Fatigue as a First-Time Presenting Symptom: Management by Family Doctors and One Year Follow-Up

Eliezer Kitai MD[1,2], Gari Blumberg MD[1,2], David Levy MD[1*], Avivit Golan-Cohen MD[1,2] and Shlomo Vinker MD[1]

[1]Department of Family Medicine, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2]Department of Family Medicine, Leumit Health Services, Tel, Aviv, Israel

ABSTRACT: **Background:** Fatigue is a common complaint in primary care and has a broad differential diagnosis, making the approach complex and often ineffective.

Objectives: To follow the course of adults without a significant known background disease who complain of fatigue for the first time, and to characterize the family physician's approach.

Methods: The study population comprised a random sample of 299 patients aged 18–45 who presented with fatigue as a first-time single complaint to their family physician. Excluded were patients with chronic diseases or states that may include signs of fatigue. We analyzed the index encounter data, the diagnostic and laboratory tests, the medications prescribed and the one year clinical outcome.

Results: Seventy percent were women, average age 30.5 years, and 69% had no known co-morbidities; 57% of the patients were physically examined at the first visit and most (78.6%) were sent for laboratory analysis. Five percent of laboratory tests were positive. Eighty patients (26.8%) were given a specific diagnosis, with the leading diagnoses being anemia and infectious diseases; 18.7% were given sick leave at the first visit. Fatigue was more common in early summer.

Conclusions: The majority of young healthy patients complaining of fatigue are not diagnosed with an organic physiological disorder. Many of the study patients were sent for laboratory tests but in most cases these tests were not contributory to the diagnosis or management. It seems likely that the most efficient strategy would be watchful follow-up with a minimum of testing.

IMAJ 2012; 14: 555-559

KEY WORDS: fatigue, differential diagnosis, workup, primary care, medical encounter

For Editorial see page 566

Fatigue is a common complaint accompanying many different disease situations, but fatigue as an isolated complaint is less common. One study with follow-up over 10 years found that 1.5% of patients complained of fatigue as an isolated complaint each year [1]. Diagnoses of fatigue have decreased due to the increase in diagnoses of fibromyalgia and chronic fatigue syndrome. Gallagher et al. [1] did not find a characteristic age for isolated fatigue, although it appears that most of the cases are between 20 and 50 years old, especially those diagnosed with a post-viral syndrome. Fatigue is rarer in youth under 18 years [1]. Cullen and associates [2] found that in patients who saw a primary care physician, 6.5% presented with fatigue as their chief complaint and an additional 19% complained of fatigue as part of other syndromes.

The sense of fatigue can be attributed to physical or psychological causes [3]. Among the psychological are depression, anxiety disorders, personality disorders, and fatigue as a side effect of medicines used to treat these conditions. Physical causes include hypothyroidism and other endocrine disorders, chronic renal failure, hepatic failure, diabetes, anemia, and occult malignancy. Viral disease, especially when due to human immunodeficiency virus, Epstein-Barr virus, tuberculosis and autoimmune disease, may present at the beginning with unexplained fatigue. Obstructive sleep apnea may cause chronic fatigue. Chronic fatigue syndrome is a separate entity as defined by the Centers for Disease Control [4].

It has been shown that patients who present with fatigue of more than 6 months duration visit their primary care physicians more often, complain more often of psychological difficulties, and although most thought their problem was organic, most doctors believed the cause was psychological [5]. This lack of agreement leads to the conclusion that the conversation between the doctor and the patient on the subject of fatigue is of major importance. Patients regard fatigue as significant since it is disabling, whereas doctors consider it as a non-specific symptom [6]. Another study showed that 9% of all registered patients visited their doctor due to fatigue; one-quarter of these patients received an explanatory diagnosis and only 3% were referred to consultants [7].

In one Dutch study, half the patients followed for fatigue did not receive any diagnosis and only 8.2% were diagnosed with clear somatic disease [8]. In a similar study (also in Holland) which dealt with other common symptoms as well, the percentage of organic diagnoses was 28.7% [9].

