

Review

Biological mechanisms of chronic fatigue

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Abstract

Chronic fatigue is a common, poorly understood and disabling phenomenon in many diseases. We aim to provide an overview of fatigue in chronic autoimmune and inflammatory disease. Fatigue measurement, prevalence and confounding factors such as depression, sleep disorders and pain are reviewed in the first half of the article. In the second half of the article, we describe explanatory models of fatigue and fatigue signalling, with an emphasis on cytokines and sickness behaviour, oxidative stress, mitochondrial dysfunction and the impact of certain genes on fatigue.

Key words: Fatigue, Rheumatic diseases, Cytokines, Oxidative stress, Genes.

Introduction

What is fatigue?

Fatigue can be defined as an overwhelming sense of tiredness, lack of energy and feeling of exhaustion [1]. It is different from normal experiences such as tiredness or sleepiness. As a symptom, it is non-specific and highly subjective [2], and therefore not easily evaluated and quantified. Fatigue is a common feature of a wide variety of conditions, such as chronic inflammatory, infectious, neurological, psychiatric diseases and cancer. Fatigue is most likely under-recognized and undertreated, as reported in patients with RA [3]; however, it clearly can be a severe and distressing phenomenon to the patient. The consequences of fatigue interfere with the patient's life, including social withdrawal, family conflicts and work disability among possible outcomes. Studies in SLE demonstrate that patients with significant fatigue have a lower quality of life than patients without [4], and fatigue interferes with emotional, physical and social functions. The total societal cost of chronic fatigue is high, primarily due to medical expenses, sick leave and loss to the work force [5].

Fatigue may be considered to have several dimensions: peripheral, physical, mental, intellectual and emotional,

among others. Peripheral fatigue is an expression originally used to describe muscle fatigability due to disorders of the muscle and neuromuscular junction transmission [6]. Physical fatigue is the bodily experience of exhaustion following strenuous physical effort and is distinguishable from central fatigue. Central or mental fatigue is the subjective self-reported feeling of fatigue, the experience patients generally report when they seek medical treatment [7]. Fatigue is complex and difficult to describe, and whether it is correct and appropriate to subdivide it into distinct dimensions is debatable, and there is no universal agreement upon this. This article is focused on central (general) fatigue, and will not consider peripheral or physical fatigue.

How to measure fatigue

There are a variety of fatigue-measuring instruments, all principally based on self-reported symptoms, feelings and problems encountered by the patients (Table 1). Some scales are designed to be disease specific, while others are validated and usable across a number of diseases and are referred to as generic instruments. Certain tests attempt to measure several aspects or domains of fatigue, whereas others force the subject to describe fatigue in a single uni-dimensional measure, for example the visual analogue scale (VAS); the optimal approach remains debatable. However, as all scales are based on self-report, it is important to acknowledge that the information derived depends on the question asked. Thus, reported fatigue prevalence is influenced by the type of fatigue-measuring instrument used, and results from the use of different scales cannot be easily compared. The inherent problem with fatigue evaluation is the lack of an objective marker consistently associated with fatigue.

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TABLE 1 Some of the most frequently used fatigue scales

Name of scale	References	Dimensions	Comments
Chalder fatigue scale	Chalder <i>et al.</i> 1993 [102]	Physical fatigue, mental fatigue	Generic
Fatigue assessment instrument	Schwartz <i>et al.</i> 1993 [103]	Fatigue severity, situation-specific fatigue, fatigue consequences, responsiveness to sleep/rest	Generic
FIS	Fisk <i>et al.</i> 1994 [104]	Physical fatigue, cognitive fatigue, psychosocial fatigue	Generic
FSS	Krupp <i>et al.</i> 1989 [2]	One-dimensional	Generic
MFI-20	Smets <i>et al.</i> 1995 [105]	General fatigue, physical fatigue, mental fatigue, reduced motivation, reduced activity	Generic
The piper fatigue scale	Piper <i>et al.</i> 1989 [106] Revised in Piper <i>et al.</i> 1998 [107]	Behavioural/severity, affective meaning, sensory and cognitive/mood	Generic
VAS		One-dimensional	Generic
Medical outcomes study short form 36 (SF-36)	Ware <i>et al.</i> 1983 [108]	Vitality subscale assesses fatigue	Generic HRQOL measure
Parkinson fatigue scale	Brown <i>et al.</i> 2005 [109]	Physical fatigue	Parkinson's disease
Profile of fatigue	Bowman <i>et al.</i> 2004 [110]	Somatic fatigue, mental fatigue, general discomfort	pSS

FIS: Fatigue impact scale; FSS: fatigue severity scale; MFI: multidimensional fatigue inventory; HRQOL: health-related quality of life.

