087650.
[2] Anaya J-M. The autoimmune tautology. A summary of evidence. Joint Bone Spine 2017;84:251–3. https://doi.org/10.1016/j.jbspin.2016.11.012.
[3] Anaya J-MM. The diagnosis and clinical significance of polyautoimmunity. Autoimmun Rev 2014;13:423–6. https://doi.org/10.1016/j.autrev.2014.01.049.
[4] Anaya J-M, Restrepo-Jimenez P, Rodriguez Y, Rodriguez-Jimenez M, Acosta-Ampudia Y, Monsalve DM, et al. Sjogren's syndrome and autoimmune thyroid disease: two sides of the same coin. Clin Rev Allergy Immunol 2018. https://doi.org/10.1007/s12016-018-8709-9.
[5] Molano-González N, Rojas M, Monsalve DM, Pacheco Y, Acosta-Ampudia Y, Rodríguez Y, et al. Cluster analysis of autoimmune rheumatic diseases based on autoantibodies. New insights for polyautoimmunity. J Autoimmun 2018 Nov 17. https://doi.org/10.1016/j.jaut.2018.11.002.
[6] Amador-Patarroyo MJ, Rodriguez-Rodriguez A, Montoya-Ortiz G. How does age at onset influence the outcome of autoimmune diseases? Autoimmune Dis 2012;1. https://doi.org/10.1155/2012/251730.
[7] Huemer C, Huemer M, Dorner T, Falger J, Schacherl H, Bernecker M, et al. Incidence of pediatric rheumatic diseases in a regional population in Austria. J Rheumatol 2001;28:2116–9.
[8] Kurtev A, Dourmishev AL. Thyroid function and autoimmunity in children and adolescents with vitiligo. J Eur Acad Dermatol Venereol 2004;18:109–11.
[9] Hughes JW, Riddlesworth TD, DiMeglio LA, Miller KM, Rickels MR, McGill JB.

Autoimmune diseases in children and adults with type 1 diabetes from the T1D exchange clinic registry. J Clin Endocrinol Metab 2016;101:4931–7. https://doi.org/10.1210/jc.2016-2478.
[10] Li SC. Scleroderma in children and adolescents: localized scleroderma and systemic sclerosis. Pediatr Clin North Am 2018;65:757–81. https://doi.org/10.1016/j.pcl.2018.04.002.
[11] Avcin T, Silverman ED. Antiphospholipid antibodies in pediatric systemic lupus erythematosus and the antiphospholipid syndrome. Lupus 2007;16:627–33. https://doi.org/10.1177/0961203307079036.
[12] Virdee S, Greenan-Barrett J, Ciurtin C. A systematic review of primary Sjogren's syndrome in male and paediatric populations. Clin Rheumatol 2017;36:2225–36. https://doi.org/10.1007/s10067-017-3745-z.
[13] Fragoso YD, Ferreira MLB, de MO Morales N, Arruda WO, JBB Brooks, DSD Carneiro, et al. Multiple sclerosis starting before the age of 18 years: the Brazilian experience. Arq Neuropsiquiatr 2013;71:783–7. https://doi.org/10.1590/0004-282X20130122.
[14] Brogan PA, Dillon MJ. Autoimmune diseases in children. Curr Paediatr 2005;15:23–31. https://doi.org/10.1016/j.cupe.2004.10.011.
[15] Sawhney S, Magalhaes CS. Paediatric rheumatology–a global perspective. Best Pract Res Clin Rheumatol 2006;20:201–21. https://doi.org/10.1016/j.berh.2005.11.007.
[16] Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. J Autoimmun 2007;29:1–9. https://doi.org/10.1016/j.jaut.2007.05.002.
[17] Ngo ST, Steyn FJ, McCombe PA. Gender differences in autoimmune disease. Front Neuroendocrinol 2014;35:347–69. https://doi.org/10.1016/j.yfrne.2014.04.004.
[18] Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. J Thyroid Res 2011;2011. https://doi.org/10.4061/2011/675703.
[19] Bay A, Coskun E, Leblebisatan G, Karaoglu O, Keskin M, Yavuz S, et al. Prevalence and clinical significance of antithyroid antibodies in children with immune thrombocytopenic purpura. Pediatr Hematol Oncol 2013;30:698–704. https://doi.org/10.3109/08880018.2012.756564.
[20] Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine 2014;81:112–7. https://doi.org/10.1016/j.jbspin.2013.09.003.
[21] Mina R, Brunner HI. Update on differences between childhood-onset and adult-onset systemic lupus erythematosus. Arthritis Res Ther 2013;15. https://doi.org/10.1186/ar4256.
[22] Hazzan R, Mukamel M, Yacobovich J, Yaniv I, Tamary H. Risk factors for future development of systemic lupus erythematosus in children with idiopathic thrombocytopenic purpura. Pediatr Blood Cancer 2006;47:657–9. https://doi.org/10.1002/pbc.20970.
[23] Annunzio G, Russo C, Tallone R, Lorini R. Autoimmune Disorders Associated to Type 1 Diabetes Mellitus in Children and Adolescents. 3. 2008. p. 136–40.
[24] Stagi S, Giani T, Simonini G, Falcini F. Thyroid function, autoimmune thyroiditis and coeliac disease in juvenile idiopathic arthritis. Rheumatology (Oxford) 2005;44:517–20. https://doi.org/10.1093/rheumatology/keh531.
[25] Yang Y, Lin X, Fu W, Luo X, Kang K. An approach to the correlation between vitiligo and autoimmune thyroiditis in Chinese children. Clin Exp Dermatol 2010;35:706–10. https://doi.org/10.1111/j.1365-2230.2009.03671.x.
[26] Burek CL, Rose NR, Guire KE, Hoffman WH. Thyroid autoantibodies in black and in white children and adolescents with type 1 diabetes mellitus and their first degree relatives. Autoimmunity 1990;7:157–67.
[27] Ergur AT, Ocal G, Berberoglu M, Adiyaman P, Siklar Z, Aycan Z, et al. Celiac disease and autoimmune thyroid disease in children with type 1 diabetes mellitus: clinical and HLA-genotyping results. J Clin Res Pediatr Endocrinol 2010;2:151–4. https://doi.org/10.4274/jcrpe.v2i4.151.
