Chapter 16

Chronic pulmonary embolism in Klippel-Trenaunay syndrome


*Equal contribution

Submitted for Publication
ABSTRACT

Background
Klippel-Trenaunay syndrome (KTS) is characterized by vascular malformations and disturbed soft tissue or bony growth, involving one or more extremities. A high incidence of venous thromboembolism (VTE) has been reported in this disorder, along with alarming cases of belated diagnosed chronic thromboembolic pulmonary hypertension (CTEPH).

We performed a cross-sectional study to investigate the prevalence of chronic thromboembolism (CTE) in KTS-patients.

Methods
Patients from our cohort of patients with KTS willing to participate were examined with a sequential diagnostic work-up including perfusion scintigraphy, computed tomography (CT) and echocardiography.

Results
Of 68 patients, 48 patients participated in the study (median age 43 years, 29 (60%) were female). Eleven (23%) patients had an abnormal perfusion scan, of whom CT-scanning showed signs of CTE in two patients (4.2%; 95% confidence interval: 1.2-14%); both patients had a history of VTE. Echocardiography showed no signs of CTEPH in these patients. In total, 23 patients (48%, 35-62%) had a history of superficial vein thrombosis and eight patients (17%, 8.7-30%) had a history of deep vein thrombosis or pulmonary embolism, which was associated with more shortness of breath.

Conclusion
A large proportion of KTS-patients had a history of VTE. The prevalence of CTE in the total KTS cohort, however, appeared less alarming than previously assumed. Based on these results, we suggest that there is only a limited indication for CTEPH screening among KTS–patients, Nevertheless, awareness for CTEPH remains appropriate, especially among patients presenting with shortness of breath and a history of VTE.
INTRODUCTION

Klippel-Trenaunay syndrome (KTS) is characterized by a combination of capillary, venous and lymphatic malformations, and a localized disturbed growth of bone and/or soft tissues (Figure 1) (1-5). The syndrome occurs in all ethnic groups; with an estimated prevalence of 1/20,000-1/100,000 live births (6-8). Clinical presentation may vary from being asymptomatic to developing potentially life threatening complications, such as deep vein thrombosis (DVT), pulmonary embolism (PE), and recurrent bleeding (4,9-11).

Venous thromboembolism (VTE) has been reported in 8-22% of KTS patients. Although up to 30 KTS case reports with PE have been published (4,10,12-21), the exact mechanism underlying the hypercoagulability in vascular malformations remains unclear; however, coagulation activation may be attributed to the stagnation of blood within the distorted, enlarged venous blood vessels (22-24). This could lead to a continuous formation of thrombi, resulting in recurrent PE, as reported in several cases (14,16,18). Moreover, unresolved recurrent PE, originating in the vascular malformations, may lead to chronic thromboembolism (CTE) or even chronic thromboembolic pulmonary hypertension (CTEPH) in KTS patients (14,16,18,21,25). Without early intervention, the prognosis of CTEPH is poor and proportional to the degree of pulmonary hypertension; estimated survival rate at five years being ~10% in patients with a mean pulmonary artery pressure (mPAP) greater than 50mmHg (26-28). In our referral center for CTEPH, we have encountered four patients with CTEPH and congenital vascular malformations (two of whom had KTS) over a five year period. In all patients, the diagnosis of CTEPH was made relatively late in the disease course. Therefore, early detection and diagnosis of chronic pulmonary embolism or CTEPH is crucial for optimal use of the available therapeutic modalities (27-29).

However, although many alarming KTS case reports with CTE or CTEPH have been published, the exact prevalence of CTE or CTEPH among KTS patients remains unknown. Therefore, we performed a cross-sectional study in a well-characterized cohort of Dutch KTS patients to investigate the prevalence of chronic pulmonary embolism.

METHODS

Patients

Adult patients (> 21 years) from a well-characterized Dutch cohort of patients with KTS were eligible. Patients were examined using a sequential diagnostic work-up including perfusion (Q) scintigraphy, contrast-enhanced computed tomography (CT) and echocardiography. The protocol was approved by the medical ethical committee in the Academic Medical Center and all patients gave written informed consent.

Data on the history of venous thromboembolic events, use of anticoagulants and co-morbidity were collected and plasma D-dimer levels were measured in all patients. The patients were
questioned on the presence of dyspnoea at inclusion time, defined as the perception of shortness of breath upon exertion or at rest.

