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DISABILITY

Chronic Fatigue Syndrome: Challenges for Evaluation

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The National Academy of Sciences Institute of Medicine (IOM) focuses on specific features to make the diagnosis of myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS). Symptoms should be present for at least 6 months and have moderate, substantial, or severe intensity at least half the time. In addition to fatigue, other necessary criteria include post-exertional malaise, unrefreshing sleep, cognitive impairment, and orthostatic-related symptoms. Although complaints of chronic fatigue are common, relatively few (75 to 267 cases per 100,000 persons, vs 1775 to 6321 cases per 100,000 persons in patients with fatigue of 6 months duration but nothing more) satisfy these criteria.[1]

2015 IOM DIAGNOSTIC CRITERIA FOR ME/CFS FROM CDC

Diagnosis requires that the patient have the following 3 symptoms:*

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest.
2. Post-exertional malaise - Worsening of a patient's symptoms and function after exposure to physical or cognitive stressors normally tolerated before disease onset.
3. Unrefreshing sleep.

At least 1 of the 2 following manifestations is also required:*

1. Cognitive impairment - Problems with thinking or executive function exacerbated by exertion, effort, stress, or time pressure.
2. Orthostatic intolerance - Worsening of symptoms upon assuming and maintaining upright posture. Symptoms are improved, although not necessarily abolished, by lying back down or elevating the feet.

*The frequency and severity of symptoms should be assessed. The diagnosis of ME or CFS should be questioned if patients do not

Table 1. Pilot Study in 8 Cases with Unexplained Tachycardia with Determination of Catecholamines and/or Amphetamines in Blood or Urine

Case	heart rate start-end	Blood Pressure start-end	% max	metanephrine/normetanephrine (upper normal range in parentheses)	remarks
1	120-166	131/108 166/105	76%	33 (280)/198 (200)	*
2	110-131	194/120 230/130	69%	30 (85)/298 (275)	*
3	91-151	158/105 177/114	90%	0.25 (0.20)/0.52 (0.45)	
4	110-142	155/116 164/77	80%	118 (85)/275 (275)	
5	93-160	148/116 180/100	60%	16 (280)/12 (200)	Opioid-medic.
6	120-160	151/85 185/91	65%	nd/nd	methamp.280 ug/ml
7	115-159	120/89 190/93	53%	34 (30-90) 358 (165-400)	*metamphetamin 100ug/ml
8	119-180	131/113 180/91	120%	nd/nd	Metamph. > 50 ng/ml

* Cases with elevated normetanephrine only nd = not done.

have these symptoms at least half of the time with moderate, substantial, or severe intensity.

Most series report that CFS is twice as common in women as in men. The predisposing etiologies include prior viral infection (eg, Epstein Barr, SARS-CoV-2), immune dysfunction, endocrine-metabolic dysfunction, neuropsychiatric factors, and prior malignancy.

CFS is a diagnostic dilemma for physicians and social scientists because of the varying nonspecific symptoms and lack of physical findings to support a diagnosis of actual pathology. In many ways, this is a disease of exclusion for other causes for chronic fatigue. The major test for determining physical disability is the treadmill exercise test, which provides valuable information if correctly performed. However, some CFS patients present with pre-procedure tachycardia that questions the results of this test, and the mental deficits of CFS are potentially compromised by a lack of objectivity of patients'complaints.

This report describes the findings of medical adjudication for social security purposes of 400 cases over 7 years from a single institution. The basic evaluation included a careful history, physical exam, laboratory tests, lung function testing, ECG, and treadmill exercise testing. In cases with mental complaints (34 cases), blood levels of the cytokine's interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were obtained because production of these cytokines have been associated with CSF-like symptoms following various illnesses.

