Incidence Trends and Mortality from Childhood Venous Thromboembolism: A Population-Based Cohort Study

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Objective To determine the incidence, incidence trend, and mortality of venous thromboembolism (VTE) in a general pediatric population during an 11-year period.

Study design The administrative health care databases of the province of Québec, Canada were used to identify all children (ages 1-17 years inclusive) diagnosed with incident VTE between January 1, 1994 and December 31, 2004. The incidence rate and trend over the 11-year study period were then analyzed.

Results In total, 487 incident cases of pediatric VTE were documented. The age-standardized incidence rate was 0.29 VTE per 10 000 person-years (95% CI 0.26-0.31). Girls had a statistically significant higher incidence rate (per 10 000 person-years) than boys, 0.37 and 0.21 per 10 000 person-years, respectively, with an incidence rate ratio comparing females with males, adjusted for age group of 1.75 (95% CI 1.46-2.10). Trend analysis illustrated no statistically significant change in the age-standardized incidence rates. Overall all-cause mortality was 11.4 per 1000 children-years (95% CI 8.1-16.1).

Conclusions Pediatric VTE is frequent, although its incidence is stable over time and all-cause mortality is lower than previously reported. Future studies that address possible sex and age group differences in the incidence of pediatric VTE are needed to help determine effective primary thromboprophylaxis strategies in children at high risk for VTE. *(J Pediatr 2016;172:175-80)*.

Pediatric venous thromboembolism (VTE) includes deep vein thrombosis (DVT) of the upper extremity, lower extremity, or central vasculature, pulmonary embolism (PE), cerebral sinus venous thrombosis (CSVT), and renal vein thrombosis (RVT) from the time of birth until 18 years of age. This condition is linked to significant morbidity and mortality, including VTE recurrence, postthrombotic syndrome, as well as death from fatal PE.[1] Because of differences in study inclusion criteria and methodology for calculating incidence rates,[2-13] the exact incidence of pediatric VTE is unknown with estimates ranging widely from 0.07-0.49 cases/10 000 children.[2,3] Moreover, some studies report a rising trend in the incidence of pediatric VTE over the past 2 decades, although these findings are not consistent.[3,14-18] As a result, a more comprehensive understanding of the epidemiology of pediatric VTE is needed to better inform clinical practices in pediatric VTE, which to date are largely extrapolated from recommendations for adult VTE.[1] We aimed to determine contemporary estimates of pediatric VTE incidence and mortality in the Canadian province of Québec.

Methods

This real-world population-based study employed the linked databases of the province of Québec, Canada to establish a cohort of residents of Quebec between 1 and 18 years of age with an incident VTE upon hospitalization or during hospitalization between January 1, 1994, and December 31, 2004.

We used the linked databases of the Maintenance et exploitation des données pour l'étude de la clientele hospitalière (MED-ECHO) and the Régie de l'assurance maladie du Québec (RAMQ). MED-ECHO is a provincial database maintained since 1967 by the Québec ministry of health with information on all hospital admissions within the province. It consists of all hospital discharges and includes admission and discharge dates, a primary discharge diagnosis, and up to 15 secondary

CSVT	Cerebral sinus venous thrombosis
DVT	Deep vein thrombosis
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
ISQ	Institut de la Statistique du Québec
MED-ECHO	Maintenance et exploitation des données pour l'étude de la clientele hospitalière
PE	Pulmonary embolism
PVT	Portal vein thrombosis
RAMQ	Régie de l'assurance maladie du Québec
RVT	Renal vein thrombosis
VTE	Venous thromboembolism

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discharge diagnoses as classified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) and up to 8 procedure codes using the Canadian classification of diagnostic therapeutic and surgical procedures.[19] RAMQ manages the Québec universal health care scheme, which is mandatory for Québec residents. The unique health insurance number allocated to RAMQ beneficiaries permits electronic linkage of RAMQ's 3 databases to MED-ECHO. Information on birth year, sex, and date of death is stored in the RAMQ demographic database, and information on all reimbursement claims submitted by physicians for medical services provided in both the in- and out-patient setting, including the type of service, date and location of service, and the diagnosis (ICD-9-CM) is present in the RAMQ medical services database. Furthermore, the RAMQ prescription database encompasses information on outpatient-dispensed drugs. The provincial insurance for prescription medication is available only to persons aged 65 years and above, welfare beneficiaries, and residents with no private medication insurance. In 2004, approximately 30% of Québec's under 18-year-olds were covered by this prescription plan.[20] In addition, Québec's death registry administered by the Institut de la Statistique du Québec (ISQ) and linked to RAMQ and MED-ECHO, has information on date and cause of death. To estimate the denominator for calculating the incidence of pediatric VTE, Québec census data for the years 1991, 1996, 2001, and 2006 was obtained from the website of Statistics Canada.[21] Statistics Canada is a branch of the Canadian government enlisted with the responsibility of undertaking the national census. Official census data for Canadian provinces is collected by this body every 5 years.

