ORIGINAL ARTICLE

Fatigue in adult patients with primary immune thrombocytopenia

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Abstract

Background: Patients with primary immune thrombocytopenia (ITP) commonly describe symptoms of fatigue. However, hematologists rarely consider fatigue a manifestation of ITP. *Objectives*: To document the prevalence of fatigue among patients with ITP and to determine the patient characteristics that are associated with fatigue. *Methods:* Using a cross-sectional design, we surveyed 1871 members of the UK ITP Support Association [585 (31%) responded], and 93 patients enrolled in the Oklahoma (US) ITP Registry [68 (73%) responded] with questions about their ITP and with validated symptom assessment scales for fatigue, daytime sleepiness, and orthostatic symptoms. *Results*: The prevalence of fatigue among both UK (39%) and US (22%) patients was significantly greater than expected compared with normal subjects ($P < 0.0001$ and $P < 0.0001$ respectively). In univariate analysis of the combined cohorts, fatigue was associated with a platelet count <100 000/μL, treatment with steroids, bleeding symptoms, presence of other medical conditions, daytime sleepiness, and orthostatic symptoms. Fatigue was not associated with age, gender, duration of ITP, or splenectomy status. Multivariate analysis of the combined cohorts was stratified for the presence or absence of bleeding symptoms. Among 107 patients with bleeding symptoms, fatigue was independently associated with a platelet count <100 000/μL and female gender. Among 491 patients without bleeding symptoms, fatigue was independently associated with a platelet count <30 000/μL, presence of other medical conditions, daytime sleepiness, and orthostatic symptoms. *Conclusions:* Fatigue is a common symptom among patients with ITP. These data provide the basis for future studies to define the clinical importance of fatigue in ITP.

Key words immune thrombocytopenia; fatigue; ITP

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Adult primary immune thrombocytopenia (ITP) is caused by antibody-mediated platelet destruction and suboptimal platelet production; it is diagnosed by the occurrence of isolated thrombocytopenia without another apparent etiology and is characterized by an insidious onset and a chronic course (1–6). Because the principal function of platelets is to provide primary hemostasis (7), the only abnormalities commonly attributed to ITP are the signs and symptoms of excessive bleeding (1–4). However, our experience, supported by recent reports (8–10), has been that patients with ITP often describe symptoms of fatigue and frequently describe their fatigue as being related to the severity of thrombocytopenia. Despite this, fatigue has not been mentioned in comprehensive reports and international guidelines on the evaluation and management of ITP (1–4). Physicians may not attribute reported symptoms of fatigue to a patient's ITP because fatigue is a common symptom among the

general population, it is perceived as difficult to quantitatively assess, and there is currently no biological basis for how fatigue may be attributable to ITP.

Recent data have confirmed that patients with ITP have symptoms other than bleeding. Using a standard health-related quality-of-life questionnaire, the Short-Form 36 (SF-36) (11), a survey of 73 patients with ITP documented abnormalities in all of the eight domains, including both physical and mental components (12). Subsequently, an ITP-specific patient assessment questionnaire (PAQ) was developed by patient focus group analyses (9). During these focus groups, fatigue was described as a significant symptom by 93% of patients (9). Using the ITP-PAQ for a web-based survey of 1002 US patients recruited from the Platelet Disease Support Association, a support group for patients with ITP, fatigue was significantly associated with the platelet count; patients with lower platelet counts had greater fatigue (10). When the ITP-PAQ was used during randomized clinical trials of romiplostim treatment for ITP, pretreatment data documented the presence of multiple symptoms, including 'physical fatigue', which improved when the platelet count increased (13). These observations suggest that fatigue is an important symptom for patients with ITP, that it may be related to the severity of thrombocytopenia, and that it is potentially treatable.

Fatigue is increasingly recognized as a symptom that occurs in other chronic autoimmune diseases (14–22). Studies of primary biliary cirrhosis, an autoimmune liver disease, have documented that fatigue is associated with autonomic nervous system dysfunction and excessive daytime sleepiness and that it is unrelated to the severity of the underlying liver disease (23–25). These studies have shown that targeted interventions to reverse autonomic symptoms and improve daytime sleepiness improved health-related quality-of-life in patients with primary biliary cirrhosis (26, 27).