[28] Gormezano NWS, Kern D, Pereira OL, Esteves GCX, Sallum AME, Aikawa NE, et al. Autoimmune hemolytic anemia in systemic lupus erythematosus at diagnosis: differences between pediatric and adult patients. Lupus 2017;26:426–30. https://doi.org/10.1177/0961203316676379.
[29] Hermann G, Thon A, Monkemoller K, Lilienthal E, Klinkert C, Holder M, et al. Comorbidity of type 1 diabetes and juvenile idiopathic arthritis. J Pediatr 2015;166:930–3. https://doi.org/10.1016/j.jpeds.2014.12.026.
[30] Kakleas K, Soldatou A, Karachaliou F, Karavanaki K. Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus (T1DM). Autoimmun Rev 2015;14:781–97. https://doi.org/10.1016/j.autrev.2015.05.002.
[31] Setoue DN, Pitta AC, Fiorot FJ, Nastri MM, Novak GV, Molinari BC, et al. Symptomatic polyautoimmunity at diagnosis of 1463 childhood-onset lupus: a Brazilian multicenter study. Autoimmun Rev 2018. https://doi.org/10.1016/j.autrev.2018.03.009. (0–1).
[32] Szanto A, Szodoray P, Kiss E, Kapitany A, Szegedi G, Zeher M. Clinical, serologic, and genetic profiles of patients with associated Sjogren's syndrome and systemic lupus erythematosus. Hum Immunol 2006;67:924–30. https://doi.org/10.1016/j.humimm.2006.06.006.
[33] Arango C, Malagón C, Gómez P, Mosquera C, Yépez R, González T, et al. Juvenile localized scleroderma : Is it a benign disease ? Rev Colomb Reumatol English Ed 2017;4:145–52. https://doi.org/10.1016/j.rcreue.2017.08.002.
[34] Ansaldi N, Palmas T, Corrias A, Barbato M, D'Altiglia MR, Campanozzi A, et al. Autoimmune thyroid disease and celiac disease in children. J Pediatr Gastroenterol Nutr 2003;37:63–6.
[35] Malagon C, Gomez P, Mosquera A, Gonzalez T, VC Yepez R. Polyautoimmunity in Colombian juvenile patients. Proceedings of the 23rd Paediatric Rheumatology European Society Congress: part two. Pediatr Rheumatol 2017;15:44. https://doi.org/10.1186/s12969-017-0142-8.
[36] Kakourou T, Kanaka-Gantenbein C, Papadopoulou A, Kaloumenou E, Chrousos GP. Increased prevalence of chronic autoimmune (Hashimoto's) thyroiditis in children and adolescents with vitiligo. J Am Acad Dermatol 2005;53:220–3. https://doi.org/10.1016/j.jaad.2005.03.032.
[37] Kroon MW, Vrijman C, Chandeck C, Wind BS, Wolkerstorfer A, Luiten RM, et al. High prevalence of autoimmune thyroiditis in children and adolescents with vitiligo. Horm Res Paediatr 2013;79:137–44. https://doi.org/10.1159/000348388.
[38] Kurtev A, Iliev E. Thyroid autoimmunity in children and adolescents with alopecia areata. Int J Dermatol 2005;44:457–61. https://doi.org/10.1111/j.1365-4632.2005.01971.x.
[39] Lombardo F, Messina MF, Salzano G, Rabbone I, Lo Presti D, Calcaterra V, et al. Prevalence, presentation and clinical evolution of Graves' disease in children and adolescents with type 1 diabetes mellitus. Horm Res Paediatr 2011;76:221–5. https://doi.org/10.1159/000327587.
[40] Riquetto ADC, de Noronha RM, Matsuo EM, Ishida EJ, Vaidergorn RE, Soares Filho MD, et al. Thyroid function and autoimmunity in children and adolescents with type 1 diabetes mellitus. Diabetes Res Clin Pract 2015;110:e9–11. https://doi.org/10.1016/j.diabres.2015.07.003.
[41] Avcin T, Cimaz R, Rozman B. The Ped-APS registry: the antiphospholipid syndrome in childhood. Lupus 2009;18:894–9. https://doi.org/10.1177/0961203309106917.
[42] Singh P, Seth A, Kumar P, Sajjan S. Coexistence of celiac disease & type 1 diabetes mellitus in children. Indian J Med Res 2017;145:28–32. https://doi.org/10.4103/ijmr.IJMR_199_15.
[43] Gattorno M, Buoncompagni A, Molinari AC, Barbano GC, Morreale G, Stalla F, et al. Antiphospholipid antibodies in paediatric systemic lupus erythematosus, juvenile chronic arthritis and overlap syndromes: SLE patients with both lupus anticoagulant and high-titre anticardiolipin antibodies are at risk for clinical manifestations related. Br J Rheumatol 1995;34:873–81.
[44] Tobon GJ, Arango A, Abad V, Garcia J, Cuervo H, Velasquez A, et al. Clinical and immunological characteristics of type 1 diabetes mellitus in a northwestern Colombian population. Diabetes Res Clin Pract 2006;72:170–5. https://doi.org/10.1016/j.diabres.2005.10.016.
[45] Anaya J-MM, Castiblanco J, Rojas-Villarraga A, Pineda-Tamayo R, Levy RA, Gómez-Puerta J, et al. The multiple autoimmune syndromes. A clue for the autoimmune tautology. Clin Rev Allergy Immunol 2012;43:256–64. https://doi.org/10.1007/s12016-012-8317-z.
[46] Valderas JM, Starfield B, Sibbald B, Salisbury C, Roland M. Defining comorbidity: implications for understanding health and health services. Ann Fam Med 2009;7:357–63. https://doi.org/10.1370/afm.983.
[47] Hartman EAR, van Royen-Kerkhof A, Jacobs JWG, Welsing PMJ, Fritsch-Stork RDE. Performance of the 2012 systemic lupus international collaborating clinics classification criteria versus the 1997 American College of Rheumatology classification criteria in adult and juvenile systemic lupus erythematosus. A systematic review and meta-an. Autoimmun Rev 2018;17:316–22. https://doi.org/10.1016/j.autrev.2018.01.007.
