Supplementary Table S1. Exploratory Firth penalized logistic regression models in individually documented patients [1,2,6-28]

Outcome	Analysis n / events	Predictor	Scale/reference	Adjusted OR (95% CI)	p value	BH-adjusted p
Any orthostatic dysregulation	29 / 9	Female sex	Female vs male	22.76 (2.31-3086.21)	0.004	0.018
Any orthostatic dysregulation	29 / 9	Age per 5 years	Per 5-year increase	0.99 (0.68-1.43)	0.974	0.974
Upper-extremity involvement	35 / 12	Female sex	Female vs male	0.82 (0.20-3.45)	0.782	0.939
Upper-extremity involvement	35 / 12	Age per 5 years	Per 5-year increase	0.64 (0.31-1.11)	0.153	0.306
Pruritus	32 / 22	Female sex	Female vs male	2.33 (0.42-14.43)	0.332	0.497
Pruritus	32 / 22	Age per 5 years	Per 5-year increase	2.91 (1.33-9.91)	0.006	0.018

Age was entered as a continuous variable per 5-year increase and centered at 14 years. Female sex was compared with male sex. Odds ratios were estimated using Firth penalized logistic regression; 95% confidence intervals were obtained by profile likelihood and p values by penalized likelihood-ratio tests. Benjamini-Hochberg correction was applied across the six prespecified regression coefficients. BH, Benjamini-Hochberg; CI, confidence interval; OR, odds ratio.

Supplementary Table S2A. Demographic and clinical features of individually documented patients [1,2,6-28]

Study/case	Age P/O	Sex	Trigger(s)	Site(s)	Symptoms	Orthostatic/autonomic
Bortoluzzi & Silver 2023, case 1	15 / 12	F	standing, heat	LE	Pruritus, warmth	None
Bortoluzzi & Silver 2023, case 2	18 / 15	M	standing	LE, trunk, face	Paraesthesia, cold sensation	None
Bortoluzzi & Silver 2023, case 3	15 / NR	M	standing, shower/bath, exercise	LE, UE during running	Pruritus, paraesthesia, warmth, prominent veins	None
Ceravalls et al. 2024	58 / 54	F	standing	LE	Pruritus	None
Yokamamoharan & Lioger 2026	20 / 8	F	standing	LE	Pruritus, hyperesthesia, weakness	OI
Bessis et al. 2016, case 1	14 / 12	F	heat	LE	Pruritus	POTS*
Bessis et al. 2016, case 2	15 / 14.17	F	standing	LE, feet	Pruritus, ankle edema	NR
Bessis et al. 2016, case 3	19 / 5-17	M	standing	LE	NR	NR
Bessis et al. 2016, case 4	0.25 / 0.25	M	compression	LE, UE	Tenderness, unilateral LE edema	NR

Study/case	Age P/O	Sex	Trigger(s)	Site(s)	Symptoms	Orthostatic/autonomic
Bessis et al. 2016, case 5	0.25 / NR	M	compression	LE	Edema of lower left limb	None
Gambichler et al. 2023	18 / 5-17	F	standing	LE	Pruritus	Mild OH
Romero-Jiménez et al. 2023, case 1	12 / NR	M	hanging arms	Hands	NR	None
Romero-Jiménez et al. 2023, case 2	15 / NR	F	standing, hanging arms	Hands, LE	NR	None
Liu et al. 2022	19 / NR	F	standing	LE	Pruritus, weakness	POTS
Baurens et al. 2022	14 / 13.58	F	standing	LE (ascending), hands	Pruritus, asthenia, cramps	POTS
Barbe et al. 2021, case 1	0.50 / NR	F	compression	LE, UE	Edema	None
Barbe et al. 2021, case 2	0.42 / NR	F	compression	LE	Tenderness, edema	None
Barbe et al. 2021, case 3	16 / NR	F	standing, activity/walking	LE	Painful	None
Guillen-Climent et al. 2021	12 / 10	F	standing	LE	Pruritus	Positive orthostatic screen
Jimenez-Gallo et al. 2018	8 / 5	M	standing	Trunk, UE	Asymptomatic	None
El Nemnom et al. 2020, case 1	13 / 13	M	standing, shower/bath	LE	Pruritus, painful	None
El Nemnom et al. 2020, case 2	13 / 10	F	shower/bath, activity/walking	LE	Pruritus, painful	None
Berrebi et al. 2021	10 / NR	M	standing, shower/bath	LE, hands	Paraesthesia, non-pitting edema	NR
Keeling et al. 2024	15 / 13	M	standing	LE	Pruritus	None
Thielmann et al. 2025	12 / 11	F	standing, activity/walking	LE	Painful	None
Saratani et al. 2026	13 / 12	M	standing	LE	Pruritus	NR
Bygum & Rasmussen 2021	17 / NR	F	standing	LE	Pruritus	NR
Gabrielli et al. 2021	14 / 12	F	standing	LE (calves to knees)	Pruritus, paraesthesia, livedo/prominent vessels	Negative orthostatic screen

