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Chronic fatigue syndrome in 57-year-old woman

Case Report

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Abstract: Chronic fatigue syndrome (CFS) is characterized by unexplained fatigue lasting for more than 6 months and accompanied by flu-like symptoms. It most commonly affects women aged between 30 and 60 years. To date, clear diagnostic criteria allowing for unambiguous diagno-sis of CFS have not been established. We present a case of a 57-year-old woman with chronic fatigue syndrome in order to showcase the symptoms of this condition and propose a diagnos-tic protocol.

Keywords: *Chronic Fatigue Syndrome • Evaluation • Autonomic Nervous System*

1. Introduction

Fatigue constitutes a symptom reported in numerous diseases, including neurological condi-tions such as multiple sclerosis, Parkinson's disease, vascular disorders of the Central Nervous System (CNS), Lyme disease, lateral sclerosis, and post-polio syndrome, as well as in infectious, neoplastic and rheumatologic diseases. Chronic fatigue syndrome (CFS) is a condi-tion in which fatigue represents the main symptom. However, comprehensive examination and exclusion of other comorbidities is required prior to establishing the diagnosis of CFS [1-3].

Chronic fatigue syndrome is characterized by unexplained fatigue persisting for longer than 6 months and associated with flu-like symptoms. US Centers for Disease Control (CDC) identi-fied this syndrome as a distinct entity for the first time in 1988. The diagnostic criteria of CFS include major and minor symptoms. While the major symptoms refer to the presence of per-sistent or recurrent fatigue for at least 6 months in an individual who was not experienced similar signs in the past, the minor manifestations comprise sore throat, lymphadenopathy, muscular and joint pain, non-localized headaches of a new kind, impaired memory or concen-tration, and sleepiness or sleeplessness. Chronic Fatigue Syndrome also affects physical func-tioning and the emotional behavior of those affected. To date, clear diagnostic criteria allow-ing for unambiguous diagnosis of CFS have not been established [1-3].

A UK study has revealed that signs of unexplained fatigue occur in 1 per 1000 individuals. American data estimates that there are as many as 17 million individuals worldwide suffering from CFS. However, the diagnosis of CFS is extremely rarely established amongst Polish patients.

Currently, CFS is poorly recognised, investigated and managed in Poland. This case study illustrates the complexity of this condition and emphasises the association with autonomic dysfunction [4].

Chronic Fatigue Syndrome is a disorder of unknown etiology, but case studies show, that the sympathetic nervous system contributes to the abnormalities present in CFS. American doctors want to treat CFS as

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a separate disease. In Europe (also in Poland) another approach is dominating. Some clinicians suggest that it is not obvious that CFS can be distinguished from depression. The investigators hypothesize that sympathetic activation underlies the patho-physiology of this disease, so the diagnosis should be confirmed using a special device for non-invasive examination of the cardiovascular system and functional assessment of the auto-nomic nervous system.

2. Materials and methods

2.1 Patient characteristics

A 57-year-old patient (anthropometric data presented in Table 1) was referred as a volunteer to the Department of Chronomedicine and Functional Examination of the Autonomic Nervous

Table 1. Anthropometric data.

Feature	Value
Age	57
Height (cm)	158
Body weight (kg)	70
Body mass index (kg/m^2)	28
Indicator of the surface of the body (m^2)	1,716

System of the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun. The patient described excessive daily sleepiness, sleep deprivation, fa-tigue, irritability, headache, and problems with concentration and memory. The patient report-ed that she easily falls asleep during monotonous activities (e.g. watching television, reading a book, or writing). Also, she experienced one episode of falling asleep while driving a car; fortunately, this did not result in an accident. At the first visitance, comprehensive interview and examinations were conducted to exclude potential comorbidities manifesting with chronic fatigue.

2.1.1 Identifying other causes of chronic fatigue

During the interview the patient did not report symptoms such as night dyspnea, chest pain, heart palpitations, nocturia, or dry mouth after waking up. Furthermore, she slept well at night, and did not snore according to her family members.

Prior to the referral to the Department of Chronomedicine and Functional Examination of the Autonomic Nervous System, the patient was subjected to polysomnographic examination, including electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), as well as recording of chest, abdomen, and limb movements, body position, air flow, and snoring; the examination excluded the presence of obstructive apnea.

