

# Chronic fatigue syndrome and chronic EBV infection: a long-term challenge in a single clinical case

V. Fiore<sup>1</sup>, P. Bagella<sup>1</sup>, F. Peruzzu<sup>1</sup>, G. Caruana<sup>1</sup>, S. Zaru<sup>2</sup>, M.S. Mura<sup>1</sup>

<sup>1</sup>Unit of Infectious Diseases, Department of Clinical and Experimental Medicine, University of Sassari, Sassari, Italy

<sup>2</sup>Unit of Gastroenterology, Santissima Annunziata Hospital, Sassari, Italy

## ABSTRACT:

- **Background:** Chronic Fatigue Syndrome (CFS) is a complex illness with different clinical definition, etiological models and treatments. A lot of studies have focused on the concomitance with herpesviridae infections, especially Epstein-Barr Virus (EBV). We report a clinical case highlighting the correlation between chronic EBV infection and CFS.
- **Results:** The patient met the CDC criteria for the diagnosis of CFS and presented a high level of EBV-DNA in blood.
- **Conclusions:** Although some studies suggest that subjects with viral infections are not more likely to develop CFS than controls, the possible connection between EBV and CFS remains unclear. EBV-DNA shows the presence of an actively replicating virus, which is known to be associated with several cancers. Whether its replication is the cause or the consequence of CSF needs further investigations.
- **Key words:** Chronic fatigue syndrome, Epstein-Barr virus, EBV-DNA.

## INTRODUCTION

The chronic fatigue syndrome (CFS) is a controversial clinical condition, which predominantly affects young adults, with a peak age of onset between 20 and 40 years, and it is most common in females than in males with a ratio of 6:1<sup>1,2</sup>.

No pathognomonic signs or diagnostic tests for this condition are available, no specific treatment does exist and CFS diagnosis can be made only by exclusion<sup>3,4</sup>. According to the Centers of Disease Control and Prevention (CDC), physicians have to suspect this condition if the individual has a severe chronic fatigue for 6 or more consecutive months, interfering with daily activities, and the patient has 4 or more of the following symptoms: unrefreshing sleep, muscle pain, headaches of a new type, polyarticular pain without swelling or redness, tender of lymph nodes in the neck or armpit, frequent or recurring sore throat<sup>5</sup>. Actually, the etiology remains unknown and a lot of conditions and viral infections have been linked to CFS, such as EBV infection.

CFS is not synonymous of chronic EBV infection or chronic infectious mononucleosis, although they have been often associated.

We report a clinical case of CFS with EBV chronic infection in a 28 years-old girl from Sassari, in Northwest Sardinia.

## CASE REPORT

The patient was referred to the Infectious Disease Unit of the University of Sassari on April 2015 for the onset of fatigue, headache, sleep disorders and muscle-skeletal pain associated to dyspeptic syndrome since 2007, right after hospitalization for EBV glandular fever.

She had a medical history of Polycystic Ovary Syndrome (PCOS) and endometriosis treated with hormonal therapy, a BMI of 25.5 kg/m<sup>2</sup> and she was not affected by other health disorders.

The cardiopulmonary physical examination was negative, only abdominal tenderness on right quadrants was present.

**Table 1.** ELISA and PCR results in a patient with chronic fatigue syndrome.

Diagnostic test	1st evaluation 30/01/2007	2nd evaluation 17/02/2007	3rd evaluation 08/04/2015	Cut off
EBV-VCA IgG	750 UL/ml	750 UL/ml	487 UL/ml	> 20 (UL/ml)
EBV-VCA IgM	160 UL/ml	160 UL/ml	61 UL/ml	> 40 (UL/ml)
EBV-EBNA IgG	172 UL/ml	145 UL/ml	481 UL/ml	> 20 (UL/ml)
EBV-EA IgG	74 UL/ml	76 UL/ml	78 UL/ml	> 40 (UL/ml)
EBV-DNA			1937 cps/ml	< 139 (copies/ml)
CMV-DNA			Not detected	< 278 (copies/ml)

Laboratory results showed normal white blood cells, with 45% of lymphocytes and 42% of neutrophils; liver, kidney and thyroid were normal; all tests for autoimmune disorders were negative; stool samples were negative for Calprotectin, *Helicobacter pylori* antigen, bacterial, ova and parasites research.

ELISA test for mononucleosis resulted positive for EBV VCA IgM and IgG, EBV-EBNA and EBV-EA (Table 1), tested on three samples from serological archive in January 30<sup>th</sup> 2007, February 17<sup>th</sup> 2007 and April 8<sup>th</sup> 2015. Tests for HIV, CMV and enteroviruses were negative. EBV-DNA was highly positive (1937 copies/ml), CMV-DNA was negative, excluding cross-reaction (Table 1).

Clinical features, according to CDC indications, were compatible with CFS.

Thereupon, the patient started therapy with low-dose steroids and multivitamins, with benefit.

EBV-DNA has persisted slightly positive during the follow-up until present day.

## DISCUSSION AND CONCLUSION

Although CFS is a syndrome of unclear origin, many theories have been postulated but further studies are needed to finally elucidate the causative agent and mechanism.

Several conditions, such as viral infections, allergies, nutritional deficiency, hormonal alterations or emotional stress may contribute to its development; a common element seems to involve immune system. Particularly, EBV infection. In fact, given its capability to create immune disorders, it has been associated with many health disorders<sup>6,7</sup>.

Most studies on the link between mononucleosis and CSF are based on antibody titres, showing discordant results. On one hand some studies sustain a correlation<sup>8</sup>, whereas others deny the association arguing that high titre of immunoglobulin G (IgG) to viral capsid antigen (VCA) of EBV in patients with CFS is an incidental finding and that there is not a difference of IgG-VCA titres between patients with CFS and healthy controls<sup>9</sup>, the same would apply to the EA titre<sup>10</sup>. No data are available about the use of IgM titres.

Of importance, the White's London cohort, which followed up 250 primary care patients presenting glandular fever, 44% EBV-related and 34% non-EBV, or upper respiratory tract infection, showed a prevalence of CFS of

9-22% six months after glandular fever, compared with 0-6% in the second group<sup>11</sup>.

The presence of other factors such as a higher BMI and hormonal dysregulation during a chronic EBV infection may probably favor the development of CFS<sup>12</sup>.

EBV-DNA is a more sensitive test for the real presence of an actively replicating virus and gives a more direct explanation of the EBV life-cycle. EBV replication may be the trigger or the consequence of CFS, likely related to an immunological unbalanced situation.

No easy conclusions can be drawn from a single case report; we believe that further studies, conducted in a larger cohort of patients including EBV DNA measurement in blood, could better clarify if there is an association between persisting EBV viremia and CFS<sup>13</sup>.

## CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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