Study/case	Age P/O	Sex	Trigger(s)	Site(s)	Symptoms	Orthostatic/autonomic
Hirohata et al. 2016	16 / 13	M	standing	LE	Pruritus, painful, edema	None
Danescu et al. 2018	11 / 11	F	standing	LE, UE	paraesthesia, pruritus	Initial OH (symptomatic)
Martin et al. 2018	13 / 11	F	standing	LE, UE	pruritus	Orthostatic disorder reported
Cunningham et al. 2021	16 / 15	M	standing	LE	stinging, burning	None
Present case	21 / 13	F	standing, heat, shower/bath	LE, hands	pruritus	POTS
Galindo-Gomez & Martinez-Osorio 2022	13 / 12	M	standing	LE	Severe pruritus	None; OH/POTS excluded
Nakayama et al. 2025	10 / 10	M	standing	LE, UE, hands	Pruritus, pain	None; OI/POTS excluded

Age P/O, age at presentation / age at onset; F, female; M, male; LE, lower extremities; UE, upper extremities; NR, not reported; OH, orthostatic hypotension; OI, orthostatic intolerance; POTS, postural orthostatic tachycardia syndrome.*2 years later diagnosed [2].

Supplementary Table S2B. Associated conditions, treatment, and outcomes of individually documented patients [1,1,6-28]

Study/case	Selected associated conditions	Treatment	Outcome
Bortoluzzi & Silver 2023, case 1	Premature delivery, fifth disease (at age <2 yo)	Cetirizine 20 mg 1x/day	Reduced frequency
Bortoluzzi & Silver 2023, case 2	Autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), dyslexia, migraines without aura, uveitis, syncope/presyncope	Cetirizine; diphenhydramine; bilastine	Reduced frequency; greater response to bilastine
Bortoluzzi & Silver 2023, case 3	ADHD, asthma, eczema	Cetirizine 20 mg 1x/day	Reduced frequency
Ceravalls et al. 2024	Breast cancer in remission, smoking cessation, upper respiratory infection (URI) (possible temporal association), instability after abrupt postural changes	Bilastine 40 mg/12 h	No drug response; spontaneous resolution at 3 months
Yokamamoharan & Lioger 2026	Chronic orthostatic intolerance, malaise, dizziness	Recumbency, cold water, compression	Allowed her to tolerate lying prone for 20 minutes
Bessis et al. 2016, case 1	Disseminated pruritic cutaneous lesions	Desloratadine 10 mg 1x/day for 7 days	Partial pruritus response; lesions unchanged
Bessis et al. 2016, case 2	NR	H1-Antihistamines, tranexamic acid	No response
Bessis et al. 2016, case 3	None	NR	Spontaneous complete regression after 2 years
Bessis et al. 2016, case 4	NR	NR	NR
Bessis et al. 2016, case 5	NR	NR	NR
Gambichler et al. 2023	None	Bilastine, fexofenadine, compression stockings	No response
Romero-Jiménez et al. 2023, case 1	None	Antihistamines	No response
Romero-Jiménez et al. 2023, case 2	None	Antihistamines	No response

Study/case	Selected associated conditions	Treatment	Outcome
Liu et al. 2022	Idiopathic gastroparesis, jejunostomy tube, POTS, lightheadedness	Ivabradine, fludrocortisone, loratadine	Partial response to ivabradine/fludrocortisone; pruritus improved with loratadine
Baurens et al. 2022	Cough, rhinorrhea (during COVID-19 pandemic), postural tachycardia	High-dose bilastine; fludrocortisone	Improved pruritus after several months
Barbe et al. 2021, case 1	NR	NR	NR
Barbe et al. 2021, case 2	NR	NR	NR
Barbe et al. 2021, case 3	NR	NR	NR
Guillen-Climent et al. 2021	Dizziness when abruptly moving from lying to standing up	Bilastine 20 mg 2x/day	Pruritus resolved; lesions unchanged
Jimenez-Gallo et al. 2018	NR	Antihistamines	No response
El Nemnom et al. 2020, case 1	Raynaud's phenomenon, overweight	Desloratadine; exercise; dietary modification	No response
El Nemnom et al. 2020, case 2	Ankle pain	Desloratadine; exercise; leg elevation	No response
Berrebi et al. 2021	Non-pitting edema (associated with episodes), developmental delay, ADHD, asthma, seasonal allergies, asymptomatic COVID-19 infection	NR	NR
Keeling et al. 2024	Dermatographia	Escalating fexofenadine; montelukast	Dose-dependent symptom reduction
Thielmann et al. 2025	None	Desloratadine 5 mg	NR
Saratani et al. 2026	Venous reflux	Bilastine 20 mg 1x/day	Partial improvement
Bygum & Rasmussen 2021	None	High-dose antihistamine	Symptomatic relief
Gabrielli et al. 2021	Chronic inducible urticaria, spontaneous urticaria	Bilastine 40 mg 2x/day; omalizumab 300 mg 1x/month	Poor bilastine response; omalizumab improved UAS but not postural symptoms
Hirohata et al. 2016	Edematous urticarial erythema	Fexofenadine, diphenhydramine	No response
Danescu et al. 2018	orthostatic hypotension	Antihistamines	No response
Martin et al. 2018	NR	NR	NR
Cunningham et al. 2021	NR	High-dose bilastine	Complete remission