According to the patient, she had not been diagnosed with comorbidities associated with per-sistent fatigue and excessive sleepiness, such as depression, hepatitis C, endocrine disorders, malignant disease, chronic pulmonary conditions, or cardiologic, gastrointestinal, liver, kidney, hematological, and mental disorders. Furthermore, the patient did not take any long-term medications.

As a result of residing in a close proximity of a forest, Lyme disease was suspected. Although the patient had a history of numerous tick bites, no erythematous lesions were documented. Serological examination revealed 60.3 BBU/ml of anti-Borrelia burgdorferi IgG (positive result). Therefore the patient was referred to hospital for further evaluation. However, the result of reference recolLine test for anti-Borrelia burgdorferi IgG proved negative, similar to the examination of cerebrospinal fluid where 4.8 BBU/ml of anti-Borrelia burgdorferi IgG suggested the lack of neuroborreliosis.

Additionally, comprehensive laboratory tests were ordered (Table 2, 3, 4) to exclude po-tential comorbidities. Aside from slightly elevated total cholesterol, all tested parameters proved normal.

Table 2. Results of the laboratory tests – biochemistry.

Biochemistry	Result	Unit	Norm
Glucose	103	mg/dl	60 - 110
Serum creatinine	0.73	mg/dl	0.5 – 0.9
eGFR (MDRD)	88	ml/min/1.73	> 80
Total bilirubin	0.35	mg/dl	0.2 – 1
Alat	19	U/l	< 31
Sodium	137	mmol/l	135 – 147
Potassium	4.16	mmol/l	3.7 – 5.1
Total Cholesterol	210 ↑	mg/dl	120 - 200
HDL Cholesterol	67	mg/dl	> 65
% HDL Cholesterol	32	%	> 20
LDL Cholesterol	125	mg/dl	< 130
Triglycerides	94	mg/dl	50 – 150

Table 3. Results of the laboratory tests – immunology.

Immunology	Result	Unit	Norm
TSH	3.670	μIU/ml	0.27 – 4.2

2.1.2 Experimental scales

The patient completed the measure of excessive daytime sleepiness the Epworth Sleepiness Scale (ESS) at the Department of Chronomedicine and Functional Examination of the Auto-nomic Nervous System. Excessive daily sleeping was revealed (15 points). The questionnaire asks the subject about probability of falling asleep on a scale from 0 to 3 for eight daily life situations (result under 10 points - lack of the exaggerated sleepiness, result above 14 points - pathological sleepiness).

Table 4. Results of the laboratory tests - haematology.

Blood count	Result	Unit	Norm
WBC – white blood cells	5.7	X10^3/uL	4-10
LYMPH %	41.1	%	18-47.5
MXD%	5.3	%	<10
NEUTH%	53.6	%	42.5-73
LYMPH	2.30	X10^3/uL	
MXD	0.30	X10^3/uL	
NEUTH	3.10	X10^3/uL	
RBC – erythrocytes	4.49	X10^6/uL	3.8-5.2
HGB – haemoglobin	13.30	g/dl	11.5-16
HCT – hematocrit	38.90	%	36-47
MCV	86.60	fL	80-100
MCH	29.60	pg	28-34
MCHC	34.20	g/dl	32-36
PLT	211	X10^3/uL	140-440
RDW – SD	36.80	fL	
PDW	11.80	fL	
MPV	14.40	fL	
P – LCR	28.00	%	

Moreover, as the patient suffered from persistent fatigue, which was present for at least six months, was not substantially relieved by rest, and did not occur in the past (major symptom), and reported disorders of memory and concentration, sore throat, muscular pain, and headache of a new kind (four minor symptoms), she was examined for the presence of chronic fatigue syndrome according to the criteria proposed by Fukuda et al.

The patient scored 86% in the Fatigue Severity Score (FSS), which examines the influence of fatigue on the activity, motivation, work, and family life.

