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BRIEF REPORT

Characteristics of pain, other symptoms and function in pediatric post-thrombotic syndrome

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Abstract

Background: Symptoms and function in pediatric post-thrombotic syndrome (PTS) remain poorly characterized.

Methods: The present cross-sectional study describes the characteristics of pain, other symptoms, and impaired function in pediatric PTS in a cohort of children with history of upper or lower limb deep vein thrombosis and PTS diagnosis. The frequency of clinical findings was compared between patients with and without pain, and between patients with upper and lower extremity PTS.

Results: Seventy-eight children were included in the study. The most common PTS symptoms were pain, tired limb and heaviness. Symptoms were usually reported to occur at mid-day or later and were typically triggered by exercise. Half the patients reported impaired endurance. Pain was reported by 45% of patients and was usually mild-moderate. Heaviness, tightness, tired limb, paresthesia, self-reported limb edema, and impaired endurance were most common in patients with than in patients without pain. Conversely, activity and participation scores, skin redness, and clinician-assessed limb edema did not differ between patients with and without pain. Lastly, there was no difference in pain intensity or frequency of paresthesia, swelling, heaviness, or impaired endurance when comparing the upper and lower extremities.

Conclusion: Tired limb, heaviness, pain, and impaired endurance were the most frequent clinical findings in pediatric PTS. Frequency of symptoms and pain intensity did not differ between upper and lower extremities. Pain was associated with the presence of other symptoms and impaired function, but not with activity limitation and participation restriction. Better tools are needed to measure these two latter aspects of health.

KEYWORDS
child, deep vein thrombosis, lower extremity, signs and symptoms, upper extremity

Essentials

- Symptoms and function in pediatric post-thrombotic syndrome (PTS) remain poorly characterized.
- Clinical features of PTS were studied in 78 children with history of limb deep vein thrombosis.
- Tired limb, heaviness, pain, and impaired endurance were the most frequent clinical findings.
- Frequency of symptoms and of impaired endurance were similar in upper and lower extremities.
- Pain was associated with the presence of other symptoms and impaired function.

1 | BACKGROUND

Post-thrombotic syndrome (PTS) is a form of secondary chronic venous insufficiency defined by the occurrence of typical signs and symptoms[1] in patients with history of deep vein thrombosis (DVT).[2–4]

In addition to the assessment of signs and symptoms, experts in pediatric thrombosis have advocated for the measurement of the functional impact of PTS in children.[5,6] The newly developed index for the Clinical Assessment of Post-Thrombotic Syndrome in children (CAPTSure™) a valid and reliable tool for diagnosis and severity rating of pediatric PTS,[7,8] not only assesses PTS signs and symptoms but also evaluates impaired endurance. Endurance is part of the "Body Functions" component of the International Classification of Functioning, Disability and Health, Children and Youth (ICF-CY) version[9] that reflects muscle function. The ICF-CY provides a framework and standardized language for the classification of health and health-related domains,[9] and was the framework used for the development of CAPTSure™.[7]

Little is known about the characteristics of clinical manifestations in pediatric PTS. The present report aimed to describe the features of pain and other symptoms and of impaired endurance reported by children with PTS, in order to increase our understanding of the clinical findings of pediatric PTS.

2 | METHODS

The present cross-sectional study enrolled a convenience sample of consecutive children aged 10-18 years, with a history of objectively confirmed upper or lower limb deep vein thrombosis (DVT), who had CAPTSure™ scores higher than 0 (ie, indicative of PTS), and completed the self-reported symptoms questionnaire in CAPTSure™. Patients enrolled in the study were assessed in the pediatric thrombosis clinic at The Hospital for Sick Children between March 2014 and August 2017, at least 6 months after their index DVT.

