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Changes in cytokines during treatment of elderly, hospitalized psychiatric patients – a naturalistic study

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ABSTRACT

Immunological abnormalities have been demonstrated in several psychiatric disorders. Predominantly, studies have focused on younger adults, and research on elderly psychiatric in-patients is scant. In this naturalistic study, we investigated changes in cytokine levels during the treatment of diagnostically unselected elderly psychiatric in-patients, and whether these changes could be related to clinical outcomes. Clinical variables, demographic data, lifestyle data, and blood samples, including 27 plasma cytokines representing a broad spectrum of inflammatory mediators, were collected from 81 patients, 60 years and older, at admission and discharge. A subgroup of 49 patients also completed a self-reported clinical, psychiatric status form, indicating their level of recovery during hospitalisation. Statistical analyses demonstrated that a broad range of cytokines fell during treatment, and the fall was associated with clinical improvement, irrespective of psychiatric and somatic diagnoses. Exploiting cytokines as biomarkers of clinical traits might to be of limited use in a general population of elderly psychiatric in-patients as the field stands now.

1. Introduction

Immunological dysfunction, including aberrant cytokine levels, has been demonstrated as an integral part of several psychiatric disorders, spanning from depression to autism (Bjorklund et al., 2016; Leighton et al., 2018; Trepanier et al., 2016). Specific cytokine patterns have also been suggested to provide clues to diagnoses, staging, treatment and prognosis (Black and Miller, 2015; Tatay-Manteiga et al., 2017). However, most of these studies do not include elderly psychiatric patients, and in particular elderly psychiatric in-patients, despite their growing importance due to the aging populations in most countries (Beard et al., 2016) and the high degree of health care utilization amongst elders (Ilinca and Calciolari, 2015). Furthermore, the studies have often been restricted to delineated psychiatric disorders, excluding patients with comorbid conditions. Though this might be considered beneficial from a methodological perspective, it leaves the question as to whether the research is relevant for the clinician working with elderly co-morbid psychiatric patients. A related issue is the naturally occurring age-related change in immunological competence, so-called immunosenescence or immune-aging (Weinberger, 2017). Accordingly, neuroinflammatory studies on younger adults are not necessarily applicable to elderly psychiatric patients (Bugge et al., 2018).

In this naturalistic study, we investigated changes in cytokine levels during the treatment of diagnostically unselected elderly psychiatric in-patients, and whether these changes could be related to clinical outcomes.

2. Material and methods

2.1. Ethics approval and consent to participate

All patients were presented oral and written information about the study. Consentual competency was assessed according to established guidelines (Pedersen et al., 2007). For patients who were considered

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unable to give individual consent due to their medical and/or psychiatric condition, information about the study was provided to their next of kin. All patients, and their next of kin when relevant, had to sign a written consent in order to participate in the study. Approval of the study was obtained from the Regional Committee for Medical and Health Research Ethics of Northern Norway (REC North, reg. nr. 2009/1388).

2.2. Declaration of interest

Declaration of interest: none.

2.3. Population

Eighty-one diagnostically unselected patients, 60 years and older, consecutively admitted to a psychiatric hospital in Tromsø, Norway (69 °N), during an 18-month period, were selected for inclusion. The patients were drawn from a catchment area of approximately 250 000 citizens. Patients that could not communicate or cooperate, for instance due to delirium or severe dementia, were excluded from the study, as were patients with medical conditions that could significantly distort inflammatory parameters, such as an ongoing infection or severe dehydration. Five eligible patients declined to participate, and two patients were excluded due to medical reasons. Demographic data, lifestyle data, clinical variables and routine blood samples including electrolytes, liver enzymes, blood cells and thyroid hormones were collected form all patients. In addition, 27 plasma cytokines representing a broad spectrum of inflammatory mediators were analysed at admission and discharge. At discharge, 49 patients (60% of all patients) completed a self-reported clinical, psychiatric status form, with five categories: Complete recovery, Almost complete recovery, Partial recovery, No recovery and Worsening.