Fatigue and non-inflammatory conditions

Fatigue is common in the general population [8], and also in several non-inflammatory conditions (Table 2). It is the defining feature of the chronic fatigue syndrome (CFS) [9], a much debated condition that causes great disadvantages to the patients affected. The prevalence of CFS varies according to the diagnostic criteria employed and the cohort investigated, and was found to be 0.23–0.46% in the USA [10]. Much effort has been put into finding the cause of the syndrome, and most researchers agree that the aetiology is multifactorial. However, the main causes are not agreed upon. A prevailing hypothesis is that CFS is a condition caused by the interplay of common viral infections and individual susceptibility factors such as genetics, immune system function, personality and psychological traits [10].

Cancer-related fatigue affects cancer patients and cancer survivors, and fatigue persisting up to 10 years after cancer remission has been reported [11]. As expected, there are major differences in the prevalence and experience of cancer-related fatigue depending on cancer type, origin, disease stage and treatment. Fatigue increases significantly during anti-cancer treatment in the majority of subjects [12], and cancer-related fatigue has been reported to be associated with production of pro-inflammatory cytokines [13–15].

Parkinson's disease, post-polio syndrome and stroke are examples of neurological conditions with no clear inflammatory component and in which fatigue is common and often debilitating [6, 16]. It is possible that the pathophysiology of fatigue in these conditions is a disturbance of neuronal trajectories involving basal ganglia, thalamus and the cerebral cortex [17, 18].

Fatigue in chronic inflammatory conditions

Inflammation is associated with fatigue, as is evident in the common lethargy of acute infections as well as the frequently reported fatigue among patients with inflammatory diseases such as multiple sclerosis (MS) [19] and RA [3]. Table 2 gives an overview of some inflammatory conditions frequently associated with fatigue.

Persistent fatigue is one of the major obstacles to optimized function for RA patients [20] as well as primary SS (pSS) [21] and SLE patients [2, 5, 22]. In RA, the experience of fatigue appears to be persistent over time [23], but seems to differ depending on gender, age and the daily activity of the patient [24]. RA patients and rheumatologists regard fatigue management as a critical outcome of medical treatment [25] and OMERACT 8 in 2006 recognized fatigue as a prevalent and significant phenomenon in RA, to be included in the core set of outcome measures for clinical trials whenever possible [26]. However, fatigue is still infrequently assessed in clinical trials [27]. Importantly, several recent studies of biological agents in RA indicate that these drugs have a beneficial effect on fatigue [28–30].

Whether fatigue is related to disease activity is not clear, and may vary across disease entities. In RA, fatigue does not seem to be related to inflammation as measured by CRP and ESR [31]. Studies in SLE that use disease activity instruments without fatigue scales consequently do not find that SLE disease activity influences fatigue [32]. However, fatigue is associated with end organ damage caused by SLE, as well as increased load of cerebral white matter hyperintensities on MRI [33], although