[48] Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet (London, England) 2007;369:767–78. https://doi.org/10.1016/S0140-6736(07)60363-8.
[49] Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
[50] Karaoglu A, Sarı E, Yeşilkaya E. Hashimoto' s thyroiditis in children and adolescents. Autoimmune Disord - Curr Concepts Adv from Bedside to Mech Insightsdvances from Bedside to Mech Insights 2011:27–40. https://doi.org/10.5772/24755.
[51] Léger J, Kaguelidou F, Alberti C, Carel JC. Graves' disease in children. Best Pract Res Clin Endocrinol Metab 2014;28:233–43. https://doi.org/10.1016/j.beem.2013.08.008.
[52] Rodeghiero F, Stasi R, Gernsheimer T, Michel M, Provan D, Donald M, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children : report from an international working group Standardization of terminology, definitions and outcome criteria in immune thrombocyt. vol. 113. 2014. p. 2386–93. https://doi.org/10.1182/blood-2008-07-162503.
[53] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306. https://doi.org/10.1111/j.1538-7836.2006.01753.x.
[54] Meroni PL, Argolini LM, Pontikaki I. What is known about pediatric antiphospholipid syndrome? Expert Rev Hematol 2016;9:977–85. https://doi.org/10.1080/17474086.2016.1235969.
[55] Ezzedine K, Lim HW, Suzuki T, Katayama I, Hamzavi I, Lan CCE, et al. Revised classification/nomenclature of vitiligo and related issues: the vitiligo global issues consensus conference. Pigment Cell Melanoma Res 2012;25:E1–13. https://doi.org/10.1111/j.1755-148X.2012.00997.x.
[56] Rider LG, Katz JD, Jones OY. Developments in the classification and treatment of the juvenile idiopathic inflammatory myopathies. Rheum Dis Clin North Am 2013;39:877–904. https://doi.org/10.1016/j.rdc.2013.06.001.
[57] Laxer RM, Zulian F. Localized scleroderma. Curr Opin Rheumatol 2006;18:606–13. https://doi.org/10.1097/01.bor.0000245727.40630.c3.
[58] Le W, Zeng C-H, Liu Z, Liu D, Yang Q, Lin R-X, et al. Validation of the Oxford classification of IgA nephropathy for pediatric patients from China. BMC Nephrol 2012;13:158. https://doi.org/10.1186/1471-2369-13-158.
[59] Trimarchi H, Barratt J, Cattran DC, Cook HT, Coppo R, Haas M, et al. Oxford classification of IgA nephropathy 2016: an update from the IgA nephropathy classification working group. Kidney Int 2017;91:1014–21. https://doi.org/10.

1016/j.kint.2017.02.003.
[60] Masani N, Jhaveri KD, Fishbane S. Update on membranoproliferative GN. Clin J Am Soc Nephrol 2014;9:600–8. https://doi.org/10.2215/CJN.06410613.
[61] Youinou P, Jamin C, Le Pottier L, Renaudineau Y, Hillion S, Pers JO. Diagnostic criteria for autoimmune neutropenia. Autoimmun Rev 2014;13:574–6. https://doi.org/10.1016/j.autrev.2014.01.001.
[62] Teachey DT, Lambert MP. Diagnosis and management of autoimmune cytopenias in childhood. Pediatr Clin North Am 2013;60:1489–511. https://doi.org/10.1016/j.pcl.2013.08.009.
[63] Elman SA, Joyce C, Nyberg F, Furukawa F, Goodfield M, Hasegawa M, et al. Development of classification criteria for discoid lupus erythematosus: results of a Delphi exercise. J Am Acad Dermatol 2017;77:261–7. https://doi.org/10.1016/j.jaad.2017.02.030.
[64] Bartunková J, Sedivá A, Vencovsky J, Nguyen VT. Primary Sjögren's syndrome in children and adolescents: proposal for diagnostic criteria. Clin Exp Rheumatol 1999;17:381–6.
[65] McDuffie FC, Sams WMJ, Maldonado JE, Andreini PH, Conn DL, Samayoa EA. Hypocomplementemia with cutaneous vasculitis and arthritis. Possible immune complex syndrome. Mayo Clin Proc 1973;48:340–8.
[66] American Diabetes Association (ADA). Standard of medical care in diabetes - 2017. Diabetes Care 2017;40(sup 1):s4–128. https://doi.org/10.2337/dc17-S003.
[67] Jabs DA. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 2005;140:509–16. https://doi.org/10.1016/j.ajo.2005.03.057.
[68] Hill QA, Stamps R, Massey E, Grainger JD, Provan D, Hill A. The diagnosis and management of primary autoimmune haemolytic anaemia. Br J Haematol 2017;176:395–411. https://doi.org/10.1111/bjh.14478.
[69] Al-Fouzan AS, Nanda A. Alopecia in children. Clin Dermatol 2000;18:735–43. https://doi.org/10.1016/S0738-081X(00)00151-6.
[70] Silverberg NB. Update on pediatric psoriasis. Cutis 2015;95:147–52. https://doi.org/10.2147/TCRM.S4908.
[71] Maverakis E, Patel F, Kronenberg D, Chung L, Fiorentino D, Allanore Y, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. J Autoimmun 2014;0:60–5. https://doi.org/10.1016/j.jaut.2014.01.020.
[72] Levine A, Koletzko S, Turner D, Escher JC, Cucchiara S, De Ridder L, et al. ESPGHAN revised Porto criteria for the diagnosis of inflammatory bowel disease in children and adolescents. J Pediatr Gastroenterol Nutr 2014;58:795–806. https://doi.org/10.1097/MPG.0000000000000239.
[73] Bien PCG, Cellucci T, Cortese I, C PR, Honnorat J, Höftberger R, et al.. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol 2017;15:391–404. https://doi.org/10.1016/S1474-4422(15)00401-9.A.