2.4. Cytokines

Within the first three days after admittance, and at the day of discharge, morning blood samples were collected from all patients. Plasma for cytokine analysis were obtained from blood collected into EDTA-tubes, immediately placed on crushed ice, centrifuged, and rapidly frozen to -70 °C, until analysed in one batch, using an immunoassay method, i.e. a Multiplex Analyser with a predefined kit (Bio-Plex Human Cytokine 27-Plex Panel; Bio-Rad Laboratories Inc., Hercules, CA). The following cytokines were analysed: IL-1β, IL-1 receptor antagonist (IL1-ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, basic fibroblast growth factor (bFGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), interferon (IFN)-γ, interferon-inducible protein (IP-10), monocyte chemotactic protein (MCP-1), macrophage inflammatory protein (MIP-1α, MIP-1β), platelet derived growth factor-BB (PDGF-BB), regulated upon activation T cell expressed and secreted (RANTES), tumour necrosis factor (TNF), and vascular endothelial growth factor (VEGF).

Two cytokines, GM-CSF and IL-15, had a high frequency of non-detectable levels. Consequently, these cytokines were excluded from further statistical analyses. An additional eight cytokines had a small number of patients with cytokine levels below the lower detection limit (number of patients with non-detectable levels): IL-2 (4), IL-10 (11), IL-13 (1), IL-17 (4), bFGF (2), G-CSF (2), PDGF-BB (2), and VEGF (4). In order to include these patients in the statistical analyses, data were imputed using SPSS, see the Statistical analyses section.

2.5. Clinical assessment

A battery of psychometric instrument were used in the clinical assessment of the patients (N = number of patients): the MINI International Neuropsychiatric Interview (Sheehan et al., 1998), N = 52, the Mini-Mental State Examination/MMSE (Folstein et al., 1975), N = 76, the Clockdrawing Test (Tuokko et al., 1992), N = 74, the Montgomery and Aasberg Depression Rating Scale/MADRS (Montgomery and Asberg, 1979), N = 60, or the Cornell Scale for Depression in Dementia (Alexopoulos et al., 1988), N = 20. The psychometric tests were applied at the discretion of the clinicians, based on the state and cooperability of the patient. Nevertheless, the majority of patients (N = 80) underwent at least one psychometric interview on depression and one test of cognitive impairment. In addition, experienced clinicians conducted standardized clinical interviews and reviews of medical records in assessment and diagnostics. When appropriate, interviews of next of kin were also undertaken. All patients were diagnosed according to the ICD-10 research criteria.

Table 1
Biological treatment during hospitalization.

Drugs	Number of patients	Percentage of patients
Antidepressants	54	67
Antipsychotics	40	49
Antidepressants + antipsychotics	26	32
Mood stabilizers	2	3
Paracetamol, Ibuprofen	13	16
Acetylsalicylic acid (low dose)	25	31
Steroids, cytostatic agent	8	10
Electroconvulsive therapy	12	15

2.6. Treatment

Patients were treated with a combination of predominantly supportive psychotherapy, psychoeducation and biological treatment, including psychotropic medication. Table 1 provides an overview of the given biological treatment.

2.7. Statistical analyses

As demonstrated by a Kolmogorov-Smirnov test, the data were not strictly normally distributed. Accordingly, the Spearman rank correlation coefficient was used to analyse differences between the rankings of two variables. A chi-square test was applied to determine if there was a significant difference between two sets of data (Pearson Chi-square, asymptomatic 2-sided). To test deviations from a theoretically expected distribution of a dichotomous variable, a binominal test was used. Due to multiple statistical analyses, false detection rate adjusted p-values (FDR-p) were calculated and applied to all analyses related to the cytokines. IBM Statistical Package for the Social Sciences, Version 23 (SPSS Inc., Chicago, Illinois, USA) software was used in the statistical analysis.

As mentioned in the Cytokine section, a small group of patients had very low or undetectable levels of eight cytokines, i.e. the analyser could not determine the cytokines levels in these patients; they were so-called non-detects (NDs). This is a normal finding for several cytokines in healthy adults. Accordingly, data from these patients should not be reported as missing data, as they might provide valuable statistical information. For the purpose of including these patients in the statistical analyses, we did single imputations, i.e. using the random number generator of SPSS, we substituted the NDs with a random, uniformly distributed value between zero and the lower detection limit (Uh et al., 2008).

3. Results

3.1. Patient characteristics

Patients were referred by general practitioners for various psychiatric conditions, depression (54%), psychosis (17%) and dementia

Table 2
Distribution of major diagnostic categories.