TABLE 2 Various non-inflammatory and inflammatory diseases with fatigue

Condition	Diagnosis of fatigue	Percentage with fatigue (approx.)	Confounding factors	Possible biological explanation	Treatment recommendations for fatigue
Non-inflammatory CFS	Unexplained fatigue >6 months duration, combined with four or more associated symptoms	100	Depression, pain, sleep disturbance	Persistent infection, increased oxidative stress, immune system dysfunction, genetic polymorphism, HPA axis dysfunction, psychological production, HPA axis dysfunction	Cognitive behavioural therapy, graded exercise therapy
Cancer-related fatigue	ICD-10: at least six out of 11 specified criteria must be met	39-90	Psychological stress, side-effects of cancer treatment, pain, hormonal disturbance	Altered or increased cytokine production, HPA axis dysfunction	Cognitive behavioural therapy, graded exercise therapy
Parkinsons disease FM	Clinical Clinical	50-60 40-70	Depression, sleep disturbance Depression, pain, sleep disturbance	Disturbance of neuronal circuits Neuroendocrine dysfunction	No recommendations Tai chi, exercise, sleep hygiene
Inflammatory MS	Clinical	66	Depression, sleep disturbance	Altered or increased cytokine production, neuronal destruction and demyelination	Caffeine, modafinil
RA	Clinical	42-80	Disability, depression, pain	Altered or increased cytokine production	Biologic agents, exercise
SLE	Clinical	80-90	Chronic pain syndrome, low physical fitness, depression, sleep disturbance	Altered or increased cytokine production, increased load of white matter hyperintensities	Biologic agents, exercise
pSS	Clinical	60-70	Depression, pain	Altered or increased cytokine production, link to sickness behaviour in animals	Biologic agents, exercise

the former finding is not universally accepted [34]. There is no consistent relationship between fatigue and routine immunological variables, such as auto-antibodies or complement activation, in SLE [35]. In pSS, a disease activity measuring instrument was only recently developed [36], and previously several disease activity surrogate markers have been explored in relation to fatigue. These include auto-antibodies, serum levels of immunoglobulins and lymphocyte counts. No consistent correlations with fatigue have been reported so far [37]. In MS, fatigue is thought to result from the CNS and immune dysfunction associated with the disorder. Strong evidence points to grey matter disease and demyelination as significant contributors to fatigue [38].

Confounding factors

Mood and sleep disorders

Fatigue is strongly associated with depression, and vice versa. Physical fatigue and loss of energy are included as a single item in the fourth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [39] criteria for major depressive disorder. Other criteria for major depressive disorder also relate to fatigue, for example difficulty in concentrating and difficulty in making decisions. There is an overlap in symptomatology between fatigue and depression [40], and this convergence is complicated by the fact that most instruments and scales designed to measure fatigue also include items that are found in scales designed to measure mood disorders [41]. Hence, patients with severe fatigue, but no depression could potentially be wrongly diagnosed as depressed. One study in pSS reported that fatigue was present in 67% of the 94 patients examined, of whom the majority were not depressed. The authors conclude that although depression is prevalent in pSS, it is not the primary cause of fatigue [42]. However, mood disorder is a confounding factor in most conditions associated with fatigue, and depression is an independent predictor of fatigue in RA [43], SLE [32, 44, 45] and MS [46]. Antidepressant medication is the pharmacological treatment of choice for depressive disorders, but fatigue appears to be one of the symptoms less responsive to this treatment [47] as does cancer-related fatigue. Cognitive behavioural therapy and psychosocial interventions are beneficial in the treatment of depression, and also seem to have a positive effect on fatigue in CFS and cancer-related fatigue [48, 49]. Approximately 10–35% of major depressive disorder patients continue to experience fatigue after remission of the depression [50].

Sleep is a restorative process, and disturbed sleep leads to tiredness and sleepiness. Fatigue is separable from sleepiness although there is an overlapping symptomatology. Patients with conditions associated with fatigue frequently have sleeping disorders [51], and in SLE fatigue is associated with sleep disorder and chronic pain syndrome [32, 33, 44, 45]. The same confounding factors are found in FM syndrome, where disordered sleep and

hyperalgesia are the main disease characteristics in addition to fatigue [52]. Disturbed sleep was also found to be more common in MS patients with fatigue than in non-fatigued patients [53].

In summary, fatigue is prevalent and disabling in non-inflammatory and inflammatory conditions. Measurement of fatigue is generally based on self-reported symptoms. Depression and sleep disorders are confounding factors to fatigue.

