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Post-thrombotic syndrome in children

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ABSTRACT

The post-thrombotic syndrome (PTS) is the most common long-term complication of pediatric deep venous thrombosis (DVT). It is a burdensome condition that can lead to severe disability and poor quality-of-life of affected children. Although its pathophysiology remains poorly understood, it is thought to be the result of chronic venous hypertension. Recent studies have shown that the inflammatory response associated with an acute DVT likely plays a key role in the development of PTS. The Manco-Johnson Instrument and the modified Villalta Scale are the most widely used instruments for the diagnosis of pediatric PTS. To date, few prognostic indicators for the development of PTS following pediatric-onset DVT have been identified and substantiated in published research, limiting our ability to identify those patients at high-risk for the development of this complication. There is also limited evidence on therapeutic strategies and long-term outcomes of pediatric PTS. Further research aimed at improving our understanding of the pathophysiology and prognostic indicators of PTS is needed to enhance the currently limited risk prediction models for pediatric PTS. Early identification of pediatric patients at risk for PTS is essential to investigate preventive and therapeutic interventions aimed at decreasing the risk and severity of this complication in children. This review aims to summarize the current available evidence on the pathophysiology, risk factors, diagnosis, and management of pediatric PTS.

1. Introduction

The incidence of pediatric venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), has dramatically increased over the last few decades, particularly among hospitalized children in whom it has become the second most common cause of preventable harm [1–3]. This is likely the result of improvements in the care of critically ill children and a heightened awareness of thrombotic complications among medical providers. VTE is a serious condition that can lead to significant long-term morbidity when it is associated with the development of the post-thrombotic syndrome (PTS).

The PTS is the most common long-term complication in pediatric patients with an extremity DVT. It is a chronic condition characterized by the development of venous insufficiency that manifest clinically as extremity swelling, pain, cramping, stasis dermatitis and ulceration of the affected limb [4]. The reported incidence of pediatric PTS varies significantly across studies, with estimates ranging from 3% to 70% among children followed for a median time of two years after an extremity DVT [4,5]. This variability is likely the result of the heterogeneity of study designs, patient populations and methods used to assess PTS across studies. A recent systematic review of the literature and meta-analysis reported a weighted average for the development of PTS of approximately 25% in children with an extremity DVT, assessed within 1 year from diagnosis, with the use of a validated pediatric instrument [5]. PTS is a burdensome condition that can lead to severe disability and poor quality-of-life (QoL) of affected patients. Prior data have shown that children with moderate to severe PTS symptoms have significantly lower QoL scores compared to their counterparts who have mild or no PTS [6]. Because children are expected to live several decades dealing with DVT-related morbidity, the development of PTS following pediatric-onset VTE results in a disproportionally higher physical, psychosocial and financial burden than that which follows adult-onset VTE [6].

Over the last decade, PTS has been increasingly recognized as a serious VTE complication, and was recently identified by the *Perinatal and Pediatric Hemostasis Scientific and Standardization Subcommittee* (*SSC*) of the International Society of Thrombosis and Hemostasis (ISTH) as "an important secondary outcome of interest" in clinical investigations [7]. Despite the recent research focus on PTS, there remains a lack of published evidence on the underlying mechanisms, prognostic factors, natural history and management of this complication. This gap in knowledge impedes the development of individualized, risk-stratified strategies to prevent or minimize the burden of PTS in pediatric DVT. It also highlights the need for further research aimed at improving our understanding of the risk factors associated with pediatric PTS with

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Table 1
Predictors of pediatric PTS.