For example, a cohort of breast cancer patients who had received chemotherapy and/or radiotherapy developed CFS-like symptoms and were found to have increased expression of RNA encoding IL-6 and TNF-α in their leucocytes.[2] Increased production of these cytokines have also been demonstrated in patients

Table 2. Results: Reasons for Initial Tachycardia in 44 Cases Pre-Treadmill Testing

Reasons	Number of cases	Remarks
Alcohol withdrawal	11	
Adiposity (BMI II-IV)	6	
Amphetamine ingestion	5	(3 with drug test, 2 with Catecholamines)
Central analgesics	5	
Bimatoprost eye drops	5	
Unexplained	4	
Hyperthyroidism	3	
Psychopharmacosis	2	
Heart failure	2	
Anemia	1	

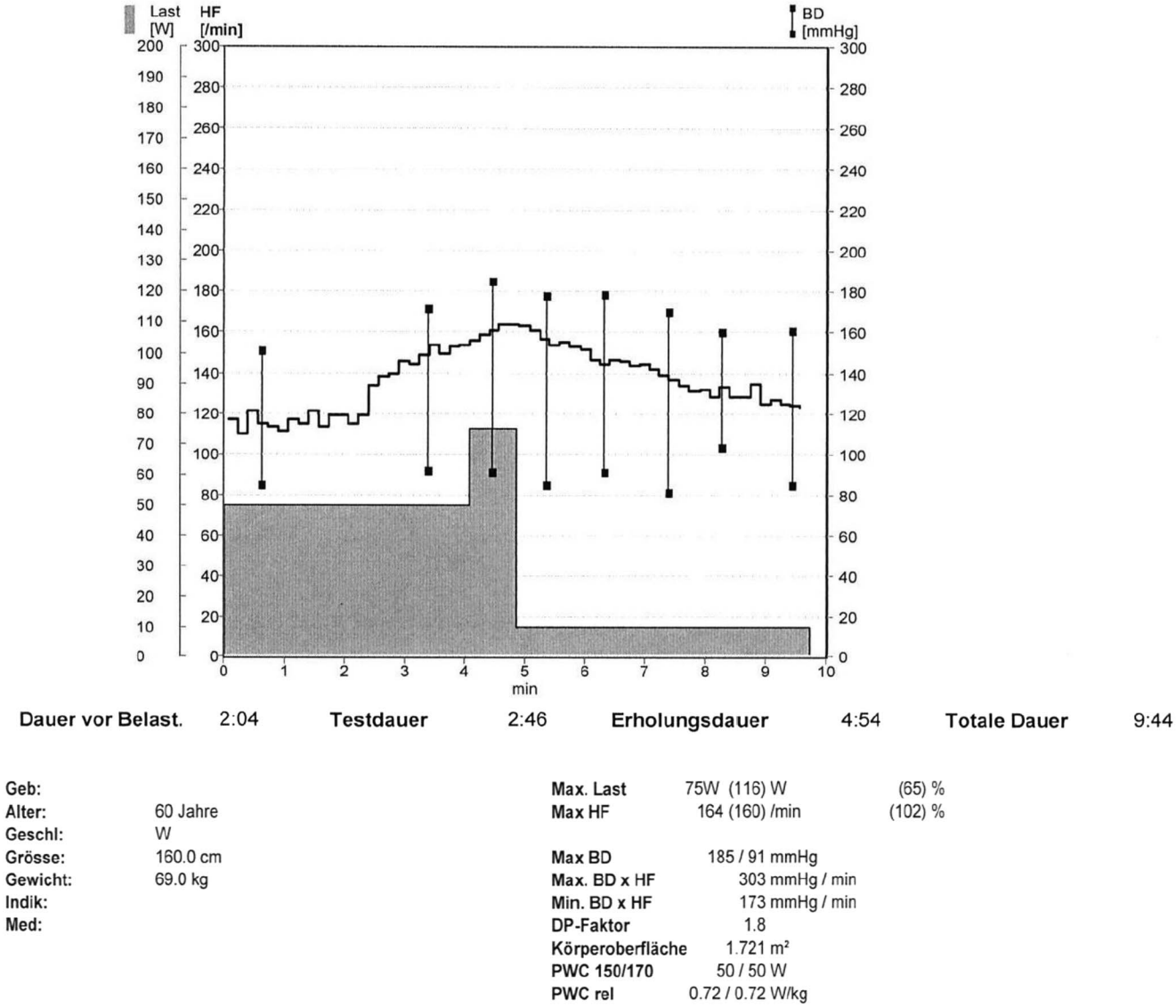


Figure 1. *Shows an example of a treadmill exercise case with breast cancer in remission for 5 years where methamphetamine was found: Heart rate start was 120/min., duration of exercise 4.5 minutes, maximal strength 65%, no normalization of heart rate.*

with prior SARS-CoV-19 infection who developed Long Covid 19.[3] TNF-α is an early cytokine to mediate pro-inflammatory responses by inducing nuclear factor kappa B (NF-kB), which is responsible for the expression of multiple proinflammatory genes in the cell nucleus.[4] This was also shown in some patients with Immune-mediated inflammatory diseases.[5]