* In partial fulfillment of the requirements for the MD degree at Tel Aviv University's Sackler Faculty of Medicine

In their review article, Nijrolder and colleagues [10] summarized 21 studies on the prognosis of chronic fatigue but were unable to pinpoint characteristics that influenced the prognosis. A study by the same researchers [11] found a 50% decrease in the severity of fatigue as reported by the patients after 1 year from onset. Skapinakis et al. [12] examined the natural history of fatigue and found that during follow-up even patients with explained fatigue (with a clear explanatory diagnosis) continued to visit the doctor with the same complaint; namely, up to 33% of patients in that study. The main reasons for long-term complaints were severity of the fatigue at the first visit and presence of a psychiatric diagnosis. A retrospective study over 4 years found that 70% of the cases with a diagnosis of fatigue were dealt with in only one visit and only the minority returned for further consultation with the primary care physician [13].

The diagnosis is largely dependent on the situation that is created during the patient-doctor encounter and therefore may be influenced by social values as well as cultural differences. Since the diagnosis of fatigue actually represents a sack of different problems, the proportional weight of the various syndromes included in the diagnosis may change from area to area and from population to population.

The aim of this study was to look at young patients who present to the family physician with fatigue as a chief complaint and to characterize the doctors' approach to the problem.

PATIENTS AND METHODS

The study population consisted of a random sample of members of Leumit Health Services (one of four health funds in Israel) aged 18–45 who were diagnosed by their primary care physician with fatigue (DSM 780.7) as a chief complaint at the first visit in 2003. The ages were chosen to reflect generally healthy patients. The computer records are filed by age group, and the next relevant age group, 46–55 years old, would have included many patients with a chronic disease. Thus the cutoff of 45 was chosen.

The Leumit Health Services database comprises a comprehensive list of both demographic and clinical data and is subject to periodic quality control testing. All primary care visits are documented in a local electronic medical record, and the coded diagnoses are transmitted to the central database. Patients were identified by their unique national identity numbers.

There is only one code required per visit and therefore there is no distinction between "reason for visit" and "diagnosis at the end of the visit." In practice, most physicians indicate a diagnosis if one is clear, but otherwise use the chief complaint as a code for the visit. Thus, in our study, fatigue was used as the reason for the visit and not the diagnosis. If the cause was clear, a specific diagnosis was used and these records were not included in the study.

EXCLUSION CRITERIA

The following were excluded from the study:

- patients who had a diagnosis of fatigue in their electronic medical record during the 2 years previous to the index encounter
- patients who had one or more of the following (as documented in their electronic medical record) – malignant disease, autoimmune disease, heart failure, renal failure, chronic liver disease, chronic lung disease, psychiatric disease
- electronic medical records that were unavailable for follow-up.

For each patient we recorded the duration of the complaint, age and gender, and medical history.

OUTCOME MEASURES

These included:

- the index encounter (with details of the physical examination, if performed),and subsequent laboratory tests, imaging, referrals to specialists, and medicines prescribed
- Follow-up over one year, with documentation of the number of visits, somatic complaints (headache, dizziness, sleep disturbances), and if a diagnosis was given that could account for the complaint.

STATISTICAL ANALYSIS

We used qualitative statistics. Associations between continuous variables were tested using the Pearson correlation test. Associations between categorical variables were tested using the chi-square test. Differences in subgroups with continuous variables were tested using ANOVA. A P value < 0.05 was considered significant. Ethical approval for our study was granted by the Ethics Committee of Tel Aviv University.

RESULTS

We investigated 486 medical records with the diagnosis of fatigue (187 were disqualified: 99 due to a previous diagnosis of fatigue, 78 with a documentation of a chronic disease in the list of exclusion criteria, and 10 files were unavailable). The study group comprised 299 patients aged 18–45 years with unexplained fatigue. Over two-thirds were women (69.7%), and the average age was 30.5 ± 7.2 years.