The goals of this study were to (i) estimate the prevalence of fatigue among patients with ITP using a validated, quantitative questionnaire, (ii) determine characteristics of ITP that are related to the occurrence of fatigue, and (iii) determine whether fatigue in ITP, as in other autoimmune diseases, is associated with excessive daytime sleepiness and autonomic dysfunction assessed by orthostatic symptoms.

Methods

Patients

Two cohorts of patients with ITP, one from the UK and one from the USA, were studied. Both cohorts included patients with active ITP as well as patients who had a history of ITP but no currently active disease. The UK Cohort was the membership of the ITP Support Association. The Association is an independent UK registered charity established in 1995. Members join by learning about the Association from its website (http://www.itpsupport.org.uk), its quarterly publication, *The Platelet*, or other information. At the time of this study, the Association had 1871 members; 97% lived in the UK. The diagnosis of ITP as reported by the patient was accepted. The US Cohort was the Oklahoma ITP Registry, established in 2004. Patients are identified by regular contacts with hematology practitioners in the State of Oklahoma; they are recruited for the Registry by being sent materials with a consent form. Patients are then contacted regularly to ask about issues related to ITP. At the time of this study, the Registry had 93 enrolled patients; all were 16 yr old or older. The diagnosis of ITP as reported by the hematology practitioners was accepted.

Symptom assessment tools

The survey was titled 'Fatigue Survey 2009'. The complete survey form is accessible in the electronic supplement. The first part contained questions about demographic information (date of birth, gender), time since diagnosis of ITP, results and date of the most recent platelet count, current medications, and whether symptoms at the time of completing the survey were typical of the previous month. Reported platelet count data were based on patient recall. Platelet counts reported only as 'normal' were considered to be $>100\,000/\mu$L. The next part contained 16 questions about characteristics of the patients' ITP. Five of the questions (numbers 1, 2, 3, 6, and 7) were developed for a 2007 survey of the ITP Support Association membership on health-related lifestyle (28); the other 11 questions were developed for this survey. Following these questions, the patients completed three validated symptom assessment tools for fatigue, daytime sleepiness, and orthostatic symptoms.

The Fatigue Impact Scale (FIS) is a validated self-report assessment tool that quantifies an individual's symptoms of fatigue. The FIS assesses patients' perceptions of how fatigue affects their cognitive, physical and psychosocial functions (29). This includes the impact of fatigue on their work, family and financial responsibilities, their mood, their reliance on others, their social activities, and their quality-of-life. The FIS has been validated for self-completion and for use in a number of fatigue-associated diseases, including primary biliary cirrhosis (30–32) and chronic fatigue syndrome (33). The FIS has 40 items. Subjects rate how each item is affected by fatigue on a 5-point scale: 0 (no problem) to 4 (extreme problem). The FIS score is calculated by adding all answers from the 40 questions. A previous study

assessed 40 normal adults (31 women, 9 men) who responded to an advertisement for research subjects and who were selected without consideration for the presence or absence of symptoms of fatigue (33). Their mean score was 14 with a SD of 13 (33). Therefore, in this study, a score of ≥40 (2 SD above the mean) was used to define the presence of fatigue. Assuming a normal distribution of FIS scores in the general population, 2.5% of the general population would be expected to have fatigue defined by an FIS score of ≥40.

The Epworth Sleepiness Scale (ESS) is a validated self-report assessment tool that quantifies the symptoms of daytime sleepiness. It consists of eight items, each graded on a scale of 0–3. Higher scores indicate greater impact of daytime sleepiness. A previous study assessed 30 control subjects who were mainly hospital employees who worked during the day and who gave a history of normal sleep habits without snoring (34, 35). Their mean score was 5.9 with an SD of 2.2. Therefore, in this study, a score of ≥10 (2 SD above the mean) was used to define the presence of daytime sleepiness.

