

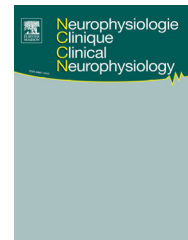


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COMPREHENSIVE REVIEW/REVUE GÉNÉRALE

# Chronic fatigue syndrome and the immune system: Where are we now?



*Le syndrome de fatigue chronique et le système immunitaire : où en sommes-nous maintenant ?*

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**Summary** Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is characterised by multiple symptoms including fatigue, headaches and cognitive impairment, which have a significantly adverse effect on the normal functioning and well-being of the individual. These symptoms are often triggered or worsened following physical or mental exertion. ME/CFS has long been thought of as having a significant immunological component, but reports describing changes in immune function are often inconsistent between study groups. Although the wide range of physical, neurocognitive and autonomic symptoms reported have seriously hampered attempts to understand pathophysiological pathways, investment in biomedical research in ME/CFS is finally increasing with a number of novel and promising investigations being published. The onset of ME/CFS may often be linked to (viral) infections which would be consistent with a variety of alterations in natural killer (NK) cell function as described by a number of different groups. Consistency in cytokine data has been lacking so far, although recently more sophisticated approaches have led to more robust data from large patient cohorts. New hope has also been given to sufferers with the possibility that therapies that deplete B cells can result in clinical improvement. To understand the pathogenic mechanism in this complex condition, it is important to consider repeated analysis in different cohorts. In this review, we will discuss the potential of different components of the immune system to be involved in the pathogenesis of ME/CFS.

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**MOTS CLÉS**

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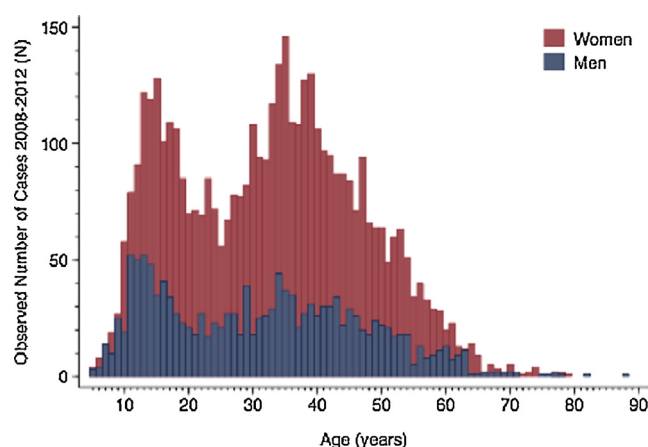
**Résumé** L'encéphalomyélite myalgique/syndrome de fatigue chronique (EM/SFC) se caractérise par des symptômes multiples, dont la fatigue, des maux de tête et des troubles cognitifs, qui ont un effet négatif significatif sur le fonctionnement normal et le bien-être de l'individu. Ces symptômes sont souvent déclenchés ou aggravés suite à un effort physique ou mental. L'EM/SFC a longtemps été considérée comme ayant une importante composante immunologique mais les études témoignant des modifications des réponses immunitaires dans ce contexte sont souvent discordantes entre les différents groupes de recherche. Bien que la vaste gamme de symptômes physiques, neurocognitifs et autonomes rapportés par les patients ait sérieusement entravé les tentatives de comprendre les mécanismes physiopathologiques impliqués, l'investissement dans la recherche biomédicale concernant l'EM/SFC augmente finalement, avec un certain nombre de publications nouvelles et prometteuses. La survenue d'une EM/SFC peut être liée à des infections (virales) qui détermineraient différentes altérations de fonctionnement des cellules *natural killer* (NK) comme décrit par beaucoup de groupes différents. La cohérence des données rapportées sur les cytokines a fait défaut jusqu'à présent, bien que récemment certaines approches plus sophistiquées aient conduit à obtenir des données plus robustes dans de grandes cohortes de patients. Un nouvel espoir a également été donné aux patients avec la possibilité que les thérapies qui provoquent une déplétion en cellules B pourraient entraîner une amélioration clinique. Pour comprendre les mécanismes physiopathologiques de ce syndrome complexe, il est important de considérer les données qui ont été reproduites dans différentes cohortes. Dans cette revue, nous discuterons du potentiel des différentes composantes du système immunitaire à être impliquées dans la pathogenèse de l'EM/SFC.

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## Introduction

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a condition characterized by multiple symptoms including fatigue, headaches, cognitive impairment, myalgia, arthralgia and postural instability [2,54]. These symptoms are often worsened by physical or mental exertion. There is currently no proven effective therapy for sufferers and the chronicity of the condition has a significant and often long-term adverse effect on the normal functioning and well-being of patients [30,57]. In the absence of a specific laboratory test, the diagnosis of ME/CFS presently rests on the exclusion of any medical or psychiatric causes of fatigue in someone with new onset persistent tiredness for over six months. Additional symptoms detailed in the Canadian Centre of Disease Control (CDC) and Fukuda diagnostic criteria are also included to aid diagnosis [14,15,24].

The problem is compounded by the fact that diagnosing this condition is primarily one of exclusion. Even comparing subjects with acute onset ME/CFS with those whose symptoms had a gradual onset confirms significant differences in premorbid personality, prognosis and response to treatment [44]. It is presently estimated that ME/CFS has a prevalence in the population of 0.2–0.4%, with an overall prevalence varying from 0.1% to 2.5%, depending on the criteria applied [19,47,53]. A recent Norwegian study has noted distinct peaks in the age prevalence of ME/CFS. As such, there is a first peak between 10 to 19 years' age and a second peak in the age group between 30 to 39 years (Fig. 1) with a higher prevalence in women than in men, as is consistent with previous studies [5,53].



**Figure 1** Observed number of ME/CFS/ME cases by sex and one-year age groups (2008), data from the Norwegian patient register 2008–2012.

Many patients with ME/CFS describe a history of viral infections prior to the onset of their illness [1,34]. This has also been suggested to underlie some of the immunological abnormalities described in patients with ME/CFS [3,6,16,36]. However, strong evidence for persistent or chronic infection is presently lacking in the majority of patients. ME/CFS has also long been thought as having a significant immunological component. However, it is still not clear whether changes in immunological parameters in patients with ME/CFS are the cause or the result of the condition. The inconsistency of the results of biomedical

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