Table 1 shows patient characteristics. Table 2 details the accessory tests that were ordered/performed on the first visit. Laboratory tests were ordered for 235 patients (78.6%). The rate of positive results was low (5%), the vast majority having an insignificant deviation from the normal range. Iron was tested more in women (40% vs. 18% in men, $P < 0.001$). Altogether, 8.6% were referred to tests or to consultants, namely electrocardiogram (n=8), chest X-ray (n=4), abdominal ultrasound (n=2), stool culture (n=1), polysomnography (n=1) and urinalysis (n=1). Five patients were referred to consultants, two to the emergency room and three to a dietician.

Fifty-six patients (18.7%) were given a sick leave note at the first visit. Only two (3.6%) of these were referred to consultants or tests as compared to 24 (8%) of those who did not receive sick leave ($P < 0.01$). In this group explanatory diagnoses were given at the same rate (21.4% vs. 27.9%, P = NS) as in the whole group.

Forty-seven patients (15.7%) were given prescriptions for 64 different medicines: 25% were pain medicines, 25% vitamin supplements, 25% were medicines to treat acute conditions, and 15% were tranquilizers (either natural or pharmacological).

Table 1. Clinical characteristics of the 299 patients with a diagnosis of "fatigue"

Duration of complaint	
Not known*	(75.9%) 227
Less than 1 week	(9.0%) 27
Less than 1 month	(7.0%) 21
More than 1 month	(8.0%) 24
Known chronic disease	(31.1%) 93
Injuries or hospitalizations in the last 6 months	(7.0%) 21
Pregnancy in the last 6 months (women)	(15.4%) 32
Patients with somatic complaints	
Any	(24.4%) 73
Dizziness	(12.4%) 37
Headache	(11.7%) 35
Sleep disturbances	(8.6%) 26
Physical examination during the visit	
Any	(56.9%) 170
Blood pressure measured	(42.8%) 128
Lungs examined	(33.4%) 100
Cardiovascular exam	(31.4%) 94
Abdominal exam	(24.8%) 74
Neck examined	(15.7%) 47
Lymph nodes palpated	(10.7%) 32

*Not specified in patient's file

Table 2. Laboratory tests given on the first visit of the 299 patients with a diagnosis of "fatigue"

Tests performed	No. of patients	Pathological results
Complete blood count	(75.6%) 226	(9.7%) 22/226
Blood chemistry	(66.2%) 198	(1.5%) 3/198
TSH	(55.9%) 167	(1.2%) 2/167
Vitamin B12	(48%) 144	(6.9%) 10/144
Iron	(41.8%) 125	(4.0%) 5/125
ESR*	(32.1%) 96	
Epstein-Barr virus serology	(11.4%) 34	(2.9%)1/34
Cytomegalovirus serology	(9.0%)27	(0%) 0/27
Other	(8.7%) 26	(19.2%)5/26
Beta-hCG subunits	**(8.7%) 18	(27%)5/18

*Number of pathological results not available
**Percentage is of women in the study population
ESR = erythrocyte sedimentation rate, hCG = human chorionic gonadotropin

PSYCHOSOMATIC COMPLAINTS

Patient complaints of psychosomatic symptoms such as dizziness, headache, insomnia and general weakness were recorded. Some patients complained of more than one such symptom, and in a few patients the symptom was not psychosomatic but connected to the explanatory diagnosis (insomnia in obstructive sleep apnea, headache in a patient suffering from migraines) The numbers in and of themselves have little significance, but what is significant is that in every case the number of such complaints in patients who received an explanatory diagnosis was much lower than in patients who did not receive a diagnosis. For instance, twice as many people without diagnoses complained of dizziness and insomnia compared to those who were given explanatory diagnoses. In the cases of headaches the increase was fourfold and in general weakness fivefold.