The Orthostatic Grading Scale (OGS) is a validated self-report assessment tool that quantifies the symptoms of orthostatic intolerance because of hypotension, with questions related to frequency and severity of symptoms and interference with daily activities (36). It consists of five items, each graded on a scale of 0–4. Higher scores indicate greater impact of orthostatic symptoms. A previous study assessed 145 patients referred to the Mayo Clinic (Rochester, MN, USA) Autonomic Reflex Laboratory who were tested for orthostatic hypotension using a standardized head-up tilt test with continuous heart rate and blood pressure monitoring to define autonomic deficits and to develop a scale described as the Composite Autonomic Severity Score (CASS). Ninety-seven patients with orthostatic hypotension had a mean score of 9.32 with a SD of 5.46; 48 patients without orthostatic hypotension had a mean score of 4.44 with a SD of 5.1 ($P < 0.001$). Using the CASS as the standard, an OGS score of ≥9 had a sensitivity of 66% and the specificity of 69% for detecting orthostatic hypotension (36). Therefore, in this study, a score of ≥9 (1 SD above the mean) was used to define the presence of orthostatic symptoms.

Study design

We used a cross-sectional study design to assess the frequency of fatigue and its associated variables at a single point in time with this survey. The same survey was sent to all members of the ITP Support Association and the Oklahoma ITP Registry in 2009. Patients who were 16 yr old or older were requested to complete and return the survey. For the UK Cohort, surveys were mailed by the ITP Support Association to all 1871 members. To increase response, surveys were mailed one additional time to patients who initially did not respond, and a reminder (without the survey form) was featured in the ITP Support Association publication, *The Platelet*. A small gift incentive was provided for completion of the survey. For the US Cohort, surveys were mailed to all 93 patients enrolled in the Oklahoma ITP Registry. To increase response, surveys were mailed one additional time to patients who had not returned the initial survey within 4 wk. If there was no response within 4 wk after the second mailing, patients were contacted by telephone. The Oklahoma ITP Registry is approved by the Institutional Review Board of the University of Oklahoma Health Sciences Center for periodic surveys.

Analysis

From the 16 questions about characteristics of the patients' ITP, six were selected for analysis (numbers 1, 2, 3, 10, 14, and 16). The other ten questions were excluded from this analysis because there were many missing responses, the responses were internally inconsistent, or they had redundant information. Descriptions of similar conditions using different words in response to questions about other diagnosed medical conditions and other factors that may contribute to fatigue were grouped together. All analyses were performed using statistical software (SAS version 9.1; SAS Institute Inc., Cary, NC, USA). Descriptive statistics for each of the analyzed parameters were calculated separately for the UK and the US cohorts. For continuous parameters, median and range were calculated; for categorical variables, percentages were calculated. For continuous variables, a Wilcoxon/Mann–Whitney test was used to determine whether the distribution of the data was different between the two groups, and for categorical variables, a chi-square test was used. Descriptive statistics were calculated separately for patients with fatigue (FIS ≥ 40) and without fatigue (FIS < 40) for each of the variables. Univariate odds ratios and 95% confidence intervals were calculated to estimate the association between fatigue and each of the variables. For variables in the US cohort that had analysis cells with no patients and therefore an odds ratio could not be calculated, a Fisher's exact test was used to determine whether that variable was related to fatigue. Multivariate analysis using logistic regression was used to calculate odds ratios and 95% confidence intervals to estimate the association between fatigue and each variable while controlling for potential confounding by the other variables.

All variables assessed by univariate analysis were included in the initial multivariable model, which contained no interaction terms. Stepwise selection was used to determine which variables entered ($\alpha \leq 0.20$) and remained

($\alpha \leq 0.20$) in the multivariable model. To examine whether the relationship between a variable (such as OGS) and fatigue is consistent across levels of another variable in the model (such as bleeding), two-way interactions (potential effect-modifying relationships) were tested among the variables that remained in the multivariable model. Interactions between two variables with an alpha of < 0.05 were considered to be significant. The final multivariable models were constructed with stratification based on the presence of interactions. When significant interactions were found, the data were then analyzed by reporting separately for one of the variables involved in interaction. For example, if bleeding interacted with other variables, then bleeding-specific models were reported. Two-way interactions were also evaluated in the stratified models as described earlier. Final models only included variables that were significant at an α of 0.05. Because we collected data from two distinct patient cohorts, one in the UK and one in the USA, the variable country was included in the final multivariable models to adjust for potential sampling differences, even though interactions between country and other variables were not significant with an α of 0.05.