**Perfusion scintigraphy**

For the evaluation of pulmonary embolism, perfusion scintigraphy was performed in all patients following the guidelines of the Society of Nuclear Medicine (SNM 2004). Q-scans were analyzed according to the Modified Prospective Investigation of Pulmonary Embolism Diagnosis (modified PIOPED) (30) criteria for the diagnosis of PE; subsequently, the images were also dichotomized in a normal or abnormal scan result. Perfusion defects with an evident extra pulmonary cause, such as raised diaphragm, were assigned as normal. All Q-scans were analyzed by experienced nuclear medicine physicians.

**Computed tomography scanning**

In case of any abnormalities on perfusion scintigraphy, a CT pulmonary angiography was performed to detect signs of CTE, defined as residual perfusion abnormalities after PE. CT pulmonary angiography was performed using a multi-detector row CT-scanner, according to standardized protocols, with standard contrast enhancement and acquisition of 0.5 to 1 mm sections. Axial images and coronal, sagittal and oblique reconstructions were studied for signs of (chronic) pulmonary embolism. Acute PE was diagnosed if contrast material outlined an intraluminal defect or if a vessel was totally occluded by low-attenuation material on at least 2
adjacent slices. Diagnostic criteria for CTE were 1) complete occlusion of a vessel that is smaller; 2) peripheral eccentric filling defect that makes an obtuse angle with the vessel wall; 3) contrast material flowing through thick-walled arteries with narrower lumen due to recanalization; and 4) the presence of bands or a web in a contrast-filled artery (31). Supportive criteria for the presence of CTE(PH) were 1) presence of mosaic attenuation in the lung parenchyma; 2) dilatation of the main pulmonary artery; and 3) bronchial artery hypertrophy. In case of totally occluded vessels, signs of ‘ballooning’ or ‘outpouching’ were also supportive of the diagnosis. All scans were analyzed by one radiologist, highly experienced in diagnosing CTEPH (OMD).

**Trans-thoracic echocardiography**
In patients with CT-scans suggestive of CTE, a transthoracic echocardiography was performed as previously described (32) to investigate signs of CTEPH. Pulmonary hypertension was defined by an echocardiographically determined sPAP >40 mmHg, in agreement with current guidelines (33).

**D-dimer measurement**
As an indirect marker of coagulation and subsequent fibrinolysis, D-dimer levels were measured (34,35). For these measurements, blood samples were collected in citrated tubes and centrifuged for 15 minutes. Plasma was stored at -80 °C and D-dimer concentrations were determined with a quantitative ELISA method (Asserachrom® D-dimer, Diagnostica Stago, Asnières, France). The cut-off for normality was 500 µg/L.

**Statistics**
All numbers are medians with corresponding ranges, unless stated otherwise. Statistical analysis was performed by using SPSS 16.0.2 (SPSS, UK). The Mann-Whitney U test was used for non-parametric numerical data; Fisher’s exact test was used for categorical data.

**RESULTS**
In total, 68 patients were eligible for inclusion in the study, of whom 20 patients did not participate because of refusal (n=8), logistical reasons (n=9) or other reasons (n=3). Clinical characteristics of the 48 included patients are detailed in Table 1. The mean age was 43 years (range 22-78 years) and 29 (60%) were female. In total, 25 (52%) patients had a documented history of VTE: seven (14.6%) had a history of DVT, three (6.3%) of PE and 23 (47.9%) of superficial vein thrombosis (SVT). There were eight patients (16.7%) who had a history of either DVT or PE, two of whom had had both (2/48, 4.2%). Seven (14.6%) patients had a bleeding history, including hematomas (n=4), bleeding from venous blebs in the capillary malformation (n=1), recurrent rectal blood loss (n=1) and prolonged bleeding after surgery (n=1).
Table 1. Baseline clinical characteristics of the patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=48</th>
</tr>
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<tbody>
<tr>
<td>Age in year, median (range)</td>
<td>43 (22-78)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>29 (60.4)</td>
</tr>
<tr>
<td>Localization</td>
<td></td>
</tr>
<tr>
<td>One upper limb, n (%)</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>One lower limb, n (%)</td>
<td>34 (70.8)</td>
</tr>
<tr>
<td>Both lower limbs, n (%)</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Diffuse, n (%)</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Half of the body, n (%)</td>
<td>3 (6.3)</td>
</tr>
<tr>
<td>Previous VTE (total, n) (%)</td>
<td>25 (52.1)</td>
</tr>
<tr>
<td>Superficial vein thrombosis, n (%)</td>
<td>23 (47.9)</td>
</tr>
<tr>
<td>Deep vein thrombosis, n (%)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Pulmonary embolism, n (%)</td>
<td>3 (6.2)</td>
</tr>
<tr>
<td>Dyspnoea, n (%)</td>
<td>10 (20.8)</td>
</tr>
<tr>
<td>Using anticoagulant medication</td>
<td></td>
</tr>
<tr>
<td>Vitamin K antagonists, n (%)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>NSAIDs, n (%)</td>
<td>5 (10.4)</td>
</tr>
<tr>
<td>Acetylic acid, n (%)</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Oral contraceptives (women only), n (%)</td>
<td>2 (6.9)</td>
</tr>
</tbody>
</table>