[74] Cheung CMG, Chee SP. Posterior scleritis in children: clinical features and treatment. Ophthalmology 2012;119:59–65. https://doi.org/10.1016/j.ophtha.2011.09.030.
[75] Ferri PM, Ferreira AR, Miranda DM, e Silva ACS. Diagnostic criteria for autoimmune hepatitis in children: a challenge for pediatric hepatologists. World J Gastroenterol 2012;18:4470–3. https://doi.org/10.3748/wjg.v18.i33.4470.
[76] Betterle C, Garelli S, Presotto F. Diagnosis and classification of autoimmune parathyroid disease. Autoimmun Rev 2014;13:417–22. https://doi.org/10.1016/j.autrev.2014.01.044.
[77] Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TAJ, Lehman TJAA, et al. The pediatric rheumatology European society/American College of Rheumatology/European league against rheumatism provisional classification criteria for juvenile systemic sclerosis. Arthritis Care Res 2007;57:203–12. https://doi.org/10.1002/art.22551.
[78] Brandão Neto RA, de Carvalho JF. Diagnosis and classification of Addison's disease (autoimmune adrenalitis). Autoimmun Rev 2014;13:408–11. https://doi.org/10.1016/j.autrev.2014.01.025.
[79] Deaver D, Horna P, Cualing H, Sokol L. Pathogenesis, diagnosis, and management of kikuchi. Fujimoto Dis 2014:313–21.
[80] Finnis MF, Jayawant S. Juvenile myasthenia gravis: a paediatric perspective. Autoimmune Dis 2011;1. https://doi.org/10.4061/2011/404101.
[81] Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40:352–8. https://doi.org/10.1097/MPA.0b013e3182142fd2.
[82] Cárdenas-Roldán J, Rojas-Villarraga A, Anaya JM. How do autoimmune diseases cluster in families? A systematic review and meta-analysis. BMC Med 2013;11:73. https://doi.org/10.1186/1741-7015-11-73.
[83] Anaya J-M, Tobon GJ, Vega P, Castiblanco J. Autoimmune disease aggregation in families with primary Sjogren's syndrome. J Rheumatol 2006;33:2227–34.
[84] Everitt BS, Landau S, Leese M, Stahl D. Cluster Analysis.Wiley Series in Probability and Statistics. 5th Editio John Wiley & Sons; 2011.
[85] Foundation TR. The R Project for Statistical Computing. 2019.
[86] Schmidt M. Eine biglandulare Erkrankung (Nebennieren und Schilddrüse) bei Morbus Addisonii. Verh Dtsch Ges Pathol 1926;21:212–21.
[87] Carpenter CC, Solomon N, Silverberg SG, Bledsoe T, Northcutt RC, Klinenberg JR, et al. Schmidt's syndrome (thyroid and adrenal insufficiency). A review of the literature and a report of fifteen new cases including ten instances of coexistent diabetes mellitus. Med (Baltimore) 1964;43:153–80.
[88] Kahaly GJ, Frommer L. Polyglandular autoimmune syndromes. J Endocrinol Invest 2018;41:91–8. https://doi.org/10.1007/s40618-017-0740-9.
[89] Prahalad S, Glass DN. A comprehensive review of the genetics of juvenile idiopathic arthritis. Pediatr Rheumatol 2008;6:1–16. https://doi.org/10.1186/1546-0096-6-11.
[90] Prahalad S, O'brien E, Fraser AM, Kerber RA, Mineau GP, Pratt D, et al. Familial aggregation of juvenile idiopathic arthritis. Arthritis Rheum 2004;50:4022–7. https://doi.org/10.1002/art.20677.
[91] Prahalad S, Zeft AS, Pimentel R, Clifford B, McNally B, Mineau GP, et al. Quantification of the familial contribution to juvenile idiopathic arthritis. Arthritis Rheum 2010;62:2525–9. https://doi.org/10.1002/art.27516.
[92] Sobel JD, Talor Z, Alroy G, Lichtig C, Valero A. Systemic lupus erythematosus, Sjogren's syndrome and glomerular nephritis. Postgrad Med J 1977;53:97–101.
[93] Saxe PA, Altman RD. Takayasu's arteritis syndrome associated with systemic lupus erythematosus. Semin Arthritis Rheum 1992;21:295–305.
[94] DeAmicis T, Mofid MZ, Cohen B, Nousari HC. Hypocomplementemic urticarial vasculitis: report of a 12-year-old girl with systemic lupus erythematosus. J Am Acad Dermatol 2002;47:S273–4.
[95] Erdogan O, Oner A, Demircin G, Bulbul M, Memis L, Uner C, et al. A boy with consecutive development of SLE and Wegener granulomatosis. Pediatr Nephrol 2004;19:438–41. https://doi.org/10.1007/s00467-003-1365-0.
[96] Usta Y, Gurakan F, Akcoren Z, Ozen S. An overlap syndrome involving autoimmune hepatitis and systemic lupus erythematosus in childhood. World J Gastroenterol 2007;13:2764–7.
[97] Deen MEJ, Porta G, Fiorot FJ, Campos LMA, Sallum AME, Silva CAA. Autoimmune hepatitis and juvenile systemic lupus erythematosus. Lupus 2009;18:747–51. https://doi.org/10.1177/0961203308100559.
[98] Patel A, Rangaraj S, Wright B, Murphy R. An unusual presentation of juvenile systemic lupus erythematosus. Clin Exp Dermatol 2012;37:249–51. https://doi.org/10.1111/j.1365-2230.2011.04206.x.
[99] Criscov GI, Rugina A, Stana AB, Azoicai AN, Moraru E. Atypical presentation of systemic lupus erythematosus: parotitis and secondary Sjogren's syndrome. Case report. Rev Med Chir Soc Med Nat Iasi 2014;118:387–91.
[100] Hirakawa E, Saito K, Hirata S, Atsumi T, Koike T, Tanaka Y. A case of catastrophic antiphospholipid antibody syndrome complicated with systemic lupus erythematosus, double positive for anti-cardiolipin/beta(2) glycoprotein I and anti-phosphatidylserine/prothrombin autoantibodies. Mod Rheumatol 2012;22:769–73. https://doi.org/10.1007/s10165-011-0563-z.
