

Between Progress and Invisibility: Are Post-Viral Fatigue Syndromes Overwhelming Medicine and Society?

Zwischen Fortschritt und Unsichtbarkeit: Überfordern postvirale Erschöpfungssyndrome Medizin und die Gesellschaft?

The Corona pandemic may be considered to be over, but its consequences, such as a dramatic rise in mortality, affect many people worldwide (36). After surviving a Sars-Cov-2 infection, some individuals have become ill, sometimes seriously and permanently with what is known as long-COVID (more than 4 weeks) and post-COVID (more than 12 weeks) (35). A more recent definition by the CDC (Centers for Disease Control and Prevention) uses the term PASC - „post-acute sequelae SARS-CoV-2 infection“, which does not require a precise time frame (35, 38).

The multicenter Baden-Württemberg EPILOC study (29) recruited 11 710 subjects from a total of 50,457 patients who had once confirmed Covid-19 infection; 28.5% of these participants suffered from PASC (equating 3289 persons, corresponding to 6.5% of the total infected adult population. T Of these subjects, 37.2% suffered from fatigue, and 31.3% of a neurocognitive disorder (29). A Swedish study reported on 204,805 SARS-CoV-2-positive patients, that in the follow-up 25% of whom were suffering from fatigue, whereas 41% of those treated in the ICU/intensive care unit had fatigue (14). There is recent evidence that these symptoms often persist for years. The gravity of this high incidence of fatigue and neurocognitive disorder becomes clear when we consider results from a British study with 112,964 participants, who found that even when the acute phase of COVID disease was mild, certain cognitive deficits persisted later. If symptoms persisted, cognitive performance decreased significantly by several IQ points (13). Regardless of the high number of cases and their political, social and not least economic dimensions, the individual suffering from a disease stands out (6). It is essentially up to society to alleviate this suffering (medicine) and not to leave those affected to fend for themselves (community solidarity), all the more so when it comes to the consequences of a global pandemic.

While the need for action in research and care is repeatedly affirmed, the situation of many people affected by PASC remains precarious. This is remarkable because post-infectious secondary diseases, which can also occur after other viral infections such as EBV (Epstein-Barr virus) (18, 19), herpes viruses (19, 31), SARS-CoV-2 (19) and other viruses (8), are neither new nor rare diseases.

Since 1969, chronic fatigue syndrome ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome) has been listed by the WHO as a neuroimmunological disease (7). In Germany alone, its prevalence is thought to exceed 250,000 (before the pandemic) with

a high number of unreported cases (11). Quality of life with ME/CFS is considered to be extremely low. It can lead to serious limitations and disabilities in all areas of life (8, 11), and in some cases to the need for care even among young people; the ramifications thereof can entail the long-term loss of professional and social participation and existential hardship, especially as existing structures in medical care and welfare system often do not apply (e.g., „rehabilitation before retirement“). There is still a lack of multimodal therapies and therapeutic concepts, while at the same time societal relevance is significant (6, 33). Often young people are unable to work and cannot participate in life (6, 29, 33).

Conventional medical classification systems and the diagnostic therapy methods derived from them reach their limits in the face of such a complex and systemic condition. In this context, it is hardly surprising that discourses surrounding these diseases are sometimes highly polarized. This corresponds to the lack of social recognition of post-viral fatigue syndromes for a very long time. This can be considered a structural problem, i.e., concerning healthcare medicine or social law; at institutional level, for example with regard to models of social and occupational inclusion and participation, including in the social environment (6). These illnesses challenge existing notions of health vs. illness or of being ill and getting well in both medicine (42) and society (22). At the same time, the medical and social (non-)recognition and invisibility (6, 15) of these illnesses (and their sufferers!) comes into view – issues that for decades have been inadequately addressed or entirely ignored.

It remains to be seen to what extent the efforts that have now been initiated at various levels will generate modernization impulses for medicine and society or whether these diseases will remain a permanent challenge. However, there is undoubtedly still an enormous need for action.

Clinical presentation and symptoms ...

Fatigue exacerbates during or after stressful situations (7). Patients avoid seeing a doctor during severe phases of fatigue, or are unable to do so. As examinations are usually carried out with the patient in a standard, rested state, PASC patients, for example in neurocognitive tests, perform better than their general condition would normally allow. The patient's symptom severity and objective diagnostic results therefore become dissociated. A key syndrome, namely Post-Exertional Malaise (PEM) is very difficult to observe as it >

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usually appears after a consultation (7,11).

High level of complexity (7, 8, 11): If, when taking the usual approach, doctors systematically identify each symptom and derive a diagnosis and therapy from this, doctors and patients reach their limits in terms of organization, time, finances, and patient resilience when many organ systems are affected. The patient is therefore the central source of information. Standardized questionnaires and patient self-reports play key roles in diagnosis and treatment, and medical consultation is becoming increasingly relevant (11, 39).