Results

Survey response rates

For the UK Cohort, 585 of 1871 surveys were returned, representing a 31% response. It is estimated that one-sixth of the membership is <16 yr old; therefore, the response rate may have been as high as 38%. For the US Cohort, 68 (73%) of 93 surveys were returned.

Survey results

Thirty-nine percent of patients in the UK cohort and 22% of patients in the US cohort reported significant fatigue, indicated by FIS scores ≥40. These frequencies are significantly more than the expected relative frequency among normal subjects of 2.5% ($P < 0.0001$ and $P < 0.0001$) (Table 1). Most patients responding to the survey were women, and most had had ITP for longer than 5 yr. Although most patients reported that they had symptoms of bruising sometimes, often, or always and that they had bleeding, bruising, or petechiae at the time they completed the survey, fewer reported that they had overt bleeding daily, weekly, or monthly. Few patients were taking medications for ITP. The reports of other diagnosed medical conditions and/or other factors that may contribute to fatigue were common, but no single medical condition or factor that may contribute to fatigue was reported by more than 10% of patients. The most commonly reported medical conditions were hypertension, arthritis, thyroid problems, and diabetes. The most commonly reported factors that may contribute to fatigue were age, depression/anxiety/stress, thyroid problems, arthritis, work, and child care. There were significant differences between the UK and US cohorts. The duration of ITP was less in the UK patients, fewer had had splenectomies, more UK patients were thrombocytopenic, more reported other diagnosed medical conditions, and more reported significant fatigue.

In response to survey questions 8 and 9, which are not included in Table 1, 82% of patients in the UK cohort and 50% of patients in the US cohort reported that their energy levels had changed since having ITP; 69% of patients in the UK cohort and 50% of patients in the US cohort reported that they had less energy when their platelet count is low.

Table 1 Responses to survey questions by the UK and US patient cohorts

Patient characteristics	UK[1]	US[1]	*P*-value
Demographics			
Age (Median, Range)	57 (16–93)	50 (19–91)	0.089
Gender (Females)	393 (72%)	52 (76%)	0.461
ITP History (%)			
Duration of ITP (>5 yr)	356 (66)	58 (85)	**0.001**
Splenectomy	149 (27)	39 (58)	**<0.001**
Clinical features			
Platelet count (%)			
<30	109 (20)	8 (12)	**0.007**
30–99	200 (37)	17 (25)	
≥100	235 (43)	43 (63)	
Medications for ITP (%)			
Steroids	96 (18)	5 (7)	0.092
Another ITP medication, no steroids	37 (7)	6 (9)	
No medication for ITP	411 (75)	57 (84)	
Bruising (Sometimes, Often, Always)	392 (72)	44 (64)	0.182
Bleeding (Daily, weekly, monthly)	97 (18)	10 (15)	0.490
Bleeding, bruising, petechiae today (Yes)	351 (65)	41 (72)	0.271
Other conditions (%)			
Other diagnosed medical conditions (Yes)	354 (66)	33 (48)	**0.005**
Other factors that may contribute to fatigue (Yes)	250 (47)	32 (47)	0.997
FIS scores			
FIS median (Range)	32 (0–158)	9 (0–127)	**0.001**
FIS ≥ 40 (%)	212 (39)	15 (22)	**0.007**
ESS scores			
ESS median (Range)	8 (0–24)	7 (0–20)	0.238
ESS ≥ 10 (%)	198 (36)	18 (26)	0.104
OGS scores			
OGS median (Range)	3 (0–17)	1 (0–12)	0.144
OGS ≥ 9 (%)	42 (8)	4 (6)	0.585

ITP, Immune thrombocytopenia; FIS, Fatigue Impact Scale; ESS, Epworth Sleepiness Scale; OGS, Orthostatic Grading Scale.
[1]Data for the UK represent responses from 531 to 544 patients; data for the USA represent responses from 57 to 68 patients. Data that are statistically significant are indicated in bold font.