[101] Patra S, Krishnamurthy S, Seth A, Beri S, Aneja S. Bilateral optic neuritis in pediatric systemic lupus erythematosus with antiphospholipid antibody syndrome. Indian J Pediatr 2011;78:234–6. https://doi.org/10.1007/s12098-010-0228-5.
[102] Lube GE, Ferriani MPL, Campos LMA, Terreri MT, Bonfa E, Magalhaes CS, et al. Evans syndrome at childhood-onset systemic lupus erythematosus diagnosis: a large multicenter study. Pediatr Blood Cancer 2016;63:1238–43. https://doi.org/10.1002/pbc.25976.
[103] Nagata M, Ogawa Y, Hisano S, Ueda K. Crohn disease in systemic lupus erythematosus: a case report. Eur J Pediatr 1989;148:525–6.
[104] Campos LMA, Kiss MH, D'Amico EA, Silva CAA. Antiphospholipid antibodies and antiphospholipid syndrome in 57 children and adolescents with systemic lupus erythematosus. Lupus 2003;12:820–6. https://doi.org/10.1191/0961203303lu471oa.
[105] Stevens HP, Ostlere LS, Rustin MH. Systemic lupus erythematosus in association with ulcerative colitis: related autoimmune diseases. Br J Dermatol 1994;130:385–9.
[106] Fraga A, Gudino J, Ramos-Niembro F, Aiarcon-Segovia D. Mixed connective tissue disease in childhood. Relationship Sjogren's syndrome. Am J Dis Child 1978;132:263–5.
[107] Paudyal B. Antiphospholipid syndrome in childhood systemic lupus erythematosus. J Nepal Health Res Counc 2010;8:51–4.
[108] Alvarez Madrid C, Gonzalez Fernandez A, Lisbona Munoz M, Molina Rodriguez MA, Merino Munoz R, Garcia-Consuegra Molina J. Thyroid disorders and childhood rheumatic diseases. An Pediatr (Barc) 2009;70:53–6. https://doi.org/10.1016/j.anpedi.2008.09.012.
[109] Falcini F, Taccetti G, Ermini M, Trapani S, Matucci Cerinic M. Catastrophic antiphospholipid antibody syndrome in pediatric systemic lupus erythematosus. J Rheumatol 1997;24:389–92.
[110] Wollina U, Schreiber G. Prednisolone pulse therapy for childhood systemic lupus erythematosus with prominent dermatomyositis. A case report. Dermatologica 1985;171:45–8.
[111] Mroczkowska-Juchkiewicz A, Postepski J, Olesinska E, Krawiec P, Pac-Kozuchowska E, Postępski J, et al. Exceptional manifestation of polyautoimmunity in a very young girl - a case report. Cent Eur J Immunol 2017;42:107–10. https://doi.org/10.5114/ceji.2017.67324.
[112] Bazso A, Sevcic K, Orban I, Poor G, Balogh Z, Kiss E. Overlapping juvenile idiopathic arthritis and systemic lupus erythematosus: a case report. Rheumatol Int 2011;31:695–8. https://doi.org/10.1007/s00296-010-1594-z.
[113] Tronconi E, Miniaci A, Pession A. The autoimmune burden in juvenile idiopathic arthritis. Ital J Pediatr 2017;43:56. https://doi.org/10.1186/s13052-017-0373-9.
[114] Saulsbury FT, Kesler RW, Kennaugh JM, Barber JC, Chevalier RL. Overlap syndrome of juvenile rheumatoid arthritis and systemic lupus erythematosus. J Rheumatol 1982;9:610–2.
[115] Rudolf MC, Genel M, Tamborlane WVJ, Dwyer JM. Juvenile rheumatoid arthritis in children with diabetes mellitus. J Pediatr 1981;99:519–24.
[116] Lepore L, Martelossi S, Pennesi M, Falcini F, Ermini ML, Ferrari R, et al. Prevalence of celiac disease in patients with juvenile chronic arthritis. J Pediatr 1996;129:311–3.
[117] Martini A, Ravelli A, Viola S, Burgio RG. Systemic lupus erythematosus with Jaccoud's arthropathy mimicking juvenile rheumatoid arthritis. Arthritis Rheum 1987;30:1062–4.
[118] Pohjankoski H, Kautiainen H, Kotaniemi K, Korppi M, Savolainen A. Autoimmune diseases in children with juvenile idiopathic arthritis. Scand J Rheumatol 2010;39:435–6.

[119] Schenck S, Rosenbauer J, Niewerth M, Klotsche J, Minden K, Schwarz T, et al. Comorbidity of type 1 diabetes mellitus in patients with juvenile idiopathic arthritis. J Pediatr 2018;192:196–203. https://doi.org/10.1016/j.jpeds.2017.07.050.
[120] Michelin CM, Aikawa NE, Diniz JC, Jesus AA, Koda YK, Silva CA. Association of systemic-onset juvenile idiopathic arthritis and celiac disease - a case report. Acta Reumatol Port 2011;36:404–7.
[121] Larizza D, Calcaterra V, De Giacomo C, De Silvestri A, Asti M, Badulli C, et al. Celiac disease in children with autoimmune thyroid disease. J Pediatr 2001;139:738–40. https://doi.org/10.1067/mpd.2001.118189.
[122] Kuzmanovska DB, Shahpazova EM, Kocova MJ, Gruevska SJ, Petrushevska G. Autoimmune thyroiditis and vitiligo in a child with minimal change nephrotic syndrome. Pediatr Nephrol 2001;16:1137–8. https://doi.org/10.1007/s004670100047.
[123] Suzuki N, Mitamura R, Ohmi H, Itoh Y, Yano K, Okuno A, et al. Hashimoto thyroiditis, distal renal tubular acidosis, pernicious anaemia and encephalopathy: a rare combination of auto-immune disorders in a 12-year-old girl. Eur J Pediatr 1994;153:78–9.