“Diffuse”: All limbs, thorax and face; “Half of the body”: one side of the body affected, including, half of the thorax, one upper, one lower limb. ¹ in most patients parts of the thorax also affected (n=4); ² in one patient thorax also affected, and in one patient also face affected; ³ in one patient the face was also affected; ⁴ Some patients had more than one type of venous thrombotic event. NSAIDs, non-steroidal anti-inflammatory drugs.

The excluded patients did not differ from those included: the mean age of the excluded patients was 40 years (range 22-69 years), 14 (70%) were female, four had a history of possible VTE (2 SVT; 1 DVT; 1 PE), four patients had shortness of breath, two of whom had normal Q-scans made earlier for other reasons. Moreover, two patients with a history of objectively confirmed CTEPH (21) had died before the start of this study and were therefore not among the 68 patients that were eligible for participation.

**Perfusion scan and CT scan**

Figure 2 depicts patient outcome with sequential testing. All 48 patients underwent perfusion lung scanning. All scans were of adequate quality for analysis. Scans were normal in 37 (77%) patients. In the other 11 (23%) patients, the scan showed diffuse irregularities in three patients and segmental and/or subsegmental defects in the other eight patients. Patients with
68 patients with KTS asked to participate

20 patients not included, due to:
- patient refusal (n = 8)
- logistical reasons (n = 9)
- other reasons (n = 3)

48 patients included in the study

Perfusion Scintigraphy

Abnormal perfusion scan:
N = 11 (22.9%)

Normal perfusion scan:
N = 37 (77.1%)

CT scanning

Scan not performed:
N = 1

Signs of chronic PE or (CTE)PH
N = 3 (6.3%, 95% CI, 2.1-16.8%)

Normal CT scan
N = 7

Echocardiography

Signs of PH
N = 0

Figure 2. Flowchart of patient management in screening of chronic pulmonary embolism or chronic thromboembolic pulmonary hypertension. CT, computed tomography; CTEPH, chronic thromboembolic pulmonary hypertension; PE, pulmonary embolism; PH, pulmonary hypertension.
abnormalities on perfusion scintigraphy proceeded to CT-scanning, with the exception of one patient who had moved abroad. This patient had several subsegmental defects on the perfusion scan, but did not have any complaints of shortness of breath at that time. In the remaining ten patients, the CT-scan showed abnormalities in three patients, of whom two had definite signs of chronic PE (2/48; 4.2%; 95% confidence interval [CI], 1.2-14%). In both
patients, the CT-scan showed a dilated main pulmonary artery, acute tapering of pulmonary artery branches, and hypertrophy of bronchial arteries. The CT-scan also showed occlusion of segmental lower lobe pulmonary arteries in patient 1 and webs in segmental branches in patient 2 (Figure 3). These two patients therefore had CTE and a suspicion of CTEPH based on the CT-scan. In the third patient, a dilated main pulmonary artery trunk was seen; however, definite signs of (chronic) pulmonary embolism were not present.

**Echocardiography**

In the three patients with abnormalities on CT-scan, trans-thoracic echocardiography was performed. It demonstrated moderate dilatation of the right atrium in the first CTE patient and moderate dilatation of the right ventricle in both CTE patients. Echocardiography revealed no abnormalities in the third possible CTE patient. Otherwise, echocardiography showed no further signs of pulmonary hypertension; in particular, estimated sPAP was normal in two patients and not measurable in the third (Table 2).

Clinical characteristics of the three patients with CT-scan abnormalities are described in Table 2. All three had a history of VTE. Two patients with signs of CTE on the CT-scan had a history of either DVT or PE, for which one patient used maintenance therapy with an oral vitamin K antagonist. The second patient used naproxen twice weekly. All three patients complained of shortness of breath. Interestingly, the third patient, in whom no definite signs of CTE were found, suffered from chronic obstructive pulmonary disease, for which she used medication. The D-dimer was elevated in the two patients with CTE, but was within the normal limits in the third patient (Table 2).