Table 2 Frequency of fatigue, defined by an FIS score of ≥40, related to patient characteristics

	Percent fatigued (FIS ≥ 40)		
Patient characteristics	UK	US	Combined UK-US
Demographics			
Age (Median, Range)	57 (16–93)	50 (19–91)	56 (16–93)
Gender (%)			
Female	41	25	39
Male	33	13	31
ITP History (%)			
Duration of ITP			
≥5 yr	37	19	36
<5yr	42	40	42
Splenectomy			
Yes	37	26	35
No	40	18	38
Clinical features (%)			
Platelet count			
<30	52	50	52
30–99	40	41	40
≥100	32	9	29
Medications for ITP			
Steroids	50	40	50
Another ITP med, no steroids	41	33	40
No medication for ITP	36	19	34
Bruising			
Sometimes/Always/Often	45	27	43
Never/Rarely	23	13	21
Bleeding			
Daily/Weekly/Monthly	62	30	59
Never/Rarely	34	21	32
Bleeding, bruising, petechiae today			
Yes	46	32	44
No	27	0	25
Other conditions (%)			
Other diagnosed medical conditions			
Yes	44	27	42
No	29	17	27
Other factors contributing to fatigue			
Yes	42	22	40
No	36	22	34
Symptom scales (%)			
ESS			
≥10	65	44	62
<10	24	14	23
OGS			
≥9	86	100	87
<9	35	17	33

FIS, Fatigue Impact Scale; ITP, immune thrombocytopenia; OGS, Orthostatic Grading Scale; ESS, Epworth Sleepiness Scale

Relationship between fatigue and patient characteristics

Table 2 describes the frequency of fatigue related to the patient characteristics in the individual and combined cohorts. Univariate analysis was performed to determine which of these characteristics were significantly associated with fatigue (Table 3). Eight of the 13 patient characteristics were significantly associated with fatigue: platelet count, steroid treatment, bruising, bleeding, bleeding-bruising-petechiae today, presence of other diagnosed medical conditions, presence of daytime sleepiness, and the presence of orthostatic symptoms. The time interval since the most recent platelet count was extremely variable, from 1 wk to many years. Although the presence of fatigue was significantly associated with lower platelet counts, the relative frequency of fatigue among patients with platelet counts ≥100 000/μL was also significantly greater than expected for normal subjects. Among patients with platelet counts ≥100 000/μL, 32% of the UK cohort and 9% of the US cohort reported fatigue (Table 2); both of these frequencies are significantly greater than the expected relative frequency among normal subjects of 2.5% ($P < 0.0001$ and $P = 0.004$, respectively). Because the score of 40 on the FIS is two SDs greater than the mean score 14 in normal subjects, only 2.5% of normal subjects would be expected to have FIS scores ≥40 (33). The five patient characteristics that were not associated with fatigue were age, gender, duration of ITP, splenectomy status, and the presence of other factors that may contribute to fatigue.

A multivariate model with stepwise selection was created to estimate the association of all 13 patient characteristics to fatigue while controlling for confounders. Five patient characteristics that were significantly associated with fatigue in the univariate analysis were also independently related to fatigue and remained in the model: low platelet count (<30 000/μL and 30 000–99 000/μL), bleeding (daily, weekly, monthly), presence of other diagnosed medical conditions, presence of daytime sleepiness, and the presence of orthostatic symptoms. Gender, which had not been significantly related to fatigue in the univariate analysis, was independently related to fatigue and remained in the multivariate model. Medications for ITP (including steroids), bruising, and bleeding-bruising-petechiae today were not independently related to fatigue. The patients' country was added to the multivariate analysis and was also independently related to fatigue and remained in the model. When these seven variables were analyzed for two-way interactions, four interactions were significant with an α of <0.05: bleeding with gender ($P = 0.033$), bleeding with platelet count of 30 000–99 000/μL ($P = 0.025$), bleeding with the presence of significant daytime sleepiness ($P = 0.042$), and other diagnosed medical conditions with the presence of orthostatic symptoms ($P = 0.021$). The country variable did not have significant interactions with any of the other six variables. Because the response to the question about bleeding