The biological origin of fatigue

Pro-inflammatory cytokines and lessons learned from sickness behaviour in animals

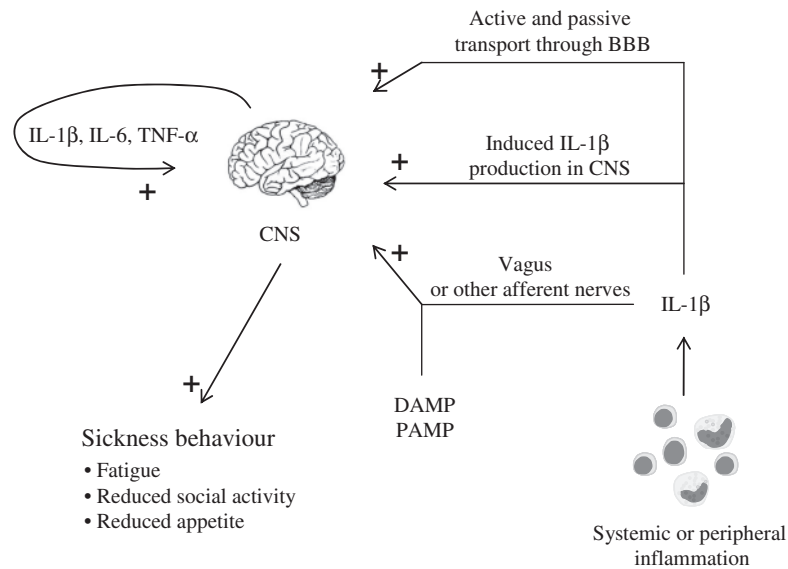
Pro-inflammatory cytokines, such as TNF- α , IL-1, IL-6, IL-12 and IL-17, are important players in the inflammatory response, and are crucial both in defence against infection and in development of autoimmune disease. Pro-inflammatory cytokines in animals act on the brain during infection and other inflammatory states to cause a behavioural response entitled sickness behaviour (Fig. 1). This phenomenon is characterized by drowsiness, loss of appetite, decreased activity and withdrawal from social interaction [54, 55], and represents a change of behaviour theorized to enhance survival of infection. Fatigue in humans could be considered a part of this biologically triggered coping mechanism.

Intra-cerebroventricular or intra-peritoneal administration of IL-1 β induces sickness behaviour in animals, and IL-1 is among the most thoroughly investigated cytokines believed to be a pivotal player in the signalling of sickness behaviour. It exists in two biologically active forms: IL-1 α is mainly expressed on the surface of monocytes and B-lymphocytes, while IL-1 β is a soluble cytokine, secreted by macrophages, monocytes and dendritic cells. The cytokine has two receptors, IL-1RI, which is membrane bound and transfers signals into the cell, and IL-1RII, which functions as a decoy receptor [56]. In addition, the system has an IL-1 receptor antagonist (IL-1Ra) which binds IL-1RI to prevent receptor signalling [57]. Thus, IL-1RII and IL-1Ra are both inhibitors of IL-1 activity.

Peripherally produced cytokines can act on the brain via four main pathways: activation of the vagus and other afferent nerves with consequential signalling to the brain, active and passive transport across the blood brain barrier (BBB) in the circumventricular organs and choroid plexus, secretion from cells in the circumventricular organs, or secretion in the BBB [58, 59] (Fig. 1).

Intra-peritoneal injection of bacterial lipopolysaccharide leads to CNS up-regulation of IL-1 β followed by IL-1Ra within a few hours. Further evidence supporting the importance of IL-1 in sickness behaviour comes from animal studies in which simultaneous intra-peritoneal injection of IL-1Ra and IL-1 β blocks changes in social behaviour and weight loss [60], and from studies on IL-1RI knock-out mice which are resistant to the sickness-inducing effects of IL-1 β administered intra-cerebroventricularly or intra-peritoneally. These observations provide strong evidence that in animals IL-1 is a fundamental regulator of sickness

Fig. 1 Sickness behaviour is mediated by pro-inflammatory cytokines acting on the brain. DAMP: damage-associated molecular patterns, PAMP: pathogen-associated molecular patterns.



behaviour, signalling via the IL-1RI [61]. Several new members of the IL-1R family have been identified in recent years, of which some are expressed on brain neuronal, astro- and microglial cells [62]. The physiological roles of these receptors in the CNS are still unclear, but potentially represent alternative signalling pathways for IL-1, possibly mediating complex behavioural reactions.