On average, there were 5.8 visits to the primary care physician in the year following the first visit (range 1–46 visits)

Figure 1. Number of visits to the family doctor per patient over the first year since the index visit

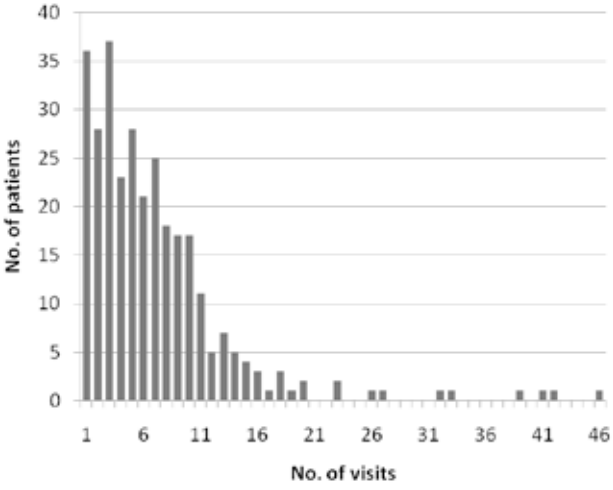
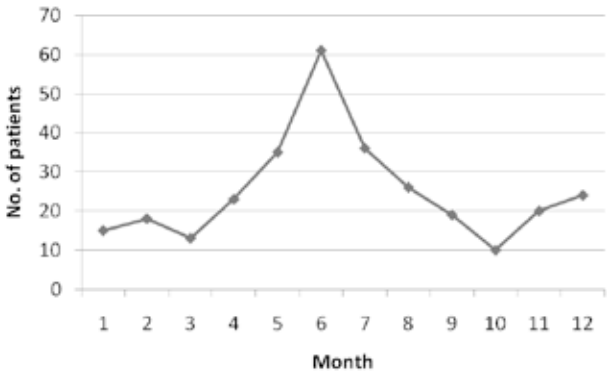


Figure 2. Number of patients presenting with fatigue according to months of the year



[Figure 1]. Figure 2 shows the seasonality of the complaints, with a peak between May and July.

DIAGNOSES EXPLAINING THE FATIGUE

Eighty patients (26.8%) were later given a diagnosis that could explain the fatigue. The most common were anemia (27 patients), vitamin B12 deficiency without anemia (n=8), infectious disease (n=19), pregnancy (n=8), and psychiatric diagnosis such as anxiety, depression or post-traumatic stress disorder (n=5). Among the other diagnoses were two cases of fibromyalgia and one each of sleep apnea, migraine, familial Mediterranean fever, hepatitis C, hypertension, and sarcoidosis.

DISCUSSION

The characteristics of the patients in our study were similar to those in previous studies [1,2,7,8,12]. Most of the patients were female (69.6%), a finding that repeats itself in a number of unexplained chronic syndromes, including fatigue [2,11,14]. It should also be noted that in general more women than men visit their primary care physician, especially those of the age group in the current study.

During follow-up a possible explanatory diagnosis was found in 27%, similar to other studies [7,9] but higher than the 8.2% recorded by Nijrolder et al. [8]. The question arises whether the diagnosis "explaining" the fatigue is the actual cause of the fatigue. The most common cause found was anemia. However, in patients who were diagnosed with mild anemia and subsequently treated, the subjective feeling of fatigue did not always dissipate [15]. Chalder et al. [16] did not find a connection between acute fatigue and concurrent or recent viral illness, although a study in Norway did find a strong association between fatigue and post-traumatic stress disorder [17].

A more focused literature search was undertaken to look at the levels of fatigue found in specific medical conditions. A recent study in Canada [18] showed that 39% of patients with chronic lung disease complained of high levels of fatigue that exacerbated their dyspnea, depression and decreased quality of life. Patients with inflammatory bowel disease, also in Canada [19], showed high levels of fatigue, mainly due to poor sleep, in those with active disease (72%) but also in those with inactive disease (30%). High levels of fatigue (47%) were also found in Dutch patients with knee and hip osteoarthritis [20]. These are all common and chronic conditions that are accompanied by higher levels of fatigue than in our study of ill-defined conditions.

An interesting finding concerned the timing of the diagnosis. Studies on chronic fatigue syndrome [21,22] show that most outbreaks occur in the winter. In contrast, we found a higher frequency in the summer months. This may be because physicians interpreted the same complaints as due to a viral infection in the winter but as unexplained fatigue in the summer. Or it may be due to the high heat load (temperature and humidity) of Israeli summers and the consequent heat stress.