Diagnoses	ICD-10	Main population (N = 81) %	Outcome population (N = 49) %
Organic, including symptomatic, mental disorders	F00-09	38	20
Mental and behavioural disorders due to psychoactive substance abuse	F10-19	1	2
Schizophrenia, schizotypal and delusional disorders	F20-29	12	16
Affective disorders	F30-39	41	53
Neurotic, stress-related and somatoform disorders	F40-48	7	8

(11%) being the most common. Women represented the majority of patients (61%). Median age was 76 year (SD 7.5). About half of the patients had undergone previous psychiatric hospitalization (47%), and a quarter of patients had two or more preceding hospitalizations. Most patients had a somatic disease (78%), cardiovascular disease being the most frequent (30%). The mean duration of admission was 39 days (median = 34 days).

Compared to the total population (N = 81), the population that completed the psychiatric status form at discharge (N = 49), henceforth the *outcome population*, had a higher proportion of female patients (71%), somewhat more patients with previous psychiatric hospitalization (57%) and patients with somatic disease (88%), but had otherwise comparable characteristics.

3.2. Diagnoses

The major diagnostic categories in the main population and the outcome population after assessment are shown in Table 2. The most common diagnosis in both populations was recurrent depressive disorder, though relatively more common in the outcome population (39%, versus 30% in the main population). The second most common in the main population was dementia in Alzheimer's disease (24%). In the outcome population, the second most common diagnosis was bipolar affective disorder (10%).

3.3. Self-reported clinical status

For analysing purposes, the five categories of the self-reported clinical, psychiatric status form, were combined into two main categories: Improvement (69% of patients, N = 49), containing patients who rated their status at discharge as Complete recovery (23%) and Almost complete recovery (46%), and Little/No improvement (31% of patients, N = 49), containing patients who rated their status at discharge as Partial recovery (21%), No recovery (8%) and Worsening (2%).

3.4. Changes in cytokine levels in the total population during treatment

In the total population (N = 81), there was a fall in cytokine levels, as median values fell for 19 cytokines and rose for three cytokines, whereas three cytokines were unchanged (Table 3). When categorizing each cytokine into two groups, Rise or Fall, depending on whether the majority of patients had a rise or fall in that cytokine, 20 cytokines were classified in the Fall-category, with a difference in median between rise and fall of 35% (difference calculated as a percentage of total number of patients, N = 81). The remaining five cytokines were classified in the Rise-category, with a difference in median between rise and fall of 9% (Fig. 1). Thus, most patients had a fall in cytokine levels during hospitalization, and the fall was more extensive than for the minority of patients that had a rise in cytokines.

Looking at the outcome population (N = 49), patients in the Improvement-group were more likely to have a fall in cytokine levels, than in the Little/no-improvement group ($p < 0.032$). Moreover, there was a positive correlation between clinical improvement and falling cytokine levels ($p < 0.033$) (Table 4).

Table 3
Change in serum levels of cytokines (pg/ml) during treatment (N = 81).

Cytokine	Median value at admission	Difference between median at admission and discharge	Percentage change in median (in-out)
IL-12	28.0	−9.6	−34
IP-10	1077	−368	−34
MCP-1	20	−6.7	−34
IL-17	43	−13	−32
RANTES	6767	−1 950	−29
IL-13	7.0	−2.0	−29
MIP-1a	11	−3.0	−27
Eotaxin	96	−23	−24
IL-10	8.0	−2.0	−25
PDGF-BB	138	31	−23
IL-5	5.0	−1.1	−22
IL-9	18	−3.0	−17
MIP-1b	45	−6.0	−13
INF-g	184	−23	−13
IL-7	21	−1.7	−8
bFGF	46	−3.1	−7
G-CSF	53	−3.0	−6
VEGF	22	−1.0	−5
TNF-a	92	−2.0	−2
IL-1ra	154	3.0	2
IL-8	13	1.0	8
IL-2	9.0	1.0	11
IL-4	3.0	0.0	0
IL-6	11	0.0	0
IL-1b	3.0	0.0	0

We did not find any significant difference in the distribution of the Little/No improvement patients among the rise and fall-category of individual cytokines. There was however, a significant difference in the distribution of Improvement patients, i.e. for 11 cytokines there was a majority of patients with clinical improvements in the fall-category (FDR-p): IL-17 (0.005), MIP-1α (0.007), INF-γ (0.009), MCP-1 (0.011), IL-6 (0.014), bFGF (0.016), IL-9 (0.018), PDGF-BB (0.020),G-CSF (0.023), IL-7 (0.025), IL-5 (0.027).

Adjusting for multiple analyses in the study population (N = 81), we did not find any statistical significant correlations (Spearman rho) between changes in plasma levels of any single cytokine during admission, and gender, age, marital status, psychiatric diagnosis, anti-inflammatory drugs, psychotropic drugs, electroconvulsive therapy, reason for admittance, smoking, vitamin supplements, alcohol consumption, length of stay, somatic disease, MADRS, MMSE and BMI. Likewise, we found no correlation between change in any single cytokine and self-reported clinical status at discharge.