**Shortness of breath**

In total, 10 of the 48 patients reported shortness of breath of any kind. Patients with an abnormal Q-scan more often (p<0.001) reported this complaint compared to patients with normal Q-scans: 7/11 (64%; 95% CI, 35% to 85%) and 3/37 (8.1%; 95% CI, 2.8% to 21%), respectively (see Figure 4A). Moreover, shortness of breath was more often reported by patients with a history of VTE (including DVT and PE) compared to patients with a history of SVT or patients without VTE in general: 6/8 (75%; 95% CI, 41% to 93%) patients with prior documented DVT/PE reported shortness of breath, compared to 3/17 (17.6%; 95% CI, 6.2% to 41%) patients with SVT, and 1/23 (4.3%; 95% CI, 0.8% to 21%) patients without known VTE of any kind, respectively (p<0.001) (see Figure 4B). The differences in shortness of breath between the groups could not be attributed to a difference in age (data not shown).

Finally, patients with abnormalities on the Q-scan more often (p=0.001) had a documented history of DVT or PE (6/11; 55%; 95% CI, 28% to 79%) compared to patients with a normal Q-scan (2/37; 5.4%; 95% CI, 1.5% to 18%).
Table 2. Characteristics of KTS patients with abnormalities on CT scan.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age</th>
<th>Location KTS-malformation</th>
<th>History VTE</th>
<th>Shortness of breath</th>
<th>Medication</th>
<th>Signs of CTE</th>
<th>Estimated sPAP (mmHg) (^1)</th>
<th>Right cardiac changes (^2)</th>
<th>D-dimer (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. M</td>
<td>47</td>
<td></td>
<td>Capillary-venous-lymphatic malformation, combined with hypertrophy in the length and girth of the left leg. Visceral organs were also affected.</td>
<td>Pulmonary embolism (3.5 years before)</td>
<td>Yes</td>
<td>Vitamin K antagonists (maintenance)</td>
<td>Yes</td>
<td>No data (^2)</td>
<td>Moderate dilation of right atrium</td>
<td>2874</td>
</tr>
<tr>
<td>2. M</td>
<td>39</td>
<td></td>
<td>Capillary-venous-lymphatic malformation, combined with hypertrophy of the right leg. Genitals and bladder were also involved (Figure 1).</td>
<td>SVT and DVT of the right leg (lastly 1 year before)</td>
<td>Yes</td>
<td>Naproxen (twice weekly)</td>
<td>Yes</td>
<td>29</td>
<td>Moderate dilation of right ventricle</td>
<td>24488</td>
</tr>
<tr>
<td>3. F</td>
<td>48</td>
<td></td>
<td>Capillary-venous-lymphatic malformation with arterio-venous fistula of the left arm, no involvement of musculature or bones</td>
<td>SVT of the left arm</td>
<td>Yes</td>
<td>COPD medication</td>
<td>No</td>
<td>34</td>
<td>No dilation</td>
<td>248</td>
</tr>
</tbody>
</table>

\(^1\) Measured with echocardiography; \(^2\) No tricuspid regurgitation, therefore sPAP not measurable. KTS, Klippel-Trenaunay syndrome; VTE, venous thromboembolism; CTE, chronic thromboembolism; NT-proBNP, N-terminal-pro brain natriuretic peptide; sPAP, systolic pulmonary artery pressure; SVT, superficial vein thrombosis; DVT, deep vein thrombosis; COPD, chronic obstructive pulmonary disease.
Figure 4. Shortness of breath in KTS patients with and without abnormalities on the perfusion scan and with and without a history of venous thromboembolism.
A) Patients with abnormal perfusion scans more often reported shortness of breath compared to patients with a normal perfusion scan (Chi$^2$ p<0.0001).
B) Patients with a history of VTE more often reported shortness of breath compared to patients without VTE (Chi$^2$ p<0.001). VTE, venous thromboembolism; SVT, superficial vein thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism.

**D-dimer test**
The median D-dimer level in the 48 included patients was 584 μg/L, with a range of 122 to 25131 μg/L. The D-dimer was above the cut-off for normal value for exclusion of VTE (500 μg/L) in 25 (52%; 95% CI, 39% to 66%) patients, and above 1000 μg/L in 18 (38%; 95% CI, 25% to 52%) patients. Patients with Q-scan abnormalities did not have higher D-dimer levels compared
to patients with normal scans \((p=0.634)\). In addition, of the 11 patients with an abnormal scan, 7 (64%) had increased D-dimer levels (ranging from 281 to 24488 μg/L), which did not differ \((p=0.514)\) from the patients with normal scans (17/37, 46%, range 122 to 25131 μg/L).