In humans, i.v. administration of IL-1 β leads to fatigue, fever, chills and headache [63]. One study found an association between IL-1 and fatigue in patients with prostate cancer undergoing radiotherapy [13], and administration of anakinra, a recombinant IL-1 receptor antagonist, to RA patients produced rapid and profound relief from fatigue [64]. IL-1Ra co-varies with IL-1 β , is easier to measure, and is therefore considered a surrogate marker of IL-1 β production. Increased levels of IL-1Ra persist in parallel with IL-1 during chronic inflammation. High IL-1Ra serum levels associated with fatigue have been documented in patients with various types of cancer [14, 15, 65, 66]. An association between fatigue and increased IL-1Ra in cerebrospinal fluid of pSS patients was recently reported by our group [67].

IL-6 is a pleiotropic cytokine known to mediate fever and the acute-phase response, to stimulate B-cell differentiation and growth, and also to stimulate differentiation of CD4⁺ T-cells to Th17 cells. Its production, mainly by macrophages, is induced by IL-1 and TNF- α , while IL-6 has a down-regulatory effect on IL-1 and TNF- α production [68]. The membrane bound IL-6 receptor, IL-6R, is found mainly on leucocytes, while sIL-6 is a soluble receptor found in plasma. The latter interacts with IL-6, whereupon the complex binds to membrane bound gp130, which is expressed ubiquitously [69]. Thus, IL-6 can act on most cells, including those lacking an IL-6

receptor. The effect of IL-6 on the CNS is less clear, and animal studies demonstrate that IL-1 induces IL-6 synthesis in neurons [70] and that elevated levels of IL-6/IL-6R α mainly activate astroglia, leaving the BBB intact [71]. However, IL-6 is capable of crossing the BBB, and injection of IL-6 induces fatigue in healthy individuals [72, 73]. Patients with SLE or RA receiving IL-6-blocking agents report significant relief from fatigue [74, 75], indicating that these agents interfere with unknown biological pathways mediating fatigue, possibly by blocking transsignalling via sIL-6R and gp130 on neuronal or endothelial cells [76].

Other biological agents interfering with immune processes seem to have a similar effect on fatigue, such as TNF- α -blocking agents in RA patients [28], which acts upstream from IL-6 and IL-1. Other examples include rituximab, a chimeric anti-CD20 mAb [77, 78] and abatacept, an inhibitor of T-cell co-stimulation [79]. These observations indicate that one mechanism for fatigue is operative early in the inflammatory cascade and is influenced by biological agents interfering with pro-inflammatory cytokine signalling.

Hypothalamus–pituitary–adrenal axis

The hormones of the hypothalamus–pituitary–adrenal (HPA) axis are corticotrophin-releasing hormone (CRH), adrenocorticotrophic hormone (ACTH) and cortisol. The axis is regulated by positive and negative feedback and is influenced by other factors such as cortical, autonomic and sensory input. As cortisol is an important hormone for well-being, disturbance of the HPA axis may influence fatigue.

Complex interaction exists between the immune system and the HPA axis; in animals, IL-1 β stimulates IL-1RI on

TABLE 3 Genes associated with fatigue

Up-regulated genes	Down-regulated	Genes coding for
CFS <i>ATP5J2, COX5B, DBI</i> <i>GZMA</i> <i>ARHC</i> <i>PSMA3, PSMA4</i> <i>HINT</i>		Energy metabolism Pro-inflammatory Ras homologue Proteasome subunit Protein kinase inhibitor Transcription factor
Breast cancer survivors <i>IL1A, IL1B, IL6, SOM</i> <i>CXCL2, CXCR5, CCL20</i> <i>IER3, ZNF331, NR4A2, NR4A3</i>	<i>STAT5A</i>	Pro-inflammatory cytokines Chemokine signalling Transcriptional activation Glucocorticoid receptor Vascular growth factor
<i>VEGFA</i>	<i>NR3C1</i>	

Table has been adapted from Saiki *et al.* [98] and Bower *et al.* [101].

cells in the hypothalamus and pituitary glands leading to the release of CRH and ACTH, respectively [80]. Infusion of IL-6 has a profound stimulatory effect on the release of ACTH in humans [81]. An increased level of circulating cortisol suppresses the activation of the immune system through negative feedback.

Approximately half of the studies included in a 2003 review of HPA axis function in CFS [82] found evidence of axial hypofunction. A blunted cortisol response to stress and dysfunction of the HPA axis have also been reported in depression, MS and breast cancer survivors with persistent fatigue [83–85].