MATERIAL AND METHODS

Between 2017 and 2023, 400 patients were referred for evaluation for complaints of physical weakness, pain, and mental impairment to satisfy disability or annuity requirements. Investigation standards were detailed history, clinical status, broad laboratory screening adopted to the underling diagnoses, abdominal

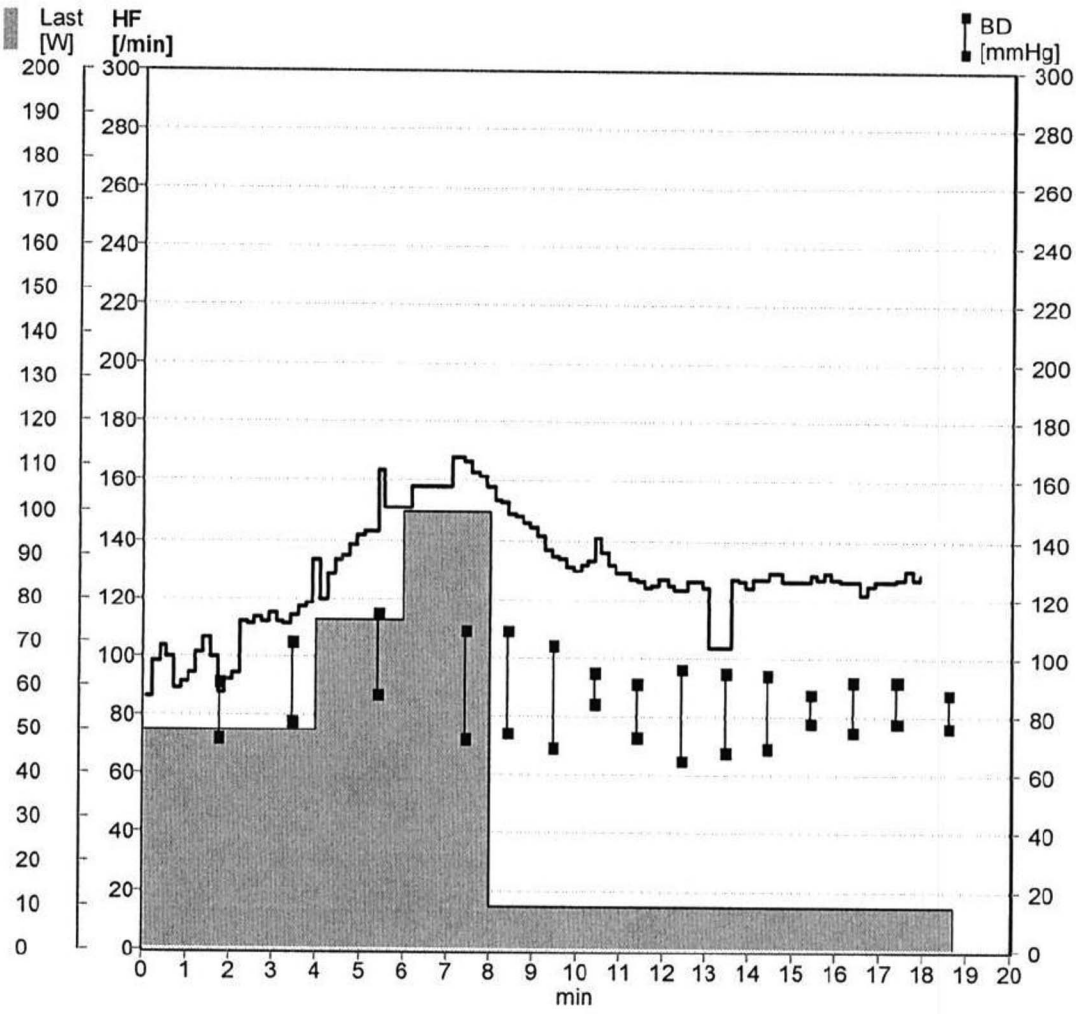


Figure 2. *Presents a case of a brain tumor in remission for 5 years, with eye drops for glaucoma as the patient's only medication. The duration of exercise was 8 minutes (normal), but tachycardia and low blood pressure did not normalize within 10 minutes after the test. Maximal strength was formerly 75%.*

ultrasound, lung function test, ECG and treadmill exercise.