Study/case	Selected associated conditions	Treatment	Outcome
Present case	ADHD, ectopial atrial tachycardia, joint hypermobility, fibromyalgia, migraines, Raynaud's phenomenon, factitial urticaria	Antihistamines	No response
Galindo-Gomez & Martinez-Osorio 2022	Palmoplantar hyperhidrosis, positive dermographism	Cetirizine 10 mg every 12 hours for 3 months	Pruritus/papules improved; provocation otherwise unchanged
Nakayama et al. 2025	Hepatoblastoma; postoperative after hepatic resection; prior chemotherapy	Fexofenadine 30 mg twice daily, tapered and stopped	Complete response; no recurrence after withdrawal

NR, not reported. Confirmed follow-up or duplicate publications were merged at patient level; the later reply concerning the initial Bessis et al. [1] patient #1 was not counted as an additional patient.

Supplementary Table S3A. Exploratory categorical patient-level associations

Association	n	Reference group	Exposed group	OR (95% CI)	p	BH-adjusted p
Female sex vs upper-extremity involvement	35	6/15 (40.0%)	6/20 (30.0%)	0.65 (0.13-3.30)	0.721	0.901
Female sex vs multisite involvement	35	6/15 (40.0%)	6/20 (30.0%)	0.65 (0.13-3.30)	0.721	0.901
Female sex vs pruritus	32	7/13 (53.8%)	15/19 (78.9%)	3.09 (0.53-20.39)	0.244	0.535
Female sex vs pain/paraesthesia	32	8/13 (61.5%)	8/19 (42.1%)	0.47 (0.08-2.37)	0.473	0.807
Female sex vs any orthostatic dysregulation	29	0/11 (0.0%)	9/18 (50.0%)	Not estimable	0.005	0.103
Any orthostatic dysregulation vs upper-extremity involvement	29	6/20 (30.0%)	4/9 (44.4%)	1.83 (0.26-12.42)	0.675	0.901
Any orthostatic dysregulation vs multisite involvement	29	6/20 (30.0%)	4/9 (44.4%)	1.83 (0.26-12.42)	0.675	0.901
Any orthostatic dysregulation vs pruritus	27	10/18 (55.6%)	9/9 (100.0%)	Not estimable	0.026	0.129
Any orthostatic dysregulation vs pain/paraesthesia	27	11/18 (61.1%)	3/9 (33.3%)	0.33 (0.04-2.20)	0.236	0.535
Any orthostatic dysregulation vs edema	27	4/18 (22.2%)	0/9 (0.0%)	0.00 (0-2.96)	0.268	0.535
Reported ADHD vs any orthostatic dysregulation	22	7/19 (36.8%)	1/3 (33.3%)	0.86 (0.01-19.57)	1.000	1.000
Reported migraine vs any orthostatic dysregulation	22	7/20 (35.0%)	1/2 (50.0%)	1.80 (0.02-156.81)	1.000	1.000

Reference and exposed groups correspond to exposure values 0 and 1, respectively. Odds ratios are conditional maximum-likelihood estimates from two-sided Fisher exact tests. BH, Benjamini-Hochberg; CI, confidence interval; OR, odds ratio.

Supplementary Table S3B. Exploratory continuous-variable comparisons

Comparison	n	Group 0, median (IQR)	Group 1, median (IQR)	Rank-biserial r	p	BH-adjusted p
Age at presentation by sex	35	15; 13 (10-15.50)	20; 14.50 (12.75-17.25)	0.27	0.186	0.535
Age at presentation by upper-extremity involvement	35	23; 15 (13-17.50)	12; 11.50 (9.50-14.25)	-0.47	0.026	0.129
Age at presentation by multisite involvement	35	23; 15 (13-16.50)	12; 12 (9.50-15)	-0.33	0.121	0.482
Age at presentation by pruritus	32	10; 9 (0.44-15)	22; 14.50 (13-16.75)	0.53	0.018	0.129
Age at presentation by pain/paraesthesia	32	16; 14.50 (12.75-17.25)	16; 13.50 (10.75-16)	-0.15	0.484	0.807

Comparison	n	Group 0, median (IQR)	Group 1, median (IQR)	Rank-biserial r	p	BH-adjusted p
Age at presentation by any orthostatic dysregulation	29	20; 13.50 (11.50-15.25)	9; 14 (13-19)	0.29	0.227	0.535
Age at onset by sex	23	10; 12.50 (10.50-13)	13; 12 (11-13)	-0.07	0.802	0.944
Disease duration by any orthostatic dysregulation	20	13; 2 (1-3)	7; 2 (1.21-5)	0.03	0.936	1.000

Group 0 and group 1 correspond to absence and presence of the binary grouping characteristic. BH, Benjamini-Hochberg; IQR, interquartile range.