TABLE 1 Characteristics of the cohort

Characteristics of the patients (n = 78)	
Sex, male to female ratio	1.7:1
Age in years, median (25-75th percentile)	15 (12-16)
DVT etiology	
CVL-related	57 (73%)
Non-CVL related	21 (27%)
Distribution of limb DVT n (%)	
Arm	30 (38%)
Leg	48 (62%)
CAPTSure™ scores, median (25-75th percentile)	19.6 (7.3-37.8)

DVT, deep vein thrombosis; CVL, central venous line; CAPTSure™, index for the Clinical Assessment of Post-thrombotic Syndrome.

The symptoms questionnaire is based on the Edinburgh Vein questionnaire (courtesy of Prof. G. Fowkes); the self-reported version is administered to children aged 10 years or older. It collects information on the frequency of heaviness, tired limb, tightness, limb swelling, paresthesia, skin redness/purple or mottled skin, and on the endurance of the affected limb. Definitions and details on measurement approach have been previously reported.[10] In addition, the questionnaire inquires about the time of the day when symptoms occur, the seasonality, and whether symptoms are worse during exercise, daily life activities, or both. Specific to pain are the assessment of intensity over the previous 4 weeks using the Faces Pain Scale–Revised (FPS-R), in addition to pain frequency, descriptors, and location, which are measured using adapted questions from the Adolescent and Pediatric Pain Tool.[10] The present report summarizes the aspects of pain, other PTS symptoms, and impaired endurance included in CAPTSure™. Patients with and without pain, and patients with upper and with lower extremity PTS were compared in terms of frequency of clinical findings and of Pediatric Outcome Data Collection Instrument (PODCI) scores,[11] when available. PODCI is a standardized tool that measures the ability of a child to perform and participate in activities of daily life, therefore evaluating activity limitations and participation restrictions, as defined by the ICF-CY.[11] PODCI provides a global score that is read on a 0 to 100 point scale, with 100 points representing the best possible score (ie, lowest impact on activity and participation). Clinical findings of patients with and without pain were compared in order to further characterize the clinical aspects of children who report pain, the most important clinical feature of pediatric PTS.[7,8]

Descriptive data were summarized with percentages or median and 25-75th percentile. Wilcoxon Rank-sum test and chi-squared test were used to compare findings of patients with and without pain, and of patients with upper and lower extremity PTS. The Spearman correlation coefficient was used to correlate pain frequency and intensity. Statistical significance was set at alpha = 0.05. Statistical analysis was performed with R (R Foundation for Statistical Computing, Vienna, Austria).

The study was approved by the Research Ethics Board of The Hospital for Sick Children. Informed consent and assent were obtained prior to study participation.

3 | RESULTS

Seventy-eight consecutive patients with CAPTSure™ scores >0 were recruited for the study at a median of 76 months post-DVT (25-75th percentile 21.7-141.1 months). The characteristics of these patients are shown in Table 1.

In general, 49% (38 of 78) of patients reported tired limb, 40% (31 of 78) heaviness, 36% (28 of 78) swollen limb, 33% (26 of 78) paresthesia, 21% (16 of 78) tightness, and 15% (12 of 78) redness/purple or blotchy skin. Impaired endurance was reported in half the patients (39 of 78); 98% of these 39 patients reported only slight impairment.

Fifty-three patients reported at least one PTS symptom, not including pain, which occurred most frequently at any time of the day (19 of 53, 36%), mid-day (13 of 53, 26%) and at the end of the day (9 of 53, 17%). Most patients reported that symptoms did not follow a seasonal variation (40 of 53, 75%), and that exercise increased the frequency of symptoms (27 of 53, 51%).

There was no statistically significant difference in the overall frequency of the four clinical findings included in CAPTSure™, excluding pain, that are common to the evaluation of upper and lower extremities, namely heaviness (34% vs. 43%, $P = .62$), paresthesia (34% vs. 33%, $P = 1.00$), swelling (24% vs. 46%, $P = .11$), impaired endurance (48% vs. 51%, $P = 1.00$), and in the distribution of global PODCI scores (median of 84 of 100 points and 93 of 100 points, $P = .44$) when comparing the upper and lower extremities.