Table 3 Univariate analysis of patients' characteristics related to the presence or absence of fatigue, defined by an FIS score of ≥40

Patient characteristics	Odds ratios (95% confidence intervals) for characteristics related to fatigue		
	UK	US	Combined UK-US
Age	1.0 (0.99, 1.01)	0.97 (0.93, 1.004)	1.0 (0.99, 1.01)
Gender			
Female	1.42 (0.96, 2.10)	2.33 (0.47, 11.66)	1.43 (0.98, 2.09)
Male	1.0	1.0	1.0
ITP history			
Duration of ITP			
≥5 yr	0.80 (0.56, 1.15)	0.35 (0.08, 1.46)	0.72 (0.51, 1.02)
<5yr	1.0	1.0	1.0
Splenectomy			
Yes	0.88 (0.60, 1.30)	1.59 (0.48, 5.29)	0.85 (0.59, 1.21)
No	1.0	1.0	1.0
Clinical features			
Platelet count			
<30	**2.29 (1.44, 3.65)**	**9.75 (1.74, 54.79)**	**2.70 (1.73, 4.21)**
30–99	1.37 (0.92, 2.03)	**6.82 (1.66, 27.99)**	**1.63 (1.12, 2.37)**
≥100	1.0	1.0	1.0
Medications for ITP			
Steroids	**1.76 (1.12, 2.75)**	2.79 (0.41, 18.76)	**1.89 (1.22, 2.91)**
Another ITP medication, no steroids	1.20 (0.60, 2.38)	2.09 (0.34, 12.91)	1.26 (0.66, 2.39)
No medication for ITP	1.0	1.0	1.0
Bruising			
Sometimes/Always/Often	**2.78 (1.81, 4.29)**	2.63 (0.66, 10.43)	**2.81 (1.87, 4.24)**
Never/Rarely	1.0	1.0	1.0
Bleeding			
Daily/Weekly/Monthly	**3.16 (2.00, 4.97)**	1.64 (0.37, 7.32)	**3.0 (1.95, 4.59)**
Never/Rarely	1.0	1.0	1.0
Bleeding, bruising, petechiae today			
Yes	**2.34 (1.60, 3.44)**	**0.012***	**2.46 (1.69, 3.57)**
No	1.0	1.0	1.0
Other Conditions			
Other diagnosed medical conditions			
Yes	**1.85 (1.27, 2.71)**	1.81 (0.57, 5.82)	**1.93 (1.35, 2.76)**
No	1.0	1.0	1.0
Other factors contributing to fatigue			
Yes	1.33 (0.94, 1.89)	0.98 (0.31, 3.09)	1.29 (0.93, 1.80)
No	1.0	1.0	1.0
Symptom Scales			
ESS			
≥10	**5.68 (3.88, 8.32)**	**4.91 (1.44, 16.74)**	**5.68 (3.95, 8.16)**
<10	1.0	1.0	1.0
OGS			
≥9	**11.08 (4.58, 26.81)**	**0.002***	**13.48 (5.61, 32.35)**
<9	1.0	1.0	1.0

ITP, Immune thrombocytopenia; ESS, Epworth Sleepiness Scale; FIS, Fatigue Impact Scale; OGS, Orthostatic Grading Scale.
**P*-value calculated by Fisher's exact test. Data that are statistically significant are indicated by bold font.

interacted with three other variables, the data were stratified based on the presence (daily, weekly, monthly) or absence (rarely, never) of bleeding. Among the 107 patients who reported bleeding symptoms, platelet counts $<100\,000/\mu$L (platelet count $<30\,000/\mu$L and platelet count 30 000–99 000/μL) and female gender were independently associated with fatigue ($P < 0.05$) (Table 4). There were no two-way interactions among these variables. Among the 491 patients who did not report bleeding problems, platelet counts $<30\,000/\mu$L, other medical conditions, daytime sleepiness, and orthostatic symptoms were independently associated with fatigue ($P < 0.05$) (Table 5). Even though the country was not independently associated with fatigue with an α of <0.05 in either of the final multivariable models, it was included to adjust for potential sampling differences.