A retrospective evaluation of these opinions was done in cases with fatigue symptoms and unexplained tachycardia at the start of treadmill-exercise testing (44 cases, 11% of the total population) that resulted in a shortened duration of exercise with a lower maximal load achieved. Evaluation of this distinct population revealed alcohol

Table 3. Characteristics of Cases with Solid Tumors in Remission and CFS

Diagnosis	Age	Duration	Phys Ability	Profession	ESR	CRP	IL-6	TNF-α	Symptoms
Breast	40	3 yrs	103%	empl	nl	nl	5.8	6.3	fatigue
Breast	57	6 yrs	100%	unemp	nl	nl	4.6	10.9	PNP
Breast	59	5 yrs	83%	unempl	nl	nl	nl	nl	fatigue/mentally impaired
Breast	33	3 yrs	nd	unempl	nl	nl	nl	nl	memory deficient
Breast	57	10 yrs	79%	unempl	nl	nl	nl	nl	Fatigue, migraines
Breast	74	12 yrs	80%	retired	nl	nl	nl	nd	leg pain
Ovary	60	5 yrs	imposs (adipos)	unempl	52	50	nd	14.4	fatigue
Teratoma	31	6 yrs	75% (glauc)	emplol	nl	nl	nl	nl	no persev
Cervix	53	6 yrs	98%	unempl	nl	nl	nd	7.5	unspecif
Bladder	30	2 yrs	100%	unempl	nl	nl	nl	nl	depress
Rectum	62	7 yrs	100%	empl	nl	nl	nl	18.0	fat, pain
H/N-Tu	58	2 yrs	72%	unempl	nl	nl	nd	9.4	fat jaw, necrosis
Mean	51	5 yrs	90%	3 empl	1 incr	1 incr	0 incr	4 incr	

Note: nd = not done, incr = increased, empl = employed, unempl = unemployed.

withdrawal (11), obesity (6), amphetamine ingestion (5), central analgesics (5), Bimatoprost eye drops (5), unexplained (4), untreated hyperthyroidism (3) psychopharmacosis (2), and anemia (2).

In a pilot study, 7 cases were investigated for catecholamines in blood or urine (metanephrine and normetanephrine). Drug screening tests in urine were made in 15 cases by an immune assay. Positive probes were verified by a HPLC certification test. A further cohort of 34 cases who presented with physical and/or mental symptoms of CFS were analyzed for IL-6 and TNF-α in the blood: There were 4 of 12 cases with solid tumors in remission, 5 of 8 cases with hematological malignancies in remission, and 14 cases with non-malignant diseases (7 long-covid syndrome, 2 cases with psoriasis, 1 with ulcerative colitis, 1 Crohńs colitis, 1 pancreatitis in remission, 1 small-fiber syndrome, 1 primary biliary cirrhosis in remission). Investigations included detailed history, assessment of clinical status, broad laboratory screening adopted to the underlying diagnosis, abdominal ultrasound, lung function tests, ECG and treadmill exercise testing.

Table 4. Characteristics of Cases with Hematological Malignancies in Remission

Diagnosis	Age	Duration	Phys.Ability	Profession	ESR	CRP	IL-6	TNF-α	Symptoms
Foll NHL	63	3 yrs	not eval	unempl	nl	nl	nl	nl	fatigue
Skin lymp	63	1 yrs	98%	unemp	nl	nl	7.2	16.4	fatigue pnp
Hodgk D	59	4 yrs.	80%	empl	nl	nl	2.5	13.1	fatigue/inpat
M-GUS	59	ongoing	80%	empl	nl	nl	2.5	13.1	fatigue/inpat
PV, NHL	61	4 yrs	79%	unempl	nl	nl	9.0	12.2	fatigue
PV treat	63	onging	not eval	unempl	nl	nl	1.5	n.d.	impulseless
Es Thrombo	57	1 yrs	60%	unempl	nl	nl	9.0	12.2	fatigue
AML,3rd rem (2 allo SCT)	33	8 yrs	80%	empl	nl	nl	4.2	14.5*	inpat
AML 1st rem (1 all SCT)	52	4 yrs	100	empl	nl	nl	1.5	nd	fatigue
Mean (8)	56	4 yrs	83%	3/5	nl	nl	3 elev	5 elev	

* Designates values from an IMMUNITE change with a higher upper normal limit of 13.1.
Note: PV = polycythemia vera, AML = acute myelocytic leukemia.