The two patients with signs of chronic pulmonary embolism on the CT-scan did not have higher D-dimer results compared with the other patients. Also, no difference was found between the D-dimer levels in patients with and without shortness of breath \((p=0.790)\) or with and without a history of VTE \((p=0.112)\).

**DISCUSSION**

Among the KTS-patients included in this cross-sectional study, we found an observed prevalence of CTE of 4% (95% CI, 1.2-14%), while echocardiography showed no definite signs of pulmonary hypertension in the patients with CTE. These results appear reassuring after our previous report on two KTS patients over a five year period referred to our hospital because of belatedly diagnosed CTEPH (21). Besides these two known and reported KTS-associated CTEPH cases, however, in the present study CTE was found in two additional patients, which is still higher than expected in a relatively young patient population.

A relatively large number of patients in this cohort had a history of VTE: 17% had a history of either DVT or PE and 52% had a history of SVT, DVT and/or PE. With a mean age of 43 years, this frequency is higher than expected based on data derived from the general population (36,37), but in line with previous findings among KTS patients (10). Moreover, the D-dimer level, a fibrin degradation product used as a marker for activation of the coagulation system, was above the cut-off for the exclusion of VTE (500 μg/L) in half of the patients and above 1000 μg/L (maximum of 25131 μg/L) in over a third of the patients. This is in support of the idea of an activated coagulation system in KTS-patients, as has also been reported in patients with venous malformations (34,35). This activated coagulation system is thought to be the underlying cause for continuous formation of thrombi, resulting in (recurrent) PE (21). Because KTS is also associated with a high risk of bleeding, physicians are usually reluctant to administer long-term anticoagulation for (superficial) thrombosis (10,24).

Another finding of interest was the high number of patients who reported shortness of breath. Patients with abnormal Q-scans and/or patients with a documented history of DVT/PE reported this complaint more frequently compared to patients with a normal Q-scan or patients without a documented history of DVT/PE. Although two patients with shortness of breath showed signs of CTE on the CT-scan, their complaints appeared not attributable to CTEPH. Unfortunately, the origin of the complaints was not determined, since this was beyond the scope of the current investigation. Two recent studies, however, found approximately half of the patients with prior PE to report persistent complaints of shortness of breath after the
initial event, for which no explanation was found (38,39). The clear association between previous VTE and shortness of breath merits further investigation.

Our study has several strengths and limitations. First, although KTS is a rare disease, we were able to include a large sample of patients from a national cohort of KTS-patients. Not all patients from the cohort were able to participate in the study, two of whom had complaints of shortness of breath for which they were not further examined. Even though the KTS-patient cohort is well-characterized, and we know that these two patients did not have a documented history of VTE, we can not completely exclude that these patients might not have suffered from CTE(PH). Second, we did not perform echocardiography in all patients. The primary aim of the present study was to determine the prevalence of CTE; secondly, we studied whether patients with signs of CTE on the CT scan suffered from CTE-related pulmonary hypertension. Third, we performed all echocardiographic measurements in resting state. Therefore, we cannot completely exclude the possibility that exercise-induced CTEPH may have been present in the CTE patients. However, the meaning of exercise-induced CTEPH is currently unclear and its practical implications are very limited (26).

In conclusion, despite the apparent frequency and severity of the earlier reported cases of CTEPH, in this well-defined Dutch KTS cohort, the prevalence of CTE and CTE-associated pulmonary hypertension (CTEPH) in particular was less alarming than previously assumed. Although a large proportion of KTS-patients had a documented history of VTE and high D-dimer levels, in relatively few patients CTE could be documented; moreover, we did not find definite signs of CTEPH in any of the patients in this cohort. Based on the current findings, we suggest that the indication for screening for CTE(PH) among patients with KTS is limited. Nevertheless, given the severity of cases previously reported and the high prevalence of VTE among patients with KTS, awareness and a low threshold for CTEPH-screening seems appropriate for patients with KTS who present with shortness of breath.

Addendum
CEO, PB, EJvB, VG and CMvdH were involved in the conception and design of the study. CEO and RAD were involved the in analysis of the data. CEO, RAD, PB, EJvB, VG and BLFvES were involved in the interpretation of the data. CEO, RAD, OvD, BJB, BLFvES and JCM were involved in the collection of data. RAD and CEO drafted the manuscript. All authors were involved in revision and final approval of the manuscript. All authors had full access to the data in the study.
REFERENCE LIST