Author Year	Study design	No of patients (Age)	PTS assessment	PTS frequency	Findings
Avila ML 2014	Retrospective cohort	158 (0–17 years)	MVS	49.3% (mild to moderate PTS)	*Predictors of UE PTS* Univariate analysis age ($P = 0.001$) Symptomatic DVT at presentation (yes vs. no, $P = 0.001$) Subclavian vein involvement (yes vs. no, $P = 0.02$) Type of treatment (no treatment or prophylaxis, anticoagulation, thrombolysis, $P = 0.003$); and length of anticoagulation treatment (<45 days vs. 45–90 days vs. >90 days, $P = 0.023$) Multivariate analysis Patients with primary (idiopathic or effort-related thrombosis) UE-DVT were 37.7 (95% CI = 10.7–133.6) times more likely to develop PTS than patients with secondary UE-DVT Patients with no resolution or with extension of thrombosis were 7.16 (95% CI = 1.5–33.4) times more likely to develop PTS than patients with complete resolution Sex, number of affected vein segments, degree of vessel occlusion (occlusive vs. non-occlusive), resolution of DVT, recurrence of DVT, and presence of thrombophilia were not significantly associated to the development of UE PTS in the univariate analysis
Avila ML 2016	Retrospective cohort	339 (0–16 years)	MVS	47.2% (mild to moderate PTS)	*Predictors of LE PTS* Lack of DVT resolution (OR 3.15, 95% CI 1.47–6.72) Sex and DVT trigger (CVC vs. Non-CVC): Male vs. females with CVC DVT (OR 2.5, 95% CI 1.25–5.00) Females with Non-CVC vs females CVC DVT (OR 4.92, 95% CI 1.97–12.3) Iliofemoral thrombosis, type of treatment and DVT recurrence were not significantly associated to the development of PTS
Goldenberg NA 2004	Prospective cohort	82 (0–20 years)	MJI	33%	*Predictors of poor outcome* (*residual thrombosis*, *VTE recurrence and/or PTS*) Elevated factor VIII, D-dimer, or both at diagnosis were predictive of poor outcome (OR: 6.1; $P = 0.008$) Persistence elevation of factor VIII, D-dimer, or both at three to six months was predictive of poor outcome (OR: 4.7; $P = 0.002$) Sex, median age, duration of anticoagulation therapy, presence of underlying inflammatory condition or lupus anticoagulant at diagnosis were not associated with an increased risk of poor outcomes
Goldenberg NA 2007	Prospective cohort (retrospective analysis)	22 (6 months–21 years)	MJI	54.5%	*Predictors of PTS* Compared to standard anticoagulation alone, thrombolytic regimen was associated with decreased odds of PTS (OR = 0.086, 95% CI = 0.011–0.655) Thrombus resolution (≥90% clot resolution at 1 year) was significantly associated with decreased odds of PTS compared with those in whom the thrombus persisted (OR = 0.089, 95% CI = 0.008–0.960; $P = 0.046$) Median age, extent of DVT and time from DVT diagnosis to initiation of anticoagulation therapy were not associated with an increased risk of PTS
Kreutz W 2006	Case-control	103 cases (<18 years)	Based on objective signs (i.e. increased ankle circumference, skin pigmentation)	32.2%	*Predictors of PTS* Thrombus extension (OR 3.9, CI 1.13–13.45) Increasing age (OR 1.2, CI 1.07–1.32) BMI (OR 1.2, CI 1.10–1.4) Factor VIII levels were not associated with an increased risk of PTS
Kuhle S 2003	Cross-sectional study	153 (<21 years)	Pediatric PTS score adapted from the MVS	63% (17% moderate PTS, no severe)	*Predictors of PTS* Lack of DVT resolution by radiographic assessment (OR 3.96, 95% CI 1.68–9.30) Number of vessels involved (OR 2.05, 95% CI 1.52–2.77) Length of follow-up (OR 1.22, 95% CI 1.08–1.39) Presence of acquired or congenital thrombophilia was not associated with an increased risk of PTS.
Kumar R 2015	Retrospective cohort	90 (0–18 years)	Validated survey instrument adapted from the MVS	72% (13% moderate to severe PTS)	*Predictors of PTS* Multivariate analysis Time between incident DVT and survey completion (OR 1.75; 95% CI: 1.08–2.84) Number of thrombosed vein segments (OR 1.40; 95% CI: 1.05–1.86) Univariate analysis BMI at survey completion ($P = 0.0009$) Ipsilateral DVT recurrence ($P = 0.029$) Age, sex, site of DVT, extent of DVT (occlusive versus partially occlusive), duration of therapy, underlying thrombophilia and radiological resolution of thrombus were not associated with an increased risk of PTS

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