Table 5. Characteristics of Cases with Non-Malignant Diseases

Diagnosis	Age	Duration	Phys Ability	Profession	ESR	CRP	IL-6	TNF-α	Symptoms
L-Covid	62	3 yrs	66% (tachyc)	unempl	nl	nl	1.8	14.9	fatigue
L-Covid	35	3 yrs	100% (tachyc)	empl	nl	nl	52	13.2	fatigue/pain
L-Covid	52	3 yrs	93%	unempl	nl	nl	5.3	16.9	cognition/pain
L-Covid	61	3 yrs	100%	unempl	nl	nl	7.1	14.4	fatigue
L-Covid	58	3 yrs	100%	empl	nl	78	3.4	12.6	anxiety/vertigo
L-Covid	57	2 yrs	100%	unempl	nl	nl	nl	9.6	pain/apraxia
L-Covid	61	4 yrs	62%	empl	nl	nl	7.9	14.8	Fatigue/pain
Psoriasis	38	15 yrs	100%	unempl	nl	nl	nl	10.1	fatigue/apraxia
Psoriasis	52	6 yrs	boycott	unempl	nl	nl	nl	nl	pain/aggression
Ulcerative Colitis	22	7 yrs	54% (tachyc)	empl	nl	nl	nd	7.5	fatigue
Chrohńs Disease	40	9 yrs	70%	empl	nl	nl	14 (IL1)	131	fatigue
Pancreatitis	22	1.5 yrs	88%	unempl	nl	nl	nl	8.3	fatigue
sm fib neu	32	9 yrs	81%	unempl	nl	n	nd	11.3	asyn. polyneuropathy
PBS	59	18 yrs	80%	unempl	nl	nl	nl	17.6	fatigue
Mean	45	6 yrs	78%	5/9	nl	nl	1 inc	11 inc	

Note: nl = normal, nd = not done, PBS = primary biliary sclerosis.

For Interleukin-6 (IL-6), the commercially available Elecsys IL-6 kit by cobas was used. This is an immunological test using a biostimulated anti-IL-6 antibody together with a monoclonal IL-6 mouse antibody marked with ruthenium complex. It measures 1.5-5000 pg/ml. In a study with 817 healthy persons, an upper-range value of 7 pg/ml was determined (95%).

For Tumor-Necrosis-Factor alpha (TNF-α) the IMMULITE 1000 system was used (solid phase, chemoimmunolescent immunometric assay). The upper-normal range was determined in 58 healthy individuals (nondetectable up to 8.1 pg/mL). Between January and June of 2024 a change oft he IMMUNITE 1000 system was used which had a higher uppernormal range of 13.1 ng/ml. The values concerned in Tables 4 and 5 are designated with an asterix (*).