4. Discussion

To the best of our knowledge, this the first study to explore changes in cytokine levels in a group of diagnostically unselected gerontopsychiatric patients in intramural treatment.

The main findings were, first, that for the majority of cytokines the plasma levels fell during hospitalization, indicating a reduction in inflammation, and second, in the outcome subpopulation, almost 70% of

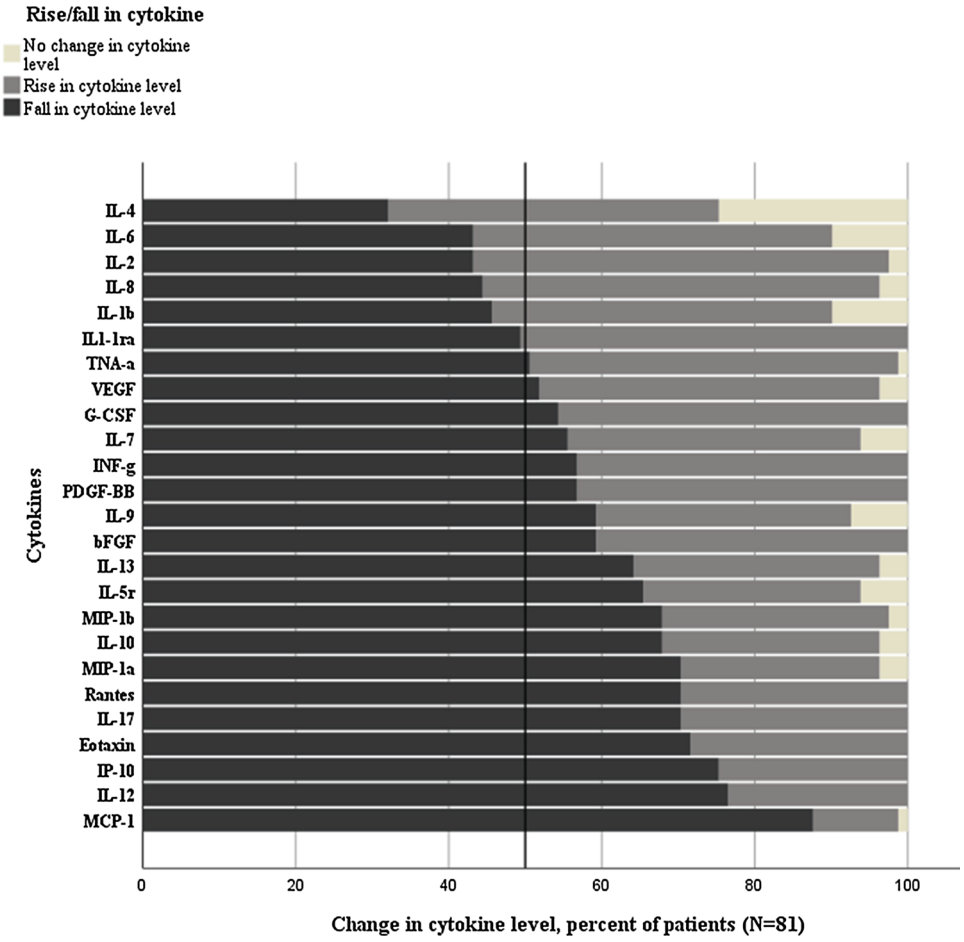

Fig. 1. Percentage change in cytokine level.

Table 4
Cytokine fall/rise in patients with Little/No improvement and Improvement (N = 49)*.

		Rise or fall in cytokine (%)		
		Rise	Fall	Total
Clinical outcome	Little/no Improvement	12 (52 %)	11 (48 %)	23**
	Improvement	5 (22 %)	18 (78 %)	23***
	Total	17 (37%)	29 (63 %)	46
Pearson Chi-square 4.572		$p < 0.032$ (asymptomatic 2-sided, df = 1)		
Spearman's rho 0.315		$p < 0.033$ (2-tailed) $p < 0.033$ (2-tailed)		

* 25 cytokines analysed in each of the two clinical outcome groups.
** Two cytokines with equal number fall/rise excluded (VEGF, IL-8).
*** Two cytokines with equal number fall/rise excluded (IL-1ra, TNF-α).

the patients reported clinical improvement accompanied with a reduction in cytokines during the hospital stay. Thus, on a group level, there seems to be a correlation between clinical improvement and falling cytokines. On the other hand, we did not find significant correlations between change in any single cytokine and clinical improvement. Neither did we find significant correlations between cytokine changes and the various demographic and clinical variables, including diagnosis.