RAMQ provided all datasets but had no role in the conduct of the study or in the interpretation of the results.

Definitions

The source population for this study was all residents of the province of Québec, Canada, who were younger than 18 years of age and were members of the provincial medical plan at some point between January 1, 1994 and December 31, 2004. From this population, all RAMQ members who had been participants in the health insurance program for at least 12 months preceding a hospitalization associated with an ICD-9-CM diagnosis code for DVT (ICD-9-CM codes 451.0, 451.1, 451.2, 451.8, 451.9, 453.1, 453.2, 453.4, 453.8, 453.9), obstetrical thromboembolism (ICD-9-CM codes 671.3, 671.4, 671.5, 671.9, 673.2, 673.8), RVT (ICD-9-CM code 453.3), PE (ICD-9-CM codes 415.0, 415.1), portal vein thrombosis (PVT) (ICD-9-CM codes 452, 453.0), CSVT (ICD-9-CM code 325, 437.6), peripheral vasculature complication of a procedure (ICD-9-CM code 997.2), lung vascular complication of a procedure (ICD-9-CM code 997.3), and without any previous VTE code dating back to 1983 (inception of database), were included in the study cohort.

The date of cohort entry was the date of the incident VTE, which was defined as the date of hospital admission for any VTE event that was coded as a primary discharge diagnosis. For those events classified as secondary discharge diagnosis, the date of a diagnostic procedure for VTE was used as the cohort entry date, and in the case of no procedural code existing then the median day of hospitalization was used. Twelve months of participation in the provincial health plan was required to ensure that we had sufficient data on all those included in the cohort to determine the presence of risk factors for incident VTE. Therefore, any cases under the age of 1 year at the time of incident VTE diagnosis that were included in the cohort were used only for the assessment of mortality and not in the calculation of population incidence rates. We obtained RAMQ, MED-ECHO, and ISQ data as far as 1 year before the first VTE episode and until death or exit from cohort (emigration from the province) or end of the study (December 31, 2005) whichever was earlier. The end of study date was chosen to allow for at least 1 year of follow-up data for those who entered the cohort in 2004.

The occurrence of death was determined from RAMQ, MED-ECHO, and ISQ. We also used MED-ECHO to identify in-hospital deaths. Cause of death was determined from ISQ.

VTE Risk Predictors

The presence of major risk factors for thrombosis was determined for all VTE events based on diagnostic or surgical codes in MED-ECHO. Risk factors included bone marrow transplant, indwelling central catheter, congenital heart disease, chronic disease (defined as cystic fibrosis, inflammatory bowel disease, sickle cell disease, systemic lupus erythematosus, and nephrotic syndrome) (within 12 months before VTE occurrence), cancer (excluding nonmelanoma skin cancer) and inherited thrombophilia disorders (within 1 year before or after VTE), major surgery (defined as any gynecologic, orthopedic, urologic, neurosurgical, or general surgery procedure), trauma and infections (including meningococcal disease, septicaemia, systemic inflammatory response syndrome, postoperative infection, and mastoiditis) (up to 90 days preceding VTE occurrence), and recent or ongoing pregnancy (within 38 weeks following VTE or within 91 days of delivery).

Statistical Analyses

The crude incidence rate of pediatric VTE was calculated using the number of new VTE cases between January 1, 1994 and December 31, 2004 as the numerator and census-estimated total person-years at risk in the Québec pediatric population during this 11-year period as the denominator. Person-year estimates were calculated using linear interpolation for each age (by individual years) for children ages 1-17 years inclusive and for each calendar year (1994-2004). Age-specific incidence rates and related 95% CIs were determined using attained age during follow-up. Consequently, patients contributed person-time in different age categories while aging during follow-up. The age-standardized incidence rate ratio and its related 95% CIs as well as age-adjusted incidence rates and their associated 95% CIs were