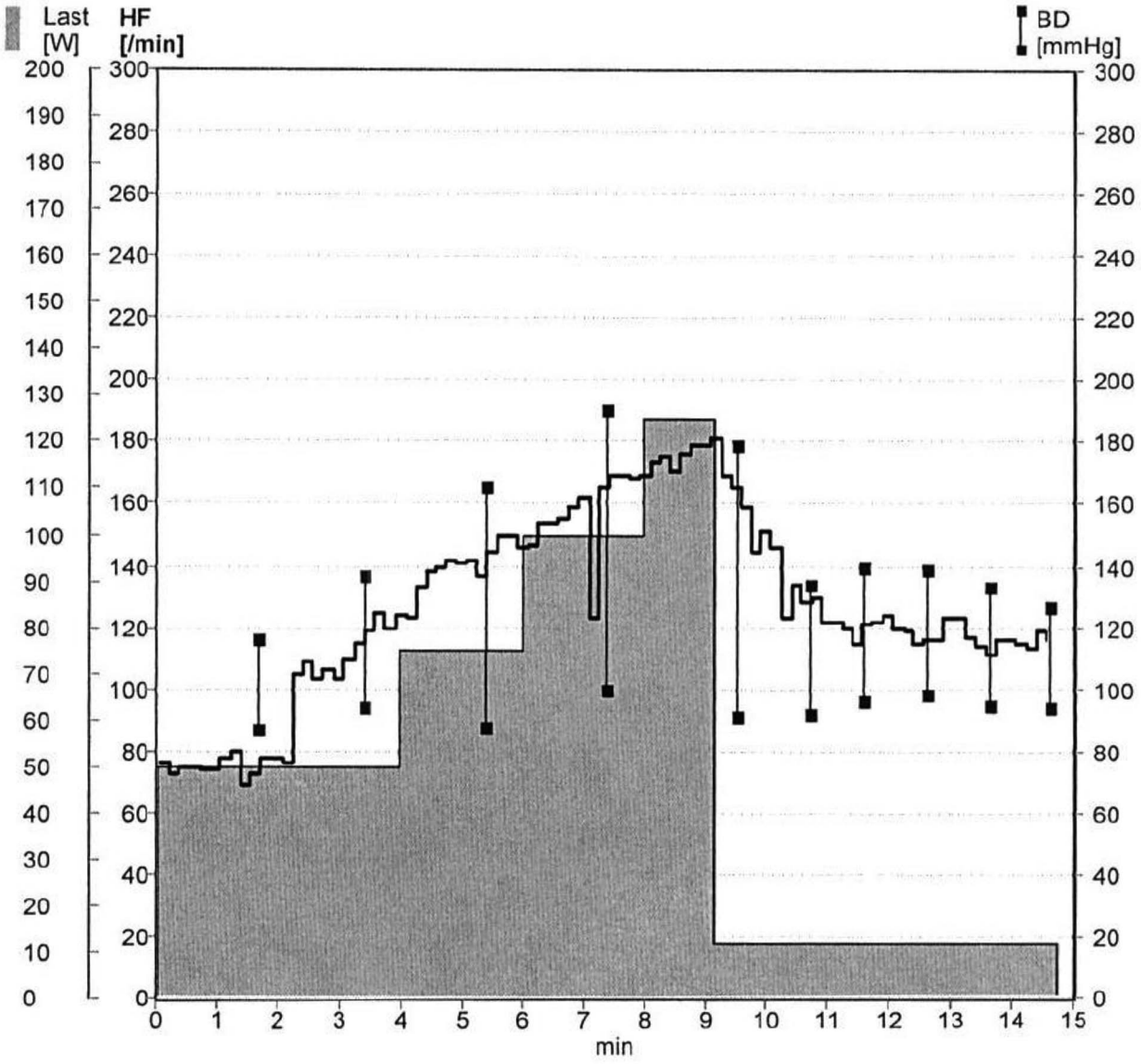
RESULTS

In an attempt to find a reason for unexpected severe tachycardia, catecholamines in the blood or urine of such cases were determined in 6 cases (Table 1). Three cases showed an increase of normetanephrine alone (marked *), 2 cases had an increase of both metanephrine and normetanephrine, while 1 case had low levels of both. The latter was explained by continuous treatment with opioids. An increase of both types of metanephrines is a usual reaction to stress or exercise. For an isolated increase of normetanephrine, however, there are only 2 explanations: either a pheochromocytoma or the administration of amphetamine, since this is the only central-acting drug that acts by inhibition of resorption of normetanephrine from the subsynaptic space. This leads to an increase of the transmitter in the blood in 30 minutes, eliciting an simultaneuous increase in heart rate.[6]

Therefore these drugs were tested in 3 cases with unequivocal positive results (case 6-8), and these data also suggest that 5 cases tried to influence the results by amphetamine ingestion.