During the first office visit in our study 56 patients (18.7%) were given sick leave and were not sent for any workup; however, the rate of explanatory diagnoses was similar to that of the whole group. This may be explained by the doctor's perception that the patient was using the complaint as a way to obtain sick leave and that giving it would solve the problem, or it may reflect the decision to take a wait-and-see approach.

It is interesting that although physical examination is considered one of the cornerstones of primary care medicine, only 56.9% of patients had documented physical examinations at the first visit. Whether this is due to doctors forgoing proper documentation or forgoing physical examination is not clear. It is possible that many doctors felt that a physical examination would not yield any results due to the generality of the complaint of fatigue and/or past experience with such patients. The Kenter study in Holland [9] showed similar rates of physical examination, so the phenomenon is not unique to our study.

In our study 78.6% of patients complaining of fatigue were sent for laboratory tests compared to only 34% in a similar study from Holland [7]. Since both studies had a similar rate of explanatory diagnoses, it might be wiser to recommend not doing laboratory tests at the first meeting. The rates of patients who were physically examined were also similar in the two studies. The high rate of laboratory tests in our study could possibly be due to preconceived notions on the part of patients (and perhaps physicians) that laboratory tests (which are free for all health fund members) are useful in all cases.

During the year of follow-up after the index visit, the study patients visited their primary physician an average of 5.8 times. This visit rate is similar to rates in patients of the same age group in Israel [23]. Follow-up of 50 patients who were defined as frequent attenders at a gastroenterology clinic showed that 80% complained of fatigue, over one-third of the women were being followed by gynecologists although they had no pathological findings, and most of the patients also had a psychiatric diagnosis [24]. Presumably more diagnoses of psychosocial states would be found in a more in-depth study of patients with fatigue in primary care.

Since this was a cross-sectional retrospective study and was based on usual-care electronic medical records, medical history, physical examination and psychosocial evaluation were neither uniform nor comprehensive. However, since our aim was to explore how doctors approach the complaint of fatigue in a usual-care setting and then analyze the results of their approach, the study design was suitable.

Our study deals with patients' first reported episode of fatigue. Unfortunately, most physicians did not record duration of the fatigue. Cornuz et al. [25] categorized fatigue as recent, prolonged, or chronic, with slightly different approaches to each. If we were able to divide our study group

by duration of fatigue we may have seen a difference in the management by the physicians.

We consider the current study as a pilot study; it has demonstrated that our findings are not that different from those in the literature and our methods are valid. A larger and prospective study is needed to strengthen our findings and will be initiated in the near future. Such a study will standardize the extent of workups done by the participating physicians, which will help us determine which elements are useful for arriving at a diagnosis.

The finding of seasonality also has significant implications. A literature search on the seasonality of fatigue and other somatic complaints did not turn up any significant studies. A further study looking at seasonal differences would be very helpful.

CONCLUSIONS

Fatigue as a primary complaint in a young healthy patient presents a challenge to the family physician who has to "separate the wheat from the chaff." It is clear from the current study that the projected prognosis is benign; significant disease was rare after one year of follow-up. This study shows that the likelihood of missing a serious disease is low even if a limited workup is performed.

Corresponding author:
Dr. G. Blumberg
Leumit Health Services, 10 Snapir St., Tel Aviv 67298, Israel
Phone: (972-3) 630-5409
Fax: (972-3) 630-5404
email: gblumberg@leumit.co.il