Other questionnaires were also used to estimate the level of fatigue in our patient; namely, a visual analogue scale (VAS). VAS is a simple method used to determine the level of subjec-tively assessed variables (e.g. fatigue), which cannot be precisely measured with any available objective method. The patient was presented with a scale consisting of a 10 cm "ruler" marked with smiling and sad emoticons at its ends and corresponding to the lack of fatigue and severe fatigue, respectively (Figure 1). Next, the subject was asked to assess the severity of experienced fatigue in a numeric scale in which 0 and 10 corresponded to the lack of fatigue and extremely severe fatigue, respectively. The patient self-assessed her fatigue as 8.

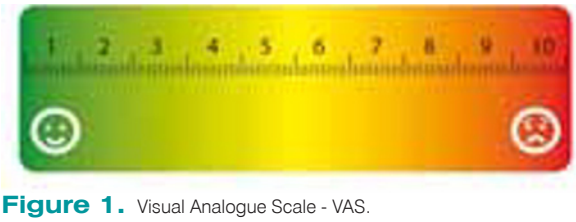

Figure 1. Visual Analogue Scale - VAS.

The scales described above were chosen for the examination, because they are frequently used in assessing patients with CFS and characterise an abnormal condition of fatigue and sleepi-nesses in CFS.

2.1.3 Examination at the Department of Chronomedicine and Functional Examination of the Autonomic Nervous System

In view of previous literature highlighting the role of autonomic dysfunction in CFS, the pa-tient was offered functional examination of cardiovascular and autonomic nervous systems with the Task Force Monitor (TFM) [5].

The examination took place under standard functional examination of the autonomic nervous system conditions. Prior to the test, the patient rested for 15 minutes in a supine position. Dur-ing the examination, room temperature was approximately 21°C and the room was quiet and darkened. The test was conducted in the morning, two hours after the last meal.

Verticalization was performed with a verticalization table, equipped with stabilizing belts to provide patient's safety. After reaching 70° decline, the patient remained in this position for 5 minutes prior to the determination of cardiovascular parameters. Their values were compared to those recorded during the initial 15-minute rest period.

The patient did not report sensations such as vertigo, seeing dark spots, tinnitus, headache, or dry mouth during the verticalization test.

The following parameters were analysed: systolic blood pressure (sBP) [mmHg], diastolic blood pressure (dBP) [mmHg], mean blood pressure (mBP) [mmHg], stroke volume (SV) [ml], cardiac output (CO) [l/min]), heart rate (HR) [bmp], total peripheral resistance (TPR) [dyn*s/cm^5], stroke index (SI) [ml/m^2], cardiac index (CI) [L/min/m^2], index of contractility (IC) [1000/s], Heather index (HI) [1/s], and left ventricular ejection time (LVET) [ms].

Additionally, the heart rate variability (HRV) parameters were examined, including normal-ized unit in low frequency domain HRV (LFnu-RRI) [%], normalized unit in high frequency domain HRV (HFnu-RRI) [%], low-frequency component of HRV spectrum (LF-RRI) [ms^2], high-frequency component of HRV spectrum (HF RRI) [ms^2], power spectral density of HRV (PSD-RRI) [ms^2], and sympathetic-vagal balance ratio (LF/HF; LF_RRI/HF_RRI).

Previous studies have suggested that these autonomic and cardiovascular parameters have the potential as bedside diagnostic tools in CFS [6].

3. Results

The passive verticalization of our patient was reflected by a decrease in stroke volume (SV), along with a decrease in cardiac output (CO). Moreover, an increase in the heart rate was documented as compared to the baseline value determined during the 15-minute rest period (HR). Furthermore, the passive verticalization was reflected by an increase in total peripheral resistance (TPR), systolic blood pressure (sBP), diastolic blood pressure (dBP), and mean blood pressure (mBP).

The autonomic dysfunction can be excluded on the basis of heart rate variability analysis. Low frequency (LF) and high frequency (HF) components can be determined during spectral analysis. The LF/HF ratio reflects relative influence of sympathetic and parasympathetic nervous system on the sinoatrial node.