Few ME/CFS and overtraining researchers have investigated **predictors of post-viral diseases and typical courses**, but typical markers and criteria still need to be developed (8, 38). PASC probably progresses in typical phases, i.e., via acute cellular and immunological activation (8, 19), and involving microthrombi (5), neuropathy (27), autoimmunity (24, 37) followed by various disorders that can also coincide with neurocognitive disorders and neuroinflammation (2), mitochondrial respiratory disorders (4), muscle atrophy (3), circulatory (12) and pulmonary diffusion disorders (34), intestinal microbiota and inflammation (in the gut-brain axis) (23, 25), secondary post-infectious mast cell syndrome (1), neuro-psychiatric symptoms (20, 25). Once the patient's clinical presentation has fully evolved into ME/CFS, therapeutic approaches are quickly overwhelmed.

Psychological stress reactions are common in postviral fatigue syndromes (25, 29, 38), but must be distinguished from genuine psychological, psychiatric or psychosomatic illnesses (20). In the case of postviral syndromes, the time of onset and infection can often be determined via careful anamnesis. Patients have often been healthy and able-bodied up until then. Of course, this means appropriate therapy - for depression and post-viral fatigue syndrome.

Predictors such as irritable bowel syndrome (17, 23), stress, allergies (40), autoimmunity (24), diet or concomitant viral infections (19, 31) suggest a transition to postviral fatigue syndrome (33, 38), but they are definitively not caused by psychological or psychosomatic factors. Genetic polymorphisms associated with high physical and mental performance and strong immunity can be predictors of postviral fatigue syndromes under unfavorable circumstances. The interrelationships between predictors, environmental factors, genetics, and concomitant diseases will be an important field of research.

Pacing vs. activation: One challenge is that coping strategies which are effective for mental well-being, such as sport, social contacts, and activities, are often not at all or only somewhat possible depending on the disease severity; pure activation is harmful in such cases (19, 20, 29, 38). On the other hand, relaxation techniques, a low-stimulus environment and pacing do help. Overall, patients must recognize their current stress limits and apply pacing strategies for each day (20, 39).

Therapy is necessary but often complex: structured diagnostics including biomarkers, classification and evaluation of the findings and disease stages (19, 33, 39, 40) can serve to derive rational therapy strategies, which can be complex overall. Obviously, too few confirmatory prospective therapy studies have been conducted on specific indications - but they are absolutely necessary. At the same time, however, we have enough knowledge to carry out rationally justified therapies that should not be withheld from those affected, who are often very seriously ill and whose future is threatened. This is an ethical obligation for all of us: society, health insurers, doctors, and therapists (42). It weighs heavily when trust erodes in our established medical aid system; in their desperation, patients may turn to questionable or completely dubious, often expensive promises of a cure.

... are hardly recognized in medicine and society

Health and illness are not just medical categories or individual fate - they are socially mediated (10, 26, 28). Post-viral fatigue syndromes illustrate this social nature of health and illness, as standard notions of being healthy and being ill do not really fit to these patients. At the same time, they once again confirm the general state of health inequality (21), for example with regard to financial opportunities for off-label therapies or the ability to obtain information.

Categories and classifications: Through evidence-based medicine, increasing differentiation and high specialization, enormous progress has been and is being made in medicine and let to improving care, diagnosis, treatment, and cure of diseases. At the same time, medicine - also as an epistemic system - struggles to deal with phenomena that cannot be assigned to standardized classification.

Attribution to mental illness: The rate of mental illness diagnoses has risen continuously in recent years (22). At the same time, we can observe the tendency to "psychologize" everyday problems and everyday social behaviors, and to use therapeutic jargon in society. This leads to a blurring of boundaries considering mental diseases (22, 30). At the same time, the attribution of someone's psychosomatic or mental illness in social interaction often has a pejorative character and is accompanied by stigmatization (6, 30, 32). The social causes (and conditions) of those forms of discrimination and misrecognition have to be further discussed and investigated in-depth elsewhere.

In the case of post-viral fatigue syndromes, classification as psychological conditions is problematic: on the one hand because this often leads to therapy methods focusing on activation. This may lead to potentially permanent deterioration if such therapeutic interventions are not individually and extremely carefully adapted to each patient's stress limits (7, 11, 20, 39).

On the other hand, mental illnesses such as depression are serious, often severe disorders that require their own careful and expert clarification and therapy; psychological diagnoses should never be lumped together with (still) unexplained or ambiguous clinical presentations. This form of equalization abbreviates and trivializes the suffering of mentally ill people and makes these illnesses arbitrary. At the same time, such misclassification has long prevented the recognition of post-viral sequelae as complex syndromes.

Body, mind, and soul should be regarded as a unit. From a holistic point of view, it is obvious that psychological, psychotherapeutic, and psychosocial approaches are necessary to train patients and their relatives to deal with the disease better and to help them to cope with their situation and their limitations (6, 11, 26, 42). We know about the benefit of such specific supportive therapies, e.g., form psycho-oncology or psycho-cardiology. It is a cause for concern when patients refuse help (6, 42) out of the - not entirely unfounded - concern of being precepted exclusively as someone with a mental illness, especially in the medical system.

