CORE
Metadata, citation and similar papers at core.ac.uk
Provided by UCL Discovery

Raised serum IL-8 levels are associated with excessive fatigue in female carriers of X-linked Chronic Granulomatous Disease in the United Kingdom

Battersby A[1], Martin AJ[1], Tarn J[1], Ng WF[1], Cale C[2], Goldblatt D[3], Gennery AR[1]

[1]Institute of Cellular Medicine, Newcastle University [2]Great Ormond Street Hospital, London [3]Institute of Child Health, University College London

Corresponding author: Andrew Gennery

andrew.gennery@newcastle.ac.uk

To the Editor,

Chronic Granulomatous Disease (CGD) is a rare primary immunodeficiency caused by defects in NADPH oxidase complex, of which around 80% of cases in the UK are X-linked (XL) [1]. Female carriers of XL-CGD have a dual population of phagocytes. It is recognised that they experience a range of infective, inflammatory, and autoimmune complications of CGD [2]. Many XL-CGD carriers also report excessive fatigue [2].

Fatigue has been reported as a significant symptom in chronic inflammatory and autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, sarcoidosis and Sjögren's syndrome. In these conditions, patients report fatigue as one of the most important and troubling symptoms which impacts significantly upon quality of life [3]. The presence of fatigue in inflammatory conditions and the association with ongoing inflammation suggests an inflammatory mechanism. Evidence of pro-inflammatory cytokine involvement in fatigue has been reported in both animal and human models [3].

Serum samples were collected during a study of the healthy female XL-CGD carriers from the UK, identified through a UK CGD Registry. Symptoms of excessive fatigue were investigated using the Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF). Stored serum from 52 subjects was measured for serum levels of pro-inflammatory cytokines (IL-1α, IL-5, IL-8, IL-10, IL-17, TGFβ1, IFNα and IFN-γ) by Cytometric Bead Array (CBA) immunoassay using a BD Biosciences LSR Fortessa X-20™ cell analyser (Becton Dickinson, Oxford, UK).

Results were compared with inflammatory disease control groups of 10 high and 10 low fatigue Sjögren's syndrome patients and 15 healthy controls. All controls were

matched for sex and age. XL-CGD carriers were divided into two groups; those who reported fatigue and those who did not. Median age of XL-CGD carriers was 41.5 years (8.5-65.9), ethnicity 96% White British. Statistical analysis was undertaken between the groups using STATA and medians were compared using a Mann-Whitney U test for non-parametric data. A p value ≤0.05 was considered statistically significant.

Forty-eight percent (25/52) of XL-CGD carriers reported suffering excessive fatigue, associated with significantly higher scores in the MFSISF ($p<0.01$). There were no differences between those with relatives with CGD who had or had not been transplanted, controlling for fatigue associated with the psychological stress of having a relative with a serious disease.

Interleukin (IL)-8 levels were significantly higher in XL-CGD carriers (mean 1459u/ml) than in healthy controls (mean 72u/ml) ($p=0.015$) and patients with Sjögren's syndrome (mean 203u/ml) ($p=0.031$) (Figure 1). IL-8 levels were also significantly higher in the group of XL-CGD carriers who reported high levels of fatigue (mean 2405u/ml) than in those not reporting fatigue (400u/ml) ($p=0.017$).

No other cytokines reached statistically significant different levels between groups. Many XL-CGD carriers reported high levels of fatigue. The significantly higher serum IL-8 levels in XL-CGD carriers than healthy and Sjögren's syndrome controls and the significantly higher levels in those reporting fatigue suggests a biological explanation for the symptoms, particularly as there were no differences in fatigue within families who had transplanted or non-transplanted index cases.

Previous studies have associated raised IL-8 with excessive fatigue [4], however this is the first study to evaluate fatigue and pro-inflammatory cytokines in XL-CGD carriers.

Although the serum samples were obtained at different time periods, they were collected at the same time as data about fatigue levels. Despite the limitations of the study, this is an important finding and demonstrates for the first time that many XL-CGD carriers, previously thought to be unaffected, experience significant fatigue for which there may be a biological cause. Previous studies have shown that gene expression of pro-inflammatory cytokines is up-regulated in neutrophils from XL-CGD patients, including IL-8 [5]. Whilst similar observations have not been demonstrated in XL-CGD carriers, it is likely that the phagocyte population expressing the mutated X-chromosome would show similar findings. Further research is required to evaluate this finding in XL-CGD carriers. Importantly, the finding of a potential biological explanation for the symptoms of fatigue opens up the possibility of therapeutic intervention for this population.

References

1. Cole T, Pearce MS, Cant AJ, Cale CM, Goldblatt D, Gennery AR. Clinical outcome in children with chronic granulomatous disease managed conservatively or with hematopoietic stem cell transplantation. The Journal of allergy and clinical immunology. 2013;132(5):1150-5.
2. Battersby AC, Cale CM, Goldblatt D, Gennery AR. Clinical Manifestations of Disease in X-Linked Carriers of Chronic Granulomatous Disease. Journal of Clinical Immunology. 2013;33(8):1276-84.
3. Norheim KB, Jonsson G, Omdal R. Biological mechanisms of chronic fatigue. Rheumatology. 2010;50(6):1009-18.
4. Sorenson M, Jason L, Lerch A et al. The Production of Interleukin-8 Is Increased in Plasma and Peripheral Blood Mononuclear Cells of Patients with Fatigue. Neuroscience and Medicine. 2012;3:47-53.
5. Kobayashi SD, Voyich JM, Braughton KR, Whitney AR, Nauseef WM, Malech HL, et al. Gene expression profiling provides insight into the pathophysiology of chronic granulomatous disease. Journal of immunology (Baltimore, Md : 1950). 2004;172(1):636-43.

Figure 1 - Log box plot of IL-8 concentration in each study group