Table 4 Multivariate analysis of variables related to fatigue in 107 patients who reported bleeding symptoms

Patient characteristics	Odds ratios (95% confidence interval)
Platelet count (<30 vs. ≥100)	3.10 (1.03, 9.33)
Platelet count (30–99 vs. ≥100)	5.51 (1.86, 16.36)
Gender (Female vs. Male)	4.18 (1.55, 11.26)
Country (UK vs. US)	0.20 (0.04, 1.0)

All variables that were significant ($P < 0.05$) in the analysis are reported. Country, although not significant, was left in the analysis to adjust for possible sampling differences.

Table 5 Multivariate analysis of variables related to fatigue in 491 patients who did not report bleeding symptoms

Patient characteristics	Odds ratios (95% confidence interval)
Epworth Sleepiness Scale (≥10 vs. <10)	5.53 (3.56, 8.60)
Orthostatic Grading Scale (≥9 vs. <9)	10.11 (3.22, 31.78)
Other medical conditions (Yes vs. No)	1.90 (1.18, 3.05)
Platelet count (<30 vs. ≥100)	2.05 (1.13, 3.74)
Platelet count (30–99 vs. ≥100)	1.10 (0.67, 1.80)
Country (UK vs. US)	0.61 (0.28, 1.33)

All variables that were significant ($P < 0.05$) in the analysis are reported. Country, although not significant, was left in the analysis to adjust for possible sampling differences.

Discussion

Data from this survey of 653 adult patients in the UK and the USA using a validated, quantitative questionnaire, the FIS (29), support previous qualitative observations(9, 10) that fatigue is a common symptom of ITP. The patients responding to this survey were mostly middle-aged women, most had had ITP for 5 or more years, most had bruising or petechiae, and approximately half had platelet counts $< 100\,000/\mu$L although only 16% and 25% of the US and UK cohorts were taking medications for ITP. There were differences in how patients in these two cohorts were identified and assembled and also differences in the characteristics of their ITP. However, both the UK and US cohorts of patients reported significantly increased frequencies of symptoms of fatigue: 39% of the UK patients and 22% of the US patients.

Among the 107 patients who reported bleeding daily, weekly, or monthly, platelet counts $< 100\,000/\mu$L (platelet count $< 30\,000/\mu$L and platelet count 30 000–99 000/μL) and female gender were independently associated with fatigue. Although steroid treatment was significantly associated with fatigue in the univariate analyses, it was not independently associated with fatigue in the multivariate analyses. The association of fatigue with thrombocytopenia was comparable to patients' responses that they had less energy when their platelet counts were low and also with previous data documenting improved health-related quality-of-life of patients with ITP who respond to treatment to increase their platelet counts (13). However, the biological basis for the associations of fatigue with thrombocytopenia and female gender is unclear. Women may be more vulnerable for fatigue, as suggested by the predominance of women among patients with the chronic fatigue syndrome (37–39). Among the 491 patients who reported that they rarely or never had bleeding symptoms, more severe thrombocytopenia with platelet counts $< 30\,000/\mu$L was still independently associated with fatigue. Among these 491 patients, daytime sleepiness, orthostatic symptoms, and the presence of other diagnosed medical conditions were also independently associated with fatigue.

Orthostatic symptoms have been reported to be associated with fatigue in other conditions (23–25, 32, 40, 41). For example, fatigue is well described in disorders such as Sjögren's syndrome and has been postulated to be related to autonomic dysfunction (20, 42, 43). Fatigue has also been associated with autonomic dysfunction in non-autoimmune disorders (32, 40, 41). A potential cause of orthostatic symptoms is abnormal cardiac function, and recent studies have suggested abnormal cardiac function in patients with primary biliary cirrhosis who manifest fatigue (44) and in patients with chronic fatigue syndrome (45). Observations of heart rate and blood pressure, using the methods that previously validated the OGS score (36), may help to determine the cause of orthostatic symptoms in patients with ITP. Although these data in other disorders suggest that orthostatic symptoms in this study may have occurred independently from fatigue, it is also possible that the orthostatic symptoms occurred as a consequence of fatigue.