[124] Latif S, Jamal A, Memon I, Yasmeen S, Tresa V, Shaikh S. Multiple autoimmune syndrome: Hashimoto's thyroiditis, coeliac disease and systemic lupus erythematosus (SLE). J Pak Med Assoc 2010;60:863–5.
[125] Dogan M, Sal E, Akbayram S, Peker E, Cesur Y, Oner AF. Concurrent celiac disease, idiopathic thrombocytopenic purpura and autoimmune thyroiditis: a case report. Clin Appl Thromb Hemost 2011;17:E13–6. https://doi.org/10.1177/1076029610378502.
[126] Maschio M, Marigliano M, Sabbion A, Morandi A, Schena D, Colato C, et al. A rare case of granuloma annulare in a 5-year-old child with type 1 diabetes and autoimmune thyroiditis. Am J Dermatopathol 2013;35:385–7. https://doi.org/10.1097/DAD.0b013e318272f6c6.
[127] Tsao CY, Mendell JR, Lo WD, Luquette M, Rennebohm R. Myasthenia gravis and associated autoimmune diseases in children. J Child Neurol 2000;15:767–9. https://doi.org/10.1177/088307380001501113.
[128] Keskin M, Savas-Erdeve S, Aycan Z. Co-existence of thyroid nodule and thyroid Cancer in children and adolescents with Hashimoto thyroiditis: a single-center study. Horm Res Paediatr 2016;85:181–7. https://doi.org/10.1159/000443143.
[129] Alves C, Robazzi TCV, Fragomeni M. Diagnosis of juvenile systemic lupus erythematosus in adolescents with Hashimoto's thyroiditis: two case reports. Acta Reumatol Port 2010;35:362–5.
[130] Bank I, Busari JO. Crohn's disease, autoimmune thyroiditis, and beta-thalassemia trait in an adolescent: an unusual combination of diseases. Eur J Pediatr 2008;167:1343–6. https://doi.org/10.1007/s00431-008-0676-3.
[131] Sahin Y, Evliyaoglu O, Erkan T, Cokugras FC, Ercan O, Kutlu T. The frequency of celiac disease in children with autoimmune thyroiditis. Acta Gastroenterol Belg 2018;81:5–8.
[132] Piatkowska E, Szalecki M. Autoimmune thyroiditis in children and adolescents with type 1 diabetes. Pediatr Endocrinol Diabetes Metab 2011;17:173–7.
[133] Prindaville B, Rivkees SA. Incidence of vitiligo in children with Graves' disease and Hashimoto's thyroiditis. Int J Pediatr Endocrinol 2011;2011:18. https://doi.org/10.1186/1687-9856-2011-18.
[134] Sattar N, Lazare F, Kacer M, Aguayo-Figueroa L, Desikan V, Garcia M, et al. Celiac disease in children, adolescents, and young adults with autoimmune thyroid disease. J Pediatr 2011;158. https://doi.org/10.1016/j.jpeds.2010.08.050. (272–5.e1).
[135] Russell GA, Coulter JB, Isherwood DM, Diver MJ, Smith DS. Autoimmune Addison's disease and thyrotoxic thyroiditis presenting as encephalopathy in twins. Arch Dis Child 1991;66:350–2.
[136] Sarkhy A, Persad R, Tarnopolsky M. Muscle weakness in a girl with autoimmune hepatitis and Graves' disease. Eur J Pediatr 2009;168:241–3. https://doi.org/10.1007/s00431-008-0738-6.
[137] Marques VLS, Gomes RC, Viola GR, Maia MM, Durigon GS, Aikawa NE, et al. Pulmonary cryptococcosis in childhood systemic lupus erythematosus and Sjogren syndrome overlap: a rare opportunistic infection. Lupus 2013;22:1409–12. https://doi.org/10.1177/0961203313502859.
[138] Gora-Gebka M, Wozniak M, Cielecka-Kuszyk J, Korpal-Szczyrska M, Sznurkowska K, Zagierski M, et al. Graves' disease, celiac disease and liver function abnormalities in a patient–clinical manifestation and diagnostic difficulties. Acta Biochim Pol 2014;61:281–4.
[139] Chintu C, McClure P. Idiopathic thrombocytopenic purpura in two children with graves disease. Am J Dis Child 1975;129:101–2.
[140] O'Brien D, Lyons DJ, Fielding JF. A case of Graves' disease associated with autoimmune haemolytic anaemia. Ir J Med Sci 1989;158:155.
[141] Ruch W, Schurmann K, Gordon P, Burgin-Wolff A, Girard J. Coexistent coeliac disease, Graves' disease and diabetes mellitus type 1 in a patient with down syndrome. Eur J Pediatr 1985;144:89–90.
[142] Lee ACW, Li CH, Wong LM. Childhood thrombocytopenia associated with graves disease is distinct from idiopathic thrombocytopenic purpura. Pediatr Hematol Oncol 2003;20:39–42.
[143] Jayabose S, Levendoglu-Tugal O, Ozkaynak MF, Sandoval C. Recurrent immune thrombocytopenic purpura in children. Pediatr Hematol Oncol 2006;23:677–82. https://doi.org/10.1080/08880010600962143.
[144] Caggiani M. Lupus eritematoso sistémico en niños y adolescentes Systemic lupus erythematosus in children and adolescents. 86. 2015. p. 273–83.
[145] Gattorno M, Falcini F, Ravelli A, Zulian F, Buoncompagni A, Martini G, et al. Outcome of primary antiphospholipid syndrome in childhood. Lupus 2003;12:449–53. https://doi.org/10.1191/0961203303lu411oa.
[146] Zamora-Ustaran A, Escarcega-Alarcon RO, Garcia-Carrasco M, Faugier E, Mendieta-Zeron S, Mendoza-Pinto C, et al. Antiphospholipid syndrome in Mexican children. Isr Med Assoc J 2012;14:286–9.
[147] Bhadauria D, Etta P, Kaul A, Prasad N. Childhood lupus with microangiopathic antiphospholipid syndrome and pulmonary hemorrhage. Indian Pediatr 2015;52:333–4.
[148] Prcic S, Djuran V, Katanic D, Vlaski J, Gajinov Z. Vitiligo and thyroid dysfunction in children and adolescents. Acta Dermatovenerol Croat 2011;19:248–54.