The passive verticalization of our patient was reflected by significant increase in LFnu-RRI, LF-RRI, PSD-RRI, and LF/HF power ratio, which suggests increased sympathetic autonomic activity. The passive verticalization caused an increase in normalized unit in low frequency domain HRV (LFnu-RRI), with accompanying increase in the low-frequency component of HRV spectrum (LF-RRI). Additionally, an increase in the power spectral density of HRV (PSD-RRI) and sympathetic-vagal balance ratio value (LF/HF) was documented. The values of these parameters are presented in Tables 5, 6, and 7.

Table 5. Descriptive statistics of parameters: sBP, dBP, SV, CO, HR, SI, CI, IC, HI, LVET and TPR (Examination 1).

Variable	Statistics - examination 1		
	Mean	Min.	Max.
sBP	111.401	92.278	133.599
dBP	75.028	62.936	97.786
mBP	92.178	77.391	115.156
SV	86.167	65.387	103.844
CO	5.222	6.528	4.251
HR	60.801	52.861	80.053
TPR	1370.796	1077.893	1805.329
SI	50.209	38.101	60.509
CI	3.043	2.477	3.804
IC	58.74	14.662	98.308
HI	0.297	0.047	0.578
LVET	321.102	262.534	348.185

sBP – systolic Blood Pressure; dBP – diastolic Blood Pressure; mBP – mean Blood Pressure; SV – Stroke Volume; CO – Cardiac Output; HR – Heart Rate; TPR - Total Peripheral Resistance; SI - Stroke Index; CI – Cardiac Index; IC – Index of contractility; HI - Heather index; LVET - Left ventricular ejection time

Table 6. Descriptive statistics of parameters: sBP, dBP, SV, CO, HR, SI, CI, IC, HI, LVET and TPR (Examination 2).

Variable	Statistics - examination 2		
	Mean	Min.	Max
sBP	132.941	117.048	146.578
dBP	96.913	82.952	109.522
mBP	113.199	98.774	124.427
SV	63.748	52.481	78.301
CO	4.054	3.388	5.325
HR	63.71	54.15	81.008
TPR	2186.49	1676.215	2603.14
SI	37.145	30.58	45.625
CI	2.362	1.974	3.103
IC	36.807	1.227	67.675
HI	0.166	0.536	0.006
LVET	322.42	258.619	347.306

sBP – systolic Blood Pressure; dBP – diastolic Blood Pressure; mBP – mean Blood Pressure; SV – Stroke Volume; CO – Cardiac Output; HR – Heart Rate; TPR - Total Peripheral Resistance; SI - Stroke Index; CI – Cardiac Index; IC – Index of contractility; HI - Heather index; LVET - Left ventricular ejection time

Table 7. Parameters of the spectrum analysis of the heart rate variability analysis.

Parameters	Unit	Mean value - lying	Mean value – division
LFnu-RRI	[%]	82.370	91.881
HFnu-RRI	[%]	17.630	8.119
LF-RRI	[ms2]	21.387	36.894
HF-RRI	[ms2]	9.716	10.552
PSD-RRI	[ms2]	30.481	46.584
LF/HF	[1]	2.291	6.210

LFnu-RRI - normalized unit in low frequency domain HRV;
HFnu-RRI - normalized unit in high frequency domain HRV;
LF-RRI - low-frequency component of HRV spectrum;
HF-RRI - high-frequency component of HRV spectrum;
PSD-RRI - power spectral density of HRV;
LF/HF – sympathetic - vagal balance ratio

4. Discussion

Our patient experienced chronic fatigue for at least half a year in accordance with the defini-tion of chronic fatigue syndrome as proposed by CDC and an international study group. Sim-ultaneously, she experienced such symptoms as sleep deprivation, sore throat, lymphadenopa-thy, muscular and joint pain, non-localized headaches of a new kind, and impaired memory and concentration. All these manifestations suggested the presence of chronic fatigue syn-drome.

Additionally, we performed necessary laboratory tests, including complete blood count, uri-nalysis, aminotransferase activity, thyroid hormones levels, glucose, urea, and creatinine, as well as accessory tests (polysomnographic examination, neuroborreliosis test), to exclude potential comorbidities manifesting with chronic fatigue. The results of all these tests were within normal ranges.