References

1. Gallagher AM, Thomas JM, Hamilton WT, White PD. Incidence of fatigue symptoms and diagnoses presenting in UK primary care from 1990 to 2001. *J R Soc Med* 2004; 97: 571-5.
2. Cullen W, Kearney Y, Bury G. Prevalence of fatigue in general practice. *Ir J Med Sci* 2002; 171: 10-12.
3. Goroll AH. Evaluation of chronic fatigue. In: Goroll AH, May LA, Mulley AG, eds. Primary Care Medicine. Philadelphia: Lippincott Williams & Wilkins, 2009: 54-60, chap 8.
4. http://www.cdc.gov/cfs/cfsdefinitionHCP.htm
5. Ridsdale L, Evans A, Jerrett W, Mandalia S, Osler K, Vora H. Patients who consult with tiredness: frequency of consultation, perceived causes of tiredness and its association with psychological distress. *Br J Gen Pract* 1994; 44 (386): 413-16.
6. Sharp M, Wilks D. ABC of psychological medicine: Fatigue. *BMJ* 2002; 325: 480-3.
7. Kenter EG, Okkes IM. Patients with fatigue in family practice: prevalence and treatment. *Ned Tijdschr Geneeskd* 1999; 143 (15): 796-801.
8. Nijrolder I, van der Windt D, de Vries H, van der Horst H. Diagnoses during follow-up of patients presenting with fatigue in primary care. *CMAJ* 2009; 181 (10): 683-7.
9. Okkes IM, Oskam SK, Lamberts H. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. *J Fam Pract* 2002; 15: 31-6.
10. Nijrolder I, van der Horst H, van der Windt D. Prognosis of fatigue: a systematic review. *J Psychosom Res* 2008; 64: 335-49.
11. Nijrolder I, van der Windt D, van der Horst H. Prognosis of fatigue and functioning in primary care: a 1-year follow-up study. *Ann Fam Med* 2008; 6: 519-27.
12. Skapinakis P, Lewis G, Mavreas V. One-year outcome of unexplained fatigue syndromes in primary care: results from an international study. *Psychol Med* 2003; 33 (5): 857-66.
13. Kenter EG, Okkes IM, Oskam SK, Lamberts H. Tiredness in Dutch family practice. Data on patients complaining of and/or diagnosed with "tiredness". *Fam Pract* 2003; 20 (4): 434-40.
14. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? *Int J Epidemiol* 2006; 35 (2): 468-76. Epub 2005 Nov 22.
15. Wood M, Elwood P. Symptoms of iron deficiency anemia: a community survey. *Br J Prev Soc Med* 1966; 20: 117-21.
16. Chalder T, Neeleman J, Reme SE, Power M, Wessely S. Factors associated with acute fatigue in primary care. *Psychol Med* 2010; 40 (8): 1289-95.
17. Lerdal A, Lee KA, Rokne B, Knudson O Jr., Wahl AK, Dahl AA. A population-based study of associations between current posttraumatic stress symptoms and current fatigue. *J Trauma Stress* 2010; 23 (5): 606-14.
18. Baltazan MA, Scott AS, Wolkove N, et al. Fatigue in COPD: prevalence and effect on outcomes in pulmonary rehabilitation. *Chron Respir Dis* 2011; 8 (2): 119-28.
19. Graff LA, Vincent N, Walker JR, et al. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis* 2011; 17 (9): 1882-9.
20. Snijders GF, van den Ende CH, Fransen J, et al. Fatigue in knee and hip osteoarthritis: the role of pain and physical function. *Rheumatology (Oxford)* 2011; 50 (10): 1894-900.
21. Zhang QW, Natelson BH, Ottenweller JE, et al. Chronic fatigue syndrome beginning suddenly occurs seasonally over the year. *Chronobiol Int* 2000; 17 (1): 95-9.
22. Jason LA, Taylor RR, Carrico AW. A community-based study of seasonal variation in the onset of chronic fatigue syndrome and idiopathic chronic fatigue. *Chronobiol Int* 2001; 18 (2): 315-19.
23. http://www.cbs.gov.il/publications/briut_survey/social_survey_h.htm
24. Bass C, Bond A, Gill D, Sharpe M. Frequent attenders without organic disease in a gastroenterology clinic. Patient characteristics and health care use. *Gen Hosp Psych* 1999; 21 (1): 30-8.
25. Cornuz J, Guessous I, Favrat B. Fatigue: a practical approach to diagnosis in primary care. *CMAJ* 2006; 174 (6): 765-7.

Life is served by the sciences, it is governed by wisdom

Seneca (4 BC-65 AD), Roman Stoic philosopher, statesman and dramatist