THE RESEARCH CONTINUES: CYTOKINE PROFILES IN THE CENTRAL DISORDERS OF HYPERSONOMNOLIENCE

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OVERVIEW

• Introduction
• Cytokine Study Description and Results
• Study Implications
• What’s Next?
**JARGON AND ABBREVIATIONS**

- **Statistical significance** – Helps us quantify whether the result we are seeing occurred by chance or represents a real phenomenon.
- **IH** – Idiopathic hypersomnia
- **NT2** - Narcolepsy type 2
- **EDS** – Group of patients that report significant, debilitating sleepiness, but when studied in the sleep lab, they do not fall into the category of a type of narcolepsy or idiopathic hypersomnia.
WHAT ARE CYTOKINES ANYWAY?

• Cytokines are a group of proteins (not "antibodies" though) that carry signals throughout the body to regulate both localized and full-body immune responses.

• Cytokines disturbances are known to underlie rheumatologic diseases like rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.

• In 1998 the FDA approved the first cytokine “regulator” – this was etanercept (brand name Enbrel) – a TNF alpha inhibitor to be used for severe rheumatoid arthritis.

• Since then cytokine inhibitors have also been approved for the cytokines IL-1 (anakinra) and IL-6 (tocilizumab), among others.


Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment

Mehmet Soy, Gökhan Kesar, Pamir Atagündüz, Fehmi Tabak, İşık Atagündüz, and Servet Kayhan

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CYTOKINES AND SLEEP

- Cytokines are the link that ties together communication from our immune system and central nervous system to influence the sleep-wake cycle.

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<thead>
<tr>
<th>Situation</th>
<th>Cytokines</th>
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<tbody>
<tr>
<td>Sleepiness of acute infections</td>
<td>IL-1β, TNF-α [12,36,37,39]</td>
</tr>
<tr>
<td>Sleepiness of chronic illness</td>
<td>TNF-α [43-46]</td>
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<tr>
<td>Sleep deprivation</td>
<td>IL-1β, TNF-α, IL-6, leptin, ghrelin [32-35,51-54]</td>
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<tr>
<td>Obstructive sleep apnea</td>
<td>TNF-α, IL-6 [7,59-61]</td>
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<tr>
<td>Chronic insomnia</td>
<td>TNF-α, IL-6 [93]</td>
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<tr>
<td>Aging-related sleep problems</td>
<td>IL-6 [116]</td>
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<tr>
<td>Alcohol-related sleep disturbance</td>
<td>TNF-α, IL-6 [119]</td>
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<tr>
<td>Depression-related sickness</td>
<td>IL-1, IL-2, IL-6 TNF-α [120,121]</td>
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<tr>
<td>Narcolepsy</td>
<td>TNF-α, IL-6 [122-124]</td>
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CYTOKINES AND SLEEP IN HEALTHY INDIVIDUALS

CYTOKINES IN PATIENTS WITH SLEEPINESS DISORDERS

STUDY DESIGN

• Patients:
  • Convenience sample of 153 patients evaluated at Emory Sleep Center in Atlanta, GA

• Diagnoses
  • Obstructive Sleep Apnea
  • Insufficient Sleep Syndrome
  • Narcolepsy Type 1
  • Narcolepsy Type 2
  • Idiopathic Hypersomnia
  • EDS
  • Controls

STUDY DESIGN

• Sleep lab examination
  • Overnight polysomnography
  • Daytime multiple sleep latency test

• Survey Data
  • Sleepiness, fatigue, depression, early bird/night owl, sleep inertia (how hard it is to "wake up" when you wake up)

• Cytokine levels (10 different cytokines in total)
  • Measured from blood samples that had been collected in clinic and stored frozen since collection
  • Reported levels of cytokines will be picograms (pg) per milliliter of blood samples
RESULTS

• Total of 111 patients (for brevity, will only discuss groups below)
  • Control: 22
  • IH: 51
  • EDS: 26
  • NT2: 12