Visibility and invisibility: Post-viral fatigue syndromes are not necessarily visible at first glance and there is still no consensus regarding organ parameters or biomarkers. Severely and very severely affected people are so grievously impaired that they are often unable to leave their home or bed and have little or no access to medical help (7, 9, 11). They become invisible and mute in the truest sense of the word.

One of the leading symptoms of post-infectious fatigue syndromes is post-exertional malaise (PEM) (11, 29, 38). This is very challenging for those affected, their social environment and medical staff. Patients can „perform“ to a certain extent, but PEM usually

only appears hours later or the next day. However, its manifestation, sometimes over days and weeks, usually remains diagnostically invisible - except to the patient's immediate environment (11, 38). This points out a socially produced, albeit unintentional invisibilization of suffering (6, 15), which exacerbates the original illness. PEM is the rationale for the pacing strategy, which provides guidance on how to keep below the expected stress limits and slowly extend them, e.g., by dividing up activity steps, using aids, taking breaks, and relaxing and changing the organization of everyday activities such as getting up, getting dressed, etc. (11). This contrasts with standard activation strategies in a therapeutic context. At a time when many people feel exhausted and drained by experiencing so many crises, fatigue may lead to misunderstandings. This also makes it more difficult to grasp and recognize the complex clinical presentations.

It can be argued that post-viral fatigue syndrome and its disease mechanisms run counter to commonly shared perceptions of health and illness, in particular the processes of becoming healthy and being ill, as well as societal ideas such as performance ethos, willingness to make an effort and the belief in continuous progress. This might explain why such symptoms are then wrongly interpreted as a sign of a lack of willpower or motivation, or the impatient expression „that's enough“. The lack of recognition of fatigue syndromes in medicine and society can therefore also be attributed to the fact that they implicitly undermine social rules and recognition (16) of how we define being ill and getting well.

Care system and welfare structures: The actors of the social and health sector have considerable problems in recognizing post-viral fatigue syndromes for decades, sometimes with existential consequences for the sufferers (6). Social policies, law and bureaucratic regulations make it easy to acknowledge a disability due to an amputation, for example. If a PASC patient has lost strength or is even in a wheelchair, care medicine has a hard time; a long-known problem of our social law is that invisible ailments and suffering is poorly recognized. The consequence of this is sometimes that support services (e.g. aids, degree of disability, care services, pension, but also at work, in schools, training, universities, etc.) either have to be fought for individually or are simply denied (42). In other words, sufferers not only have to (learn to) live with their (severe or most serious) limitations, they almost always also have to struggle for recognition and support in their social environment and from institutions (6). This also applies to necessary therapies (33), for which reimbursement is often refused despite rational therapy strategies exist.

We can assume that personal integrity (16) can be compromised by both the illness itself and how society deals with it. Professional practices and bureaucratic routines in the medical and care system, for example, can exert structural violence without intending to; they are part and parcel of power relationships in society (6, 41). However, we also need to consider the discourses that are held about this illness and the people suffering from it. They influence perceptions in medicine and society as well.

Conclusions

The complexity of post-viral fatigue syndromes requires significant efforts to improve our capacity to differentiate in medicine and society:

- These efforts include believing patients and their descriptions of suffering and acknowledging their situation. On the part of physicians, this gives rise to an ethical obligation to help people, some of whose entire future may be at stake. It is not incidental when practitioners complain about a legally secure framework.
- Patients are entitled to medical aids and medication, and not just when they are privately insured or financially better off, or when a sympathetic employee working in a health or social insurance institution makes an exceptional decision.
- The German Federal Social Court (BSG of 19.03.2002, Ref.: B 1 KR 37/00 R) actually permits the reimbursement of treatment costs „in the case of serious (life-threatening or permanently impairing the quality of life) illnesses“ if „knowledge gained outside an approval procedure has been published enabling reliable, scientifically verifiable statements on a given drug's quality and efficacy a new application area and relying on consensus in the relevant specialist circles about a probable benefit“. This enables the reimbursement of costs, although the social courts in Germany often interpret this (far too) narrowly.
- PASC can progress to ME/CFS, which complicates everything. Treating early before clinical ME/CFS has fully developed rather than postponing therapy is probably the better strategy. Further medical research is urgently needed to develop effective therapies.
- A holistic understanding and therapy options are needed which interlock the different therapeutic and disciplinary spheres. This also involves novel methods of telemedical consultation and patient education.
- PASC and ME/CFS urgently need to be officially acknowledged at welfare-state and socio-political levels. Qualifying for severely disabled status and a higher care classification are often essential to giving patients existential security, i.e., enabling them to cope with everyday life and participate in the workplace.
- We should pay more attention on societal conditions of health and illness and their social and medical consequences: for individuals, in the medical care and support system and on the level of the community as a whole. ■

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