The criteria for classification of other likely reasons for tachycardia were as follows:

- Alcohol withdrawal: reported consumption, clinical signs (tremor, sweat, etc), liver US, liver enzymes, carboxy-deficient transferrin
- Adiposity BMI grade II-IV: body mass index above 35 with lack of other reasons
- Use of central acting analgetics: opioids, tilidine, amphetamine, etc
- Use of psychopharmacology
- Use of eye drops with atropin-like components (Bimatoprost)



Geb:	
Alter:	41 Jahre
Geschl:	M
Grösse:	167.0 cm
Gewicht:	68.0 kg
Indik:	
Med:	

Max. Last	125W (178) W	(70) %
Max HF	181 (179) /min	(101) %
Max BD	190 / 100 mmHg	
Max. BD x HF	- mmHg / min	
Min. BD x HF	89 mmHg / min	
DP-Faktor	-	
Körperoberfläche	1.765 m²	
PWC 150/170	82 / 110 W	
PWC rel	1.21 / 1.62 W/kg	

Figure 3. *Shows treadmill exercise of a case with Crohńs disease since 9 years in partial remission under treatment with persisting fatigue. Test duration was 9 minutes, maximal strength 70%, CRP and ESR normal, TNF-α 131 ng/ml.*

- Hyperthyroidism: as measured by TSH, fT3, fT4
- Heart failure: ECG, treadmill exercise, edema, dyspnoea, nocturia
- Anemia: Hb <7.6 mmol/L
- Unknown/other causes: omission of cardiac medications

The results are given in Table 2 according to incidence: alcohol withdrawal symptoms were most frequent, followed by adiposity, but drugs like opioids, amphetamine, psychopharmacologics and Bimatoprost-containing eye drops for glaucoma (all of 5 cases) were similarly important. (See figures 1 & 2).

Investigations of cytokine levels (IL-6 and/or TNF-a) in the blood were done in 34 cases with mental complaints and fatigue. Data are presented regarding main diagnosis, age, duration of CFS, strength, professional status, ESR and CRP-values, IL-6 and TNF-a-levels and main symptoms.

Table 3 gives the results in 12 cases with solid tumors in remission. TNF-a levels were modestly increased in 4 cases, but 2 of these had signs of infection. Physical ability was mainly preserved (90%).

Table 4 shows the results in 8 cases with hematological malignancies in remission. TNF-a-levels were modestly elevated in 5 of them, physical ability was moderately derceased 83%, while ESR and CRP were normal.

Table 5 shows the results in 14 cases with non-malignant diseases: There were 7 cases with long-COVID syndrome, all of which had moderately increased TNF-a levels, 2 psoriatic diseases (1 increased), 2 gut diseases (1 markedly increased), 1 small-fiber neuropathy and 1 primary biliary liver cirrhosis and 1 pancreatitis (borderline). (See Figure 3).

CONCLUSIONS

In cases of patients complaining of general weakness meeting the criteria for CFS, treadmill exercise is the major objective parameter to determine the degree of physical impairment. It is compromised in about 11% of the cases by an unexplained elevated heart rate, which may lead to falsely low results. This experience in a single institution shows that there are several typical reasons for this problem which should be considered for a correct evaluation: these are, according to frequency: alcohol withdrawal symptoms, adiposity, fraud by amphetamine ingestion, continuous use of central acting analgetics, side effects of glaucoma treatment by eyedrops, hyperthyroidism, use of psychopharmacologics, heart failure, and anemia. A broadened investigation is needed to identify these conditions.

In cases with significant mental complaints, it is even more difficult to obtain objective parameters for the impairment. Others have shown that cytokines like IL-6 and TNF-α play a role in breast cancer patients who develop fatigue syndrome during therapy. Our experience includes 34 cases describing clinical symptoms of chronic fatigue syndrome. Even after many years of successful therapy of their disease, cytokines, in particular TNF-α, are elevated while standard biomarkers for infection are not. While this was a rare observation in cases with solid cancers in remission (4 in 12, two with infectious reasons), it was a common observation in cases with hematological malignancies in remission (5 of 8). In cases with non-malignant diseases complaining of chronic fatigue, increased TNF-α was found in 11 of 14 cases, in particular in all 7 cases with long-COVID syndrome.

The findings of TNF-α are an association without proof of causality. However, it may suggest that chronic fatigue syndrome is based on a common biological mechanism that involves a long-term production of TNF-α in many different diseases, which leads to impairment of physical and mental capabilities of the persons affected. Although the exact mechanism is not entirely understood, the determination of TNF-α may help to verify a chronic fatigue syndrome in the setting of social medical expertise, a previously unmet problem.

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