• Average age: 33.8 years
• Average BMI: 23.9 kg/m²
• Average sleep per week: 65.1 hours
STUDY RESULTS – CYTOKINE DATA (CONTEXT)

• Age can affect cytokine levels
• BMI can affect cytokines levels
• Gender can affect cytokine levels
• Interestingly, the effect of these factors was not consistent across our groups of patients
AGE AND CYTOKINE LEVELS

- Controls: Age did not correlate with any cytokines
- IH: Age did not correlate with any cytokine
- EDS: Age was negatively correlated with TNF alpha and IL-10 concentration
- NT2: Age negatively correlated with TNF alpha concentration
BMI AND CYTOKINE LEVELS

Controls: Significant positive correlation with IFN G, IL6, IL8

IH: Significant positive correlation with IL-6

EDS: Negative correlation with IL-4 and TNF-alpha

NT2: No significant correlations with BMI
**GENDER AND CYTOKINE LEVELS**

**TNF alpha Concentration by Diagnosis**

- **Control**: Mean 2.0 pg/mL, Error bars: 95% CI.
- **EDS**: Mean 3.5 pg/mL, Error bars: 95% CI.
- **IH**: Mean 3.0 pg/mL, Error bars: 95% CI.
- **NT2**: Mean 2.5 pg/mL, Error bars: 95% CI.

**IL-10 Concentration by Diagnosis**

- **Control**: Mean 0.5 pg/mL, Error bars: 95% CI.
- **EDS**: Mean 1.0 pg/mL, Error bars: 95% CI.
- **IH**: Mean 0.5 pg/mL, Error bars: 95% CI.
- **NT2**: Mean 0.5 pg/mL, Error bars: 95% CI.

**Red = Female**

**Blue = Male**
**Gender and Cytokine Levels**

- Red = Female
- Blue = Male

**GCSF Concentration by Diagnosis**

- Control
- EDS
- IH
- NT2

Mean GCSF Concentration (pg/mL)

Error bars: 95% CI
CYTOKINES AND SYMPTOMS IN SLEEPINESS DISORDERS
Cytokines and Symptoms in Sleepiness Disorders
Cytokines and Symptoms in Sleepiness Disorders

GCSF and Sleep Inertia in Patients

R² Linear = 0.070

y = 10.35 - 0.28x
WHAT IS GOING WRONG TO CAUSE THIS? IN CONTROLS, MORE SLEEP = HIGHER GCSF
In sleepy patients, GCSF doesn’t necessary increase with more sleep.
GCSF and Depression in Patients

Cytokines and Symptoms in Sleepiness Disorders
GCSF and Sleep Inertia in Patients

Cytokines and Symptoms in Sleepiness Disorders

R² Linear = 0.070

y = 10.35 - 0.28x
Utility of lumping: If certain symptoms of sleepiness disorders are correlated with certain cytokines (ex. GCSF), therapies that target that cytokines can be used to treat symptoms.

Utility of splitting: Levels of cytokines varied for each of the four diagnoses we covered (controls, IH, NT2, and EDS) and between men and women. Could we use cytokines help tell us what disorder a patient has? Or could we use similar cytokines levels to create new diagnosis “clusters”?
**NEXT STEPS**

- Use similar cytokines profiles to create “clusters” of patient diagnoses and compare those to current diagnoses as defined by sleep study results
  - What can we learn from these differences and similarities as to the causes and characteristics of disorders of sleepiness?
- Many cytokines fluctuate on a circadian schedule, and even over weeks-months. Future studies will quantify these fluctuations and see if diagnosis also has an effect.
- Etanercept (TNF alpha blocker) has been used by prior authors (Vgontzas et al., 2004), to treat symptoms of sleepiness in sleep apnea, could this or other cytokine mimics/blockers be used to treatment symptoms of IH, NT2, or EDS?


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