In patients without bleeding symptoms, the presence of other medical conditions may contribute to fatigue in addition to their ITP, because the presence of other diagnosed medical conditions was independently associated with fatigue in these patients. The significance of the reported other diagnosed medical conditions is difficult to interpret because some patients listed multiple conditions but even the most commonly reported individual medical conditions occurred in $< 10\%$ of patients. Some conditions, such as cancer and depression, would be expected to be associated with fatigue; the association of others with fatigue is less clear. Future studies of patients with ITP should include of measures of depression and anxiety to assess the contribution of the stress of living with a chronic disease to fatigue in these patients.

The data from this study suggest that symptoms of fatigue should be considered in patient management. Current treatment of ITP is directed toward prevention of clinically important bleeding and risks for bleeding by achieving a safe platelet count, not necessarily a normal

platelet count (1–4). The rationale for this goal is to prevent risks associated with excessive treatment with corticosteroids (46, 47) and other treatments. Recent clinical trials of treatment for ITP that have incorporated an ITP-specific health-related quality-of-life measure have documented that patients whose platelet counts improved with treatment also had improved quality-of-life (13). Studies quantifying fatigue as an endpoint will be important in future clinical trials to determine whether ITP treatments and concurrent platelet counts are associated with fatigue.

There are limitations for the interpretation of this study. Patients who join the ITP Support Association and who are identified for the Oklahoma Registry may be more symptomatic than other patients with ITP. Also, patients who are members of the ITP Support Association may be more aware of symptoms such as fatigue that are commonly discussed in patient forums. An additional potential for bias was the announcement to the patients that the survey was designed to investigate fatigue. The low response rate to the survey may indicate that this cohort selectively included patients who were more symptomatic than patients who did not return their surveys. Although the response rate of the Oklahoma cohort was higher, the number of patients was small. The data on patients' platelet counts are limited by the absence of concurrent measurements. In this study, platelet count data were only what the patients could recall and the platelet counts may not have been recent. The survey questions concerning bleeding symptoms were developed specifically for this survey and have not been validated by use in other groups of patients with ITP. The normal values for the FIS scores were established on a small number of normal subjects, and they may not be representative of the normal population. The ESS and OGS scales have also been validated on only small numbers of subjects, and the sensitivity (66%) and specificity (69%) of the OGS were not high.

There are also important strengths of this study. It is the first study to systematically and quantitatively address fatigue in patients with ITP. Fatigue is described by many patients with ITP as a common and important problem that until now has been largely overlooked or avoided. The large number of patients from two different countries who were identified by different methods suggests that these data may be generalizable to other patients with ITP. Standardized questionnaires to quantitatively assess fatigue were used. Therefore, these quantitative data objectively document that fatigue is a common symptom among adult patients with ITP.

In conclusion, this study addressed a common complaint of patients with ITP and has objectively quantified the occurrence of fatigue in ITP for the first time, documenting that it is a common symptom that may significantly impact the quality-of-life of patients with ITP. The frequency of fatigue among patients with ITP and its association with orthostatic symptoms and daytime sleepiness are similar to primary biliary cirrhosis, chronic fatigue syndrome, and other disorders (48), suggesting that interventions that have the potential to improve symptoms of fatigue in these other disorders(26, 48) may also be helpful for patients with ITP. These data provide the basis for future studies to more accurately determine the frequency and severity of fatigue in patients with ITP and define the relation of fatigue to the severity of thrombocytopenia.

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Conflicts of interest

Drs. George and Terrell have served as consultants and investigators for the development of romiplostim for Amgen, Inc. Dr. Bolton-Maggs has served as a clinical advisor for Amgen, Inc. and GlaxoSmithKline, Inc.

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