In addition, the patient was examined with the Task Force Monitor (TFM) system in order to assess the integrity of the cardiovascular and autonomic nervous systems. Previously pub-lished studies with verticalization table revealed that chronic fatigue syndrome is associated with abnormalities of autonomic regulatory mechanisms. According to the literature, when compared to the controls, many CFS patients are characterized by orthostatic disorders and lower blood pressure, both possibly resulting from the abnormal functioning of ANS. Howev-er, to date, this phenomenon has not been fully elucidated [5,7-10]. Using the Task Force Monitor might allow us to develop objective tools to diagnose CFS and perhaps allow us to diagnose it earlier.

The heart rate variability (HRV) parameters analysis attempts to assess cardiac autonomic regulation through quantification of sinus rhythm variability and presents and allows early detection of irregularities of the autonomic nervous system. Further work is needed to answer the questions these findings raise [11,16].

Due to the normal functioning of reflexes, the passive verticalization of healthy individuals is reflected by about 25% decrease in the stroke volume and 30% increase in both the heart rate and total peripheral resistance. Orthostatic hypotonia is diagnosed if systolic or diastolic blood pressure decreases by 20 mmHg or 10 mmHg, respectively, 3 minutes after passive verticali-zation [12-14].

Previous studies revealed the predominance of sympathetic nervous system in the regulation of cardiovascular function in CFS patients. Higher values of LF/HF ratio observed in chronic fatigue syndrome, both during the day and at night, suggest the impairment of sympathetic-parasympathetic equilibrium in favour of the sympathetic nervous system. Our patient also showed higher value of LF/HF at rest, which was equal to 2.291 (norm: 1-1.5).

Moreover, a significant increase in LFnu-RRI, LF-RRI, PSD-RRI, and LF/HF ratio was ob-served in our patient as a result of passive verticalization; this suggests the activation of the sympathetic component. Although some authors suggest that the response of CFS patients to passive verticalization is similar to that of healthy individuals, it has been shown that the activation of the sympathetic nervous system can be more pronounced as was documented in our patient [15-23].
The evaluation of chronic fatigue syndrome remains challenging. Medical history is not suffi-cient to confirm or exclude CFS; additional tests are required to exclude other comorbidities. This is further hindered by the unexplained etiology of chronic fatigue syndrome, which has been hotly debated and dramatically altered in the recent years. Theories of genetic, immuno-logical, and psychological background of CFS have been proposed; moreover, hormonal dis-orders or viral infection have also been suggested. A number of experts believe that Chronic Fatigue Syndrome develops from a combination of different factors such as: stress-related hormonal abnormalities, brain abnormalities. Abnormal levels of certain chemicals in the brain system known as the hypothalamus-pituitary-adrenal (HPA) axis have been proposed as a cause of CFS, because this system controls important functions like: the stress response, depression and sleep. CFS has sometimes been referred to as the “chronic fatigue immune dysfunction syndrome”, because a number of studies have found irregularities of the immune system. Recently, the role of abnormal autonomic function in the pathogenesis of chronic fa-tigue syndrome has been investigated, suggesting potential significance in the diagnostic pro-cess of this condition in the future [24-29].

5. Conclusion

Currently there are no objective diagnostic tests for Chronic Fatigue Syndrome. This case shows, that the best diagnostic approach is to firstly determine whether the patient matches the diagnostic criteria for CFS including ruling out other possible causes of symptoms. A number of studies, in addition to this case report, have highlighted irregularities of the auto-nomic nervous system in cases with CFS. Stimulation of the sympathetic nervous system through analysis of the heart rate variability (HRV) parameters appears to potential important element in the CFS diagnosis. The Task Force Monitor has a role to play in the objective di-agnosis of autonomic nervous system abnormalities in CFS. Further research explaining auto-nomic disorders in CFS is necessary to improve the diagnostic protocol of Chronic Fatigue Syndrome.

Currently, CFS appears to be infrequently diagnosed in Poland. It is unlikely to be because it is less common in Poland but rather that it is underrecognised. CFS is a debilitating condition that impacts significantly upon quality of life, recognising and managing it are important steps towards understanding how common it is in Poland and what services might be needed for those affected.

Conflict of interest

Authors state no conflict of interests.

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