In principle, the treatment-related drop in cytokines seems to correspond to previous studies in both elderly and younger adults (Dahl et al., 2014; Hannestad et al., 2011; Hestad et al., 2003; Moreira et al., 2015; Tuglu et al., 2003). However, these studies have predominantly focused on selected cytokines in delineated psychiatric disorders, whereas the cytokine changes in our study appear to be broad-based and without any demonstrable patternicity. Pertaining to the latter, earlier research has hypothesised that specific cytokine patterns might provide markers of diagnosis, treatment options and prognosis (Goldsmith et al., 2016; Maes et al., 2012; Pedrini et al., 2012). Though this might be true at specific stages for some psychiatric disorders in younger adults, our study suggests that cytokine changes are widespread and non-specific in elderly psychiatric patients, perhaps due to the presence of several conditions. Multimorbidity, defined as the co-existence of more than two chronic diseases, is common in the elderly, with a prevalence of more than 60% for those aged 65–74 years and more than 80% for those aged ≥85 years (Salive, 2013). In our population, almost 78% of the patients had a comorbid somatic disorder, and more than 90% of these patients had more than one somatic disorder, i.e. several potential sources of inflammation. The picture is further complicated by the use of drugs with possible immunomodulatory effects (Baumeister et al., 2016), and by age-related immunological changes and variability (de Groot et al., 2004; Santoni et al., 2015). Consequently, exploiting cytokines as biomarkers of clinical traits might to be of limited use in a general population of elderly psychiatric in-patients as the field stands now. Likewise, the outcomes from our study indicate that extrapolating results from research on younger subjects to elderly patients, is a somewhat precarious undertaking.

The heterogeneity and the size of our population calls for caution when interpreting the results. The lack of a control group also represents a limitation of the study. Moreover, it should be noted that single imputation of data to substitute NDs (see the Statistical analysis section) could lead to skewed statistics, but analyses without the NDs

did not produce any significant change. We did not perform power analyses in advance, but in an exploratory study such as ours, power analyses are notoriously difficult. Furthermore, use of high-sensitivity C-reactive protein could have provide complementary information about the inflammatory processes. Finally, we did not have information about use of statins, a group of drugs known to exhibit anti-inflammatory and immunomodulary effects.

Clearly, the complexity of inflammatory processes in elderly psychiatric patients with comorbid disorders is difficult to untangle. This is not unique to the elderly, though, as we still have not mapped out the inflammatory mechanisms behind systemic cytokine changes in psychiatric disorders. Hence, more research is needed on both elderly and younger adults, including healthy individuals and individuals with psychiatric disorders. Longitudinal studies, including genomic and proteomic methodology, could also help to shed light upon the neuroimmunological processes that take place during the course of a psychiatric illness.

5. Conclusions

A broad range of cytokines fall during treatment of elderly psychiatric in-patients with multimorbidity, and the fall seem to correlate with clinical improvement, irrespective of psychiatric and somatic diagnoses.

All patients were presented oral and written information about the study. Consentual competency was assessed according to established guidelines (Pedersen et al., 2007). For patients who were considered unable to give individual consent due to their medical and/or psychiatric condition, information about the study was provided to their next of kin. All patients, and their next of kin when relevant, had to sign a written consent in order to participate in the study. Approval of the study was obtained from the Regional Committee for Medical and Health Research Ethics of Northern Norway (REC North, reg. nr. 2009/1388).

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CRediT authorship contribution statement

Erlend Bugge: Conceptualization, Supervision, Funding acquisition, Project administration, Methodology, Resources, Software, Investigation, Validation, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Rolf Wynn:** Conceptualization, Supervision, Funding acquisition, Project administration, Methodology, Resources, Software, Investigation, Validation, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. **Tom Eirik Mollnes:** Formal analysis, Visualization, Writing - review & editing. **Solveig Klæbo Reitan:** Formal analysis, Visualization, Writing - review & editing. **Maria I. Lapid:** Formal analysis, Visualization, Writing - review & editing. **Ole Kristian Grønli:** Conceptualization, Supervision, Funding acquisition, Project administration, Methodology, Resources, Software, Investigation, Validation, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing.

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