Pain was reported by 55% of patients (43 of 78) and was most commonly reported to occur with a frequency of "less than once a week" (13 of 43, 30%), followed by "about once a week" (11 of 43, 28%), and "several times a week" (12 of 43, 26%). Only one patient had pain every day. The median intensity of pain was 3.8 out of 10 points (25-75th percentile 2-4.5). The highest intensity was 6.3 out of 10 points and was reported by a patient affected by upper extremity PTS. Pain frequency and intensity did not differ significantly between the upper and lower extremities (pain frequency of 43% and 63% for upper and lower extremities, respectively, $P = .16$; median pain intensity of 3.0 out of 10 points and of 3.8 out of 10 points for upper and lower limbs, respectively, $P = .95$).

Patients referring pain were more likely to refer impaired endurance and other symptoms, except for redness/purple or blotchy skin (Table 2). PODCI scores did not differ significantly between patients with and without pain. Forty-seven out of the 78 patients (60%) reported two or more symptoms, including pain.

Regarding pain distribution, most patients indicated pain in only a part of the arm or leg, and only 8 children reported pain affecting the entire extremity, which usually excluded hands and feet. Pain located between the shoulder and elbow was seen in 4 patients and pain between the elbow and wrist was reported by 2 patients; pain located between the hip and knee was more frequent than pain between the knee and ankle (12 vs. 6 patients).

The most frequently mentioned descriptors of pain are shown in Table 3. Lastly, there was a very strong correlation between frequency and intensity of pain (r_s 0.84, $P < .001$).

4 | DISCUSSION

Overall, our study showed impaired endurance to be the most common clinical finding in children with PTS, followed by tired limb, pain, and heaviness. In addition, we observed that PTS symptoms tended to occur at mid-day or later, and with exercise. Pain was generally mild (ie, between 1 and 3.9 out of 10 points of the FPS-R); no episodes of severe pain were recorded.

Although it has been hypothesized that clinical findings might be milder in children with upper extremity PTS,[6,10] we found no significant difference in pain intensity or frequency of other symptoms

TABLE 2 Characteristics of patients with and without pain

	Patients without pain, n = 35	Patients with pain, n = 43	*P* value
Symptoms n (%)			
Tired limb (n = 73)	6 (17%)	32 (74%)	<.001
Heaviness (n = 78)	7 (20%)	24 (56%)	.002
Swollen limb (self-reported) (n = 78)	5 (14%)	23 (68%)	<.001
Paresthesia (n = 77)	5 (14%)	21 (49%)	.003
Tightness (n = 73)	2 (6%)	14 (33%)	.008
Redness in skin (n = 73)	3 (9%)	9 (21%)	.23
Function			
Impaired endurance (n = 78)	7 (20%)	32 (74%)	<.001
Limb circumference difference >1 cm (as compared to contralateral limb) n (%)	21 (60%)	24 (56%)	.89
Global PODCI scores, median (25-75th percentile, n = 64)	94 (92-98)	91 (83-95)	.051

PODCI, Pediatric Outcome Data Collection Instrument.

TABLE 3 Pain descriptors ranked by frequency

Descriptor	Frequency n (%)	Descriptor	Frequency n (%)
Annoying	21 (49%)	Numb	7 (16%)
Aching/like an ache	16 (37%)	Hot	6 (14%)
Cramping	15 (35%)	Sneaks up	6 (14%)
Sore	14 (33%)	Itching	5 (12%)
Uncomfortable	13 (30%)	Like a sharp knife/ sharp	5 (12%)
Swollen	12 (28%)	Sometimes	4 (9%)
Tight	11 (26%)	Stinging/like a sting	4 (9%)
Hurting	10 (23%)	Comes on all of a sudden	3 (7%)
Stiff	10 (23%)	Pounding	3 (7%)
Pressure	9 (21%)	Like a pin	3 (7%)
Throbbing	9 (21%)	Hitting	2 (5%)
Comes and goes	9 (21%)	Steady	2 (5%)
Off and on	8 (19%)	Uncontrollable	2 (5%)
Once in a while	7 (16%)	Bad	2 (5%)

when comparing the upper and lower extremities. In fact, the highest pain intensity recorded in this cohort occurred in a patient with upper extremity PTS.