The anti-inflammatory effect of glucocorticoids in humans has been acknowledged for >60 years [86], and is due to reduced transcription of pro-inflammatory genes [87] with subsequent down-regulation of IL-1, IL-6 and TNF- α . Accordingly, studies have been conducted using CSs as a treatment for fatigue. Some positive effect on fatigue was reported in two of the three studies conducted in CFS patients [88–90].

Oxidative stress and mitochondrial dysfunction

Oxidative stress is a state caused by an imbalance between the formation of a reactive oxygen species and the ability to detoxify the reactive intermediates or repair the resulting damage to the host [91]. The extent of oxidative stress can be measured in blood, urine, cerebrospinal fluid and tissue by a large number of biomarkers, such as change in concentration or activity of antioxidants, or various measures of lipid, protein and DNA oxidation [92, 93].

Increased oxidative stress is a frequent finding in chronic inflammatory disorders such as RA and SLE. A study in SLE found a significant association between lipid oxidation levels and fatigue, but not between fatigue and measures of inflammation, disease activity or end-organ damage [94]. A limitation to several of these studies is the use of different methods to detect oxidative stress as some methods may be less robust. Such factors make the interpretation of the studies difficult.

Exactly how and whether the increased oxidative stress leads to fatigue is presently unknown, but it could involve the mitochondria, in turn acting as both the source of and target for reactive oxygen species. The mitochondrion serves essential cellular functions, such as energy homeostasis, cell signalling and apoptosis. As much as $\geq 90\%$ of cellular energy is produced in the mitochondria as adenosine triphosphate (ATP) [95]. Several diseases and conditions are associated with dysfunction of the mitochondrion, such as neurodegenerative diseases and cancer [96]. Mitochondrial dysfunction is one of the main causes of oxidative stress. One of the most frequent markers used to assess mitochondrial dysfunction is deficiency in Complex I activity [97].

Genes and fatigue

The association between certain genes and a disease or a phenomenon can be investigated by genotyping studies in which gene mutations or polymorphisms are identified, or by gene expression studies. The latter employ real-time PCR or microarrays to detect mRNA in order to investigate the activation of a large number of genes.

Most studies on genes and fatigue focus on patients with post-infectious fatigue. Although certain genes are identified as marker genes for CFS [98, 99], there are several limitations to these studies. Patient numbers are small, and results are inconsistent regarding identification of specific genes. Also, patients with CFS often have heterogeneous disorders and conditions associated with fatigue. Nevertheless, some genes have been identified in more than one study (Table 3) [98–100], and could imply a genetic inheritance for long-standing fatigue.

A recent study on breast cancer survivors revealed interesting differences in gene expression between subjects with and without fatigue [101]. Applying genome-wide expression microarrays on leucocytes increased expression of genes coding for pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-6) and other immune-activation factors were found. Further, glucocorticoid receptor

genes were down-regulated, adding even more to the pro-inflammatory activity.

Studies like this are important because they bridge the gap between clinical observations, proteomic and genomic data, and provide a step forward to understand fatigue in its entirety. Genetic studies including high numbers of patients with well-defined rheumatic diseases and high levels of fatigue must be performed. In this way, new and more concise pathways for fatigue may be revealed in the future.

Conclusion

Fatigue is a disabling phenomenon with potentially serious consequences not only for patients, but also for society in terms of health-care expense and loss to the work force. Fatigue is common across a number of diseases, and is highly prevalent in RA, SLE and pSS. Mood disorders strongly contribute to the multifactorial aetiology of fatigue. However, a substantial percentage of patients suffering from fatigue are not depressed, and in these patients other explanatory mechanisms must be found. Sickness behaviour in animals, induced by pro-inflammatory cytokines and IL-1 β in particular, parallels fatigue in several aspects. Induction of fatigue by cytokine injections in humans, and relief of fatigue in RA after treatment with biologics, support this hypothesis, and may give rise to future fatigue-specific treatment. Exploration of oxidative stress and gene studies in relation to fatigue offers hope for further understanding of this complex phenomenon.

Rheumatology key messages

- There are biological and psychological mechanisms for chronic fatigue.
- Pro-inflammatory cytokines, oxidative stress and genetic susceptibility seem to contribute to fatigue.
- Biological-based therapies offer future treatment options for chronic fatigue.

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