[149] Madden BP, Walker F, Gaffney E, Keogh JA. A case of IgA nephropathy associated with vitiligo, primary hypothyroidism and primary adrenocortical insufficiency. Ir J Med Sci 1989;158:153–4.
[150] Uncu S, Yayli S, Bahadir S, Okten A, Alpay K. Relevance of autoimmune thyroiditis in children and adolescents with vitiligo. Int J Dermatol 2011;50:175–9. https://doi.org/10.1111/j.1365-4632.2010.04665.x.
[151] Bakar-Dertlioğlu S, Uçak H, Çiçek D, Bitiren M. Coexistence of vitiligo and psoriasis: three case reports. Turk J Pediatr 2012;54:77–9.
[152] Walters TR, Lerner AB, Nordlund JJ. Autoimmune Hemolytic Anemia Vitiligo. 2015.
[153] Cho SB, Kim JH, Cho S, Park JM, Park YK, Oh SH. Vitiligo in children and adolescents: association with thyroid dysfunction. J Eur Acad Dermatology Venereol 2011;25:64–7. https://doi.org/10.1111/j.1468-3083.2010.03694.x.
[154] Iacovelli P, Sinagra JLM, Vidolin AP, Marenda S, Capitanio B, Leone G, et al. Relevance of thyroiditis and of other autoimmune diseases in children with vitiligo. Dermatology 2005;210:26–30. https://doi.org/10.1159/000081479.
[155] Go T, Mitsuyoshi I. Juvenile dermatomyositis associated with subclinical hypothyroidism due to auto-immune thyroiditis. Eur J Pediatr 2002;161:358–9. https://doi.org/10.1007/s00431-002-0947-3.
[156] Holmes MV, Ioannou Y, Borysiewicz C, Sen D. Juvenile dermatomyositis with Sjogren's syndrome. Clin Rheumatol 2008;27(Suppl. 1):S3–5. https://doi.org/10.1007/s10067-007-0795-7.
[157] Kobayashi T, Asakawa H, Komoike Y, Nakano Y, Tamaki Y, Monden M. A patient with Graves' disease, myasthenia gravis, and polymyositis. Thyroid 1997;7:631–2. https://doi.org/10.1089/thy.1997.7.631.
[158] Koves IH, Cameron FJ, Kornberg AJ. Ocular myasthenia gravis and graves disease in a 10-year-old child. J Child Neurol 2009;24:615–7. https://doi.org/10.1177/0883073808324777.
[159] Kitthaweesin K, Auvichayapat N, Panamonta O. Ocular myasthenia gravis and auto-immune thyroiditis in children. J Med Assoc Thai 2005;88(Suppl. 9):S131–3.
[160] Palcoux JB, Janin-Mercier A, Campagne D, Fonck Y, Betail G. Sjogren syndrome and lupus erythematosus nephritis. Arch Dis Child 1984;59:175–7.
[161] Franklin DJ, Smith RJ, Person DA. Sjogren's syndrome in children. Otolaryngol Head Neck Surg 1986;94:230–5. https://doi.org/10.1177/019459988609400217.
[162] Tasdemir M, Hasan C, Agbas A, Kasapcopur O, Canpolat N, Sever L, et al. Sjögren's syndrome associated with systemic lupus erythematosus. Türk Pediatr Arşivi 2016;51:166–8. https://doi.org/10.5152/TurkPediatriArs.2016.2001.
[163] Miconi F, Savarese E, Miconi G, Cabiati G, Rapaccini V, Principi N, et al. Unusual onset of celiac disease and addison's disease in a 12-year-old boy. Int J Environ Res Public Health 2017;14:4–9. https://doi.org/10.3390/ijerph14080855.
[164] Mukamel M, Rosenbach Y, Zahavi I, Mimouni M, Dinari G. Celiac disease associated with systemic lupus erythematosus. Isr J Med Sci 1994;30:656–8.
[165] Zeglaoui H, Landolsi H, Mankai A, Ghedira I, Bouajina E. Type 1 diabetes mellitus, celiac disease, systemic lupus erythematosus and systemic scleroderma in a 15-year-old girl. Rheumatol Int 2010;30:793–5. https://doi.org/10.1007/s00296-009-0988-2.
[166] Fischer T, Biedermann T, Hermann K-GA, Diekmann F, Braun J, Hamm B, et al. Sacroiliitis in children with spondyloarthropathy: therapeutic effect of CT-Guided intra-articular corticosteroid injection. Rofo 2003;175:814–21. https://doi.org/10.1055/s-2003-39925.
[167] Hansen D, Bennedbaek FN, Hansen LK, Hoier-Madsen M, Jacobsen BB, Hegedus L. Thyroid function, morphology and autoimmunity in young patients with insulin-dependent diabetes mellitus. Eur J Endocrinol 1999;140:512–8.
[168] Tulpar S, Poyrazoglu MH, Patiroglu TE, Kendirci M, Bastug F, Gunduz Z, et al. Lupus nephritis in a child with type I diabetes mellitus. J Trop Pediatr 2011;57:396–8. https://doi.org/10.1093/tropej/fmq103.
[169] Nagy KH, Lukacs K, Sipos P, Hermann R, Madacsy L, Soltesz G. Type 1 diabetes associated with Hashimoto's thyroiditis and juvenile rheumatoid arthritis: a case report with clinical and genetic investigations. Pediatr Diabetes 2010;11:579–82. https://doi.org/10.1111/j.1399-5448.2010.00676.x.
[170] Radetti G, Paganini C, Gentili L, Bernasconi S, Betterle C, Borkenstein M, et al. Frequency of Hashimoto's thyroiditis in children with type 1 diabetes mellitus. Acta Diabetol 1995;32:121–4.
[171] Nasir A, Jurayyan M. Autoimmune disorders associated with type 1 diabetes mellitus in Saudi children and adolescent. J Med Clin Sci 2014;3:136–40.
