NADPH oxidases (NOX) enzymes induced oxidative stress in CIDP patients

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Background

NADPH-oxidases enzymes (NOX) are key regulators of neuroinflammation, a pathological hallmark of some neurological disorders such as Amyotrophic Lateral Sclerosis (ALS), Parkinson's Disease (PD) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP).

NOX catalyze the formation of Reactive Oxygen Species (ROS) that play a role in the development of neurological pathologies, particularly the phagocytic isoform NOX2, leading to oxidative modifications of macromolecules which modulate transcription and other signalling pathways controlling neuroinflammation.

CIDP is an acquired immunomediated condition affecting the peripheral nervous system; its pathogenesis includes several humoral and cell-mediated mechanisms and, although the exact process of myelin destruction is still unknown, CIDP is presumably an autoimmune disease where macrophages are the primary effector cells for demyelination.

Objectives

This study aims to elucidate the links between neuroinflammation, NOX2 activity and neurodegenerative diseases. Specifically, based on the increased ROS generation seen in different neurological pathologies, our research aims to clarify NOX role in CIDP, in particular to prospectively assess NOX2 action by measuring oxidative burst in a cohort of patients and healthy controls.

Methods

Thirty CIDP patients (mean age 61.9±15.9 years) and 30 healthy control subjects (61.2±14.4 years) have been enrolled. Sixteen of these patients were treated with Intravenous Immunoglobulin (IVIg).

To evaluate NOX2 activity, neutrophils and monocytes oxidative burst was measured directly in fresh whole blood using Phagoburst™ (Orpegen Pharma, Germany) assay by flow cytometry. The mean fluorescence intensity (MFI) in response to different stimuli, which lead to produce ROS, corresponds to the GeoMean that represents the percentage of oxidizing cells and their enzymatic activity. We also measured oxidative burst values before and after the IVIg administration in CIDP patients in order to understand whether the treatment modified the MFI value.

Fig 1a

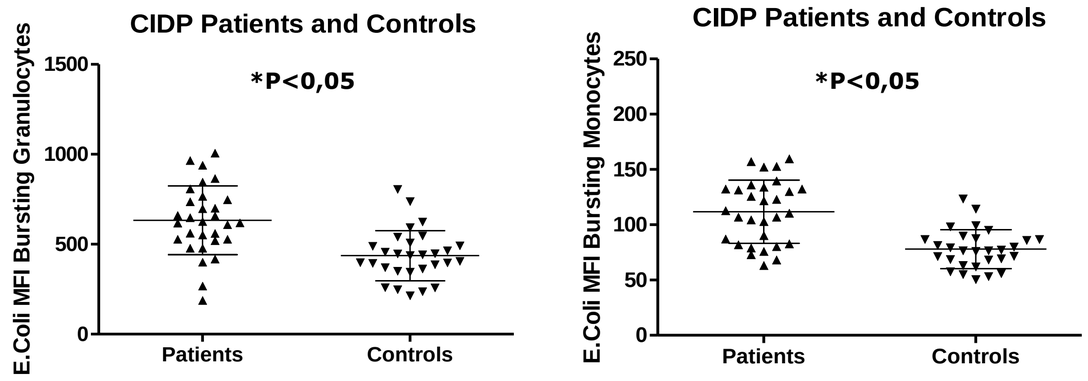
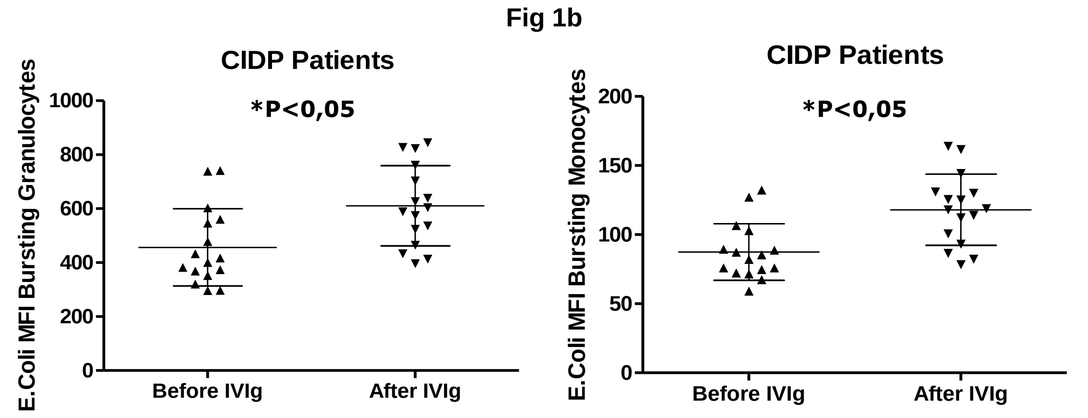


Fig 1b



Results

In CIDP patients the MFI values for granulocytes and monocytes burst (mean 633.3, SD 191; mean 111.8, SD 28.5) were statistically different compared to those measured in controls (mean 436.6, SD 137.0; mean 78.2, SD 17.3) (p=0.0003) (p=0.000001). This significant differences among the NOX2 enzymatic activity was also confirmed for granulocytes and monocyte burst before and after IVIg administration (p=0.005 and p=0.0009), with the second values higher than the first (Fig. 1 a; b)

Discussion and Conclusions

Our data may suggest an involvement of NOX2 enzymes in ROS formation in CIDP patients.

Additional enrollments of more subjects and next follow-up of these patients/controls will be needed to corroborate this hypothesis, to better evaluate their role and eventually to establish markers to identify patients and potentially effective but unproven novel therapies. Moreover, ROS production could be one of the potential mechanisms responsible for the efficacy of the IVIg therapies.

Our findings indicate that modulation of NOX enzymes activity may help to better understand important cell processes and mechanisms leading to neuroinflammation-mediated brain dysfunction.

Acknowledgements

This study was supported by the European Community's Health Seventh Framework Programme (FP7/2007–2013 under grant agreement 259867), Fondazione Vialli e Mauro per la ricerca e lo sport and the Fondazione Franco e Marilisa Caligara (research grant to GM).

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XLVI Evento Nazionale Società Italiana Neurologia - Genova 10-13 ottobre 2015

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