A strong correlation was found between pain intensity and frequency. A study conducted among adult patients has shown a high correlation between frequency and intensity of items of the Functional Assessment of Chronic Illness Therapy tool.[12] Nevertheless, the relation between the intensity and the frequency of a symptom remains poorly explored.[10]

Since by definition PTS is a collection of signs and symptoms, it is conceptually related to the impairment of the "Body Structures" and "Body Functions" components of the ICF-CY.[9] As mentioned above, CAPTSure™ assesses impaired endurance (Body Functions) in addition to typical signs and symptoms (Body Structures).

Although clinicians and researchers often intuitively attempt to evaluate diseases from a more global perspective and refer to functional outcomes as the impact of the disease on activities and participation, it must be noted that "Activities" and "Participation" are distinct components in the ICF-CY framework, different from the "Body Structures" and "Body Functions" components that are at the center of the definition of PTS, as mentioned above. In a previous study we showed that PODCI, which measures activities and participation in children, might be a reasonably good approximation to assess the impact of PTS on the lower extremities. However, PODCI was not sensitive enough to measure the impact of PTS on the upper extremities.[13] This is likely due to the fact that children with impaired endurance may find that most of the activities listed in PODCI for the evaluation of upper extremities are easy to perform. In contrast, some of the activities listed for the evaluation of lower extremities are more challenging and require better endurance.

In addition, according to the ICF-CY framework, the term *functioning* includes "all body functions, activities and participation". Since the Perinatal/Paediatric Haemostasis Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis recommends assessment of the different aspects of *functioning* in pediatric patients with PTS,[5,6] comparison of PTS scores with those of tools that assess activity limitation and participation restriction is relevant. Nonetheless, the extent to which PTS interferes with activity and participation remains poorly explored and a more specific instrument for evaluation activity limitation and participation restriction in children with PTS is needed.

Lastly, we found no statistically significant association between pain and PODCI scores, even though impaired endurance was more frequently seen in patients with pain. Moreover, PODCI scores in patients with pain were only slightly below the mean score for healthy children (mean of 97 out of 100 points, with a standard deviation of 2-4, depending on the age of the patient),[14] once again suggesting that specific instruments are required for assessment of more global aspects of the impact of PTS.

Our study needs to be interpreted in the light of potential limitations. For example, symptoms were generally recorded in terms of frequency rather than intensity. However, the high correlation between these two characteristics has been highlighted before, and patient cognitive burden as a result of an increased length of a questionnaire inquiring about both intensity and frequency was taken into account when choosing the design of the symptoms questionnaire.

Given the population included in the study, results are expected to be generalizable to older children who sustained limb DVT.

In conclusion, impaired endurance, tired limb, and pain were the most frequent findings in this cohort of children with PTS. As opposed to what is commonly hypothesized, we found no difference in pain intensity and frequency of other symptoms when comparing the upper and the lower extremities. Lastly, although patients with pain usually reported other PTS symptoms as well as impaired function, there was no difference in activity limitation

and participation restriction, as measured by PODCI. This suggests, once again, that in order to investigate how pediatric PTS affects the health of children, a specific instrument able to detect the consequences of PTS-related impaired body structures and function should be developed.

RELATIONSHIP DISCLOSURE

None of the authors have any disclosures relevant to this paper.

AUTHOR CONTRIBUTIONS

LA, LB, SW, CL, and MM performed measurements and administered questionnaires. CL and MM assisted with study and data management. LA performed statistical analysis and wrote the manuscript. LB, MM, SW, JS, CL, and BF critically reviewed the manuscript.

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