[172] Joseph J, Saroha V, Payne H, Paul P, Didi M, Isherwood D, et al. Thyroid function at diagnosis of type I diabetes. Arch Dis Child 2011;96:777–9. https://doi.org/10.1136/adc.2009.168799.
[173] Jung ES, Han DK, Yang EM, Kim MS, Lee D-Y, Kim CJ. Thyroid autoimmunity in children and adolescents with newly diagnosed type 1 diabetes mellitus. Ann Pediatr Endocrinol Metab 2014;19:76–9. https://doi.org/10.6065/apem.2014.19.2.76.
[174] Nowier SR, Eldeen NS, Farid MM, Rasol HAA, Mekhemer SM. Prevalence of celiac disease among type 1 diabetic Egyptian patients and the association with autoimmune thyroid disease. Bratisl Lek Listy 2009;110:258–62.
[175] Agrawal S, Desai MP. Simultaneous occurrence of type I diabetes mellitus and juvenile rheumatoid arthritis. Indian Pediatr 2003;40:568–71.
[176] Najafi M, Zamani MM, Rezaei N, Sabbaghian M. Autoimmunity in inflammatory bowel disease: a case of ulcerative colitis with diabetes mellitus, autoimmune

hepatitis and autoimmune hypothyroidism. Turk J Pediatr 2012;54:651–3.
[177] Ordonez F, Lacaille F, Canioni D, Talbotec C, Fournet JC, Cerf-Bensussan N, et al. Pediatric ulcerative colitis associated with autoimmune diseases: a distinct form of inflammatory bowel disease? Inflamm Bowel Dis 2012;18:1809–17. https://doi.org/10.1002/ibd.22864.
[178] Giraldo Escobar LM, Crespo Madrid N, Vila Miravet V, Pujol Muncunill G, Varea Calderón V, Martín De Carpi J. Colitis ulcerosa asociada a hepatitis autoinmune: ¿una forma diferencial de enfermedad inflamatoria intestinal? An Pediatr 2014;82:e78–81. https://doi.org/10.1016/j.anpedi.2013.11.013.
[179] Lin H-K, Wang J-D, Fu L-S. Juvenile diffuse systemic sclerosis/systemic lupus erythematosus overlap syndrome–a case report. Rheumatol Int 2012;32:1809–11. https://doi.org/10.1007/s00296-011-1937-4.
[180] Jarasvaraparn C, Imran H, Siddiqui A, Wilson F, Gremse DA. Association of autoimmune hepatitis type 1 in a child with Evans syndrome. World J Hepatol 2017;9:1008–12. https://doi.org/10.4254/wjh.v9.i23.1008.
[181] Kinouchi R, Kinouchi M, Ishibazawa A, Yoshida A. Macular capillary recovery in systemic lupus erythematosus complicated by Kikuchi-Fujimoto disease. Int Ophthalmol 2018;38:1797–801. https://doi.org/10.1007/s10792-017-0650-z.
[182] Martins SS, Buscatti IM, Freire PS, Cavalcante EG, Sallum AM, Campos LMA, et al. Kikuchi-Fujimoto disease prior to childhood-systemic lupus erythematosus diagnosis. Rev Bras Reumatol 2014;54:400–3. https://doi.org/10.1016/j.rbr.2013.03.003.
[183] Rojas-Villarraga A, Toro C-EE, Espinosa G, Rodriguez-Velosa Y, Duarte-Rey C, Mantilla RDRD, et al. Factors influencing polyautoimmunity in systemic lupus erythematosus. Autoimmun Rev 2010;9:229–32. https://doi.org/10.1016/j.autrev.2009.10.001.
[184] Ho KT, Ahn CW, Alarcón GS, Baethge BA, Tan FK, Roseman J, et al. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXVIII. Factors predictive of thrombotic events. Rheumatology 2005;44:1303–7. https://doi.org/10.1093/rheumatology/kei014.
[185] Mihailova D, Grigorova R, Vassileva B, Mladenova G, Ivanova N, Stephanov S, et al. Autoimmune thyroid disorders in juvenile chronic arthritis and systemic lupus erythematosus. Adv Exp Med Biol 1999;455:55–60.
[186] Alpigiani MG, Cerboni M, Bertini I, D'Annunzio G, Haupt R, Iester A, et al. Endocrine autoimmunity in young patients with juvenile chronic arthritis. Clin Exp Rheumatol 2002;20:565–8.
[187] Bliddal S, Nielsen CH, Feldt-Rasmussen U. Recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polyautoimmunity. F1000Research 2017;6:1776. https://doi.org/10.12688/f1000research.11535.1.
[188] Brunner HI, Silverman ED, To T, Bombardier C, Feldman BM. Risk factors for damage in childhood-onset systemic lupus erythematosus: cumulative disease activity and medication use predict disease damage. Arthritis Rheum 2002;46:436–44. https://doi.org/10.1002/art.10072.
[189] Ravelli A, Caporali R, Di Fuccia G, Zonta L, Montecucco C, Martini A. Anticardiolipin antibodies in pediatric systemic lupus erythematosus. Arch Pediatr Adolesc Med 1994;148:398–402.
[190] Narita T, Oiso N, Fukai K, Kabashima K, Kawada A, Suzuki T. Generalized vitiligo and associated autoimmune diseases in Japanese patients and their families. Allergol Int 2011;60:505–8. https://doi.org/10.2332/allergolint.11-OA-0303.
[191] Krzewska A, Ben-Skowronek I. Effect of associated autoimmune diseases on type 1 diabetes mellitus incidence and metabolic control in children and adolescents. Biomed Res Int 2016;2016:6219730. https://doi.org/10.1155/2016/6219730.
[192] Parra-Medina R, Molano-Gonzalez NN, Rojas-Villarraga A, Agmon-Levin N, Arango M-TT, Shoenfeld Y, et al. Prevalence of celiac disease in Latin America: a systematic review and meta-regression. PLoS One 2015;10:1–19. https://doi.org/10.1371/journal.pone.0124040.
[193] Karavanaki K, Kakleas K, Paschali E, Kefalas N, Konstantopoulos I, Petrou V, et al. Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res 2009;71:201–6. https://doi.org/10.1159/000201108.