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Elevated neutrophil to lymphocyte ratio in non-affective psychotic adolescent inpatients: Evidence for early association between inflammation and psychosis

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ABSTRACT

Accumulating data suggest an association between inflammation and schizophrenia and related psychosis. While several studies have established this immune-psychosis association in adult schizophrenia patients, there is very limited data associating inflammation with acute psychosis in children and adolescents. The ratio between neutrophils and lymphocyte, computed from routine blood counts, has been shown to correlate with traditional markers of inflammation, and is therefore considered a proxy-marker for inflammation. Here we report elevated neutrophil to lymphocyte ratio and total leukocyte count in psychotic adolescent inpatients (n = 81, mean age 14.7 years, 52% males) compared to non-psychotic adolescent inpatient (n = 285, mean age 15.9 years, 58% males), in a population of adolescent inpatients with no affective symptomatology. The elevated neutrophil to lymphocyte ratio remained significant after controlling for confounders such as age, BMI, smoking and antipsychotic medication. In a subset of psychotic adolescent inpatients (n = 20, mean duration between blood test 157 days), we found significant decrease in neutrophil to lymphocyte ratio at clinical remission compared with the acute psychotic state. The results suggest that psychosis is associated with peripheral markers of inflammation early in the course of psychiatric pathology, and that inflammation may represent a state that accompanies psychosis and decreases during clinical remission.

1. Introduction

The immune system has a role in affecting brain and behavior through established biological mechanisms (Quan and Banks, 2007). While the initial literature focused on the role of inflammation in affective states (Miller et al., 2009), mostly due to the mediation of sickness behavior through pro-inflammatory cytokines (Maes, 1995), more recent studies reported consistent well replicated data indicating an association between inflammation and schizophrenia and related psychosis (for reviews:(Khandaker et al., 2015; Khandaker and Dantzer, 2016; Miller and Goldsmith, 2017)). Several studies that explored this association focused on measuring cytokines (for meta analyses: (Goldsmith et al., 2016; Miller et al., 2011; Potvin et al., 2008; Upthegrove et al., 2014)), indicating increased levels of peripheral pro-inflammatory cytokines, and suggesting that some may present psychosis-state markers, that are normalized after acute treatment of psychosis. More recent large sample studies and meta-analyses reported a robust and consistent association between elevated C- reactive protein (CRP) levels, a non-specific marker of inflammation, and schizophrenia spectrum disorders (Fernandes et al., 2016; Inoshita et al., 2016; Miller et al., 2014; Wium-Andersen et al., 2014). These later studies may indicate that non-specific peripheral markers of sub-chronic inflammation, that does not cross the threshold of what is clinically considered classical signs of systemic inflammation (i.e. fever and malaise), may be useful to identify the immune-psychosis association, rather than specific cytokines. This approach may thus enable research to focus on accessible proxy markers of inflammation that are often measured in routine psychiatric clinical populations, such as total and differential leukocytes counts.

Leukocytes play a central role in mediating inflammation, therefore changes in different leukocytes populations reflect the dynamic response of the immune system during inflammation (Zahorec, 2001). Neutrophils are often responsible for active inflammation through secretion of inflammatory mediators and outnumber other leukocyte

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population during inflammation (Azab et al., 2010; Nathan, 2006; Wright et al., 2010). The ratio between neutrophils and lymphocytes was previously suggested as a proxy-marker of inflammatory state (Zahorec, 2001). Since then, studies have shown significant correlations of neutrophil/lymphocyte ratio (NLR) with established markers of inflammation like CRP and other pro-inflammatory cytokines (Gao et al., 2015; Kantola et al., 2012; Motomura et al., 2013), consequently suggesting NLR as a prognostic marker. Specifically, the NLR has been found to be elevated in specific inflammatory-related conditions in children. These include infection-related conditions (Bekdas et al., 2014; Eryilmaz et al., 2015; Han et al., 2016; Kelly et al., 2015; Mentis et al., 2016), autoimmune conditions (Dogru et al., 2016; Dogru and Yesiltepe Mutlu, 2016; Duksal et al., 2015; Gao et al., 2015; Güneş et al., 2015; Ha et al., 2015), and metabolic syndrome-related conditions (Aydın et al., 2015; Prats-Puig et al., 2015).

The growing interest of inflammation role in psychiatric disorders and the availability of blood counts in clinical populations, have resulted in few studies showing increased NLR in psychiatric patients, mostly in patients with affective symptoms (Atli et al., 2015; Aydin Sunbul et al., 2016; Çakır et al., 2015; Demircan et al., 2016; Kalelioglu et al., 2015), but also with psychosis (Kulaksizoglu and Kulaksizoglu, 2016; Semiz et al., 2014). There is a paucity of studies that examine the association between psychiatric symptomatology and inflammation in children and adolescents (Mitchell and Goldstein, 2014). Specifically, very few studies with small sample sizes examined the association between inflammatory state and psychosis in children and adolescents, with conflicting data (Falcone et al., 2015; Gariup et al., 2015; Şimşek et al., 2016). In the current study, we investigated the association between elevated NLR as a proxy marker of inflammation with psychosis in adolescent inpatients.

2. Experimental methods

2.1. Design

The study employed a retrospective cross-sectional design. Data were retrieved from the electronic medical records of all consecutive admittances between March 2010 and September 2015, in a single adolescent acute ward at the Geha Mental Health Center (GMHC), a regional mental health center, with a catchment area of approximately 500,000 inhabitants. The GMHC institutional review board approved the study and waived the need for informed consent due to the retrospective nature of the study.

2.2. Subjects

We included in the study all adolescent inpatients aged 10–19 years, with a blood count within 3 days from admittance (taken as routine practice in the ward), who were hospitalized in the acute adolescent ward without evidence of affective episodes (depressive, manic, hypomanic or mixed episodes), based on the Diagnostic and Statistical Manual of Mental Disorders-5 Edition(DSM-5) criteria. We included the first hospitalization for patients that had more than one admission during the study period. All included patients were classified as psychotic (N = 81), or non-psychotic (N = 285), in accordance with the definitions of a psychotic disorder based on DSM-5 criteria. Namely, patients were considered psychotic if they presented with either of the following: delusions, hallucinations, disorganized thinking (speech) or grossly disorganized motor behavior, as documented in their electronic medical record. At least four child and adolescent psychiatrists (YB, RB, MA and MLS) reviewed patients' files and consensus was achieved for all cases. Patients with leukocytosis (WBC count > 14,000/mm^3, n = 2), and patients taking Lithium (n = 4) were excluded. None of the patients had fever (temp > 37.9 °C) at admission. For a subset of patients with longer hospitalizations, a second blood count was taken as part of good clinical practice conducted at the inpatient unit that requires periodic routine blood tests for patients that are hospitalized for more than 5 months.

2.3. Variables

Sociodemographic and clinical data that were retrieved from the patients' electronic medical records included age at hospitalization, sex, body mass index (BMI), medication at admittance, family history of a psychotic disorder and duration of hospitalization, as documented in the electronic record. Blood count parameters included total leukocyte counts, platelet counts, and the ratio between neutrophil to lymphocyte counts (NLR). Absolute neutrophil and lymphocyte counts can be found in supplementary data. Clinician global impression severity (CGI-S) for all psychotic patients and improvement (CGI-I) scores for the patients who achieved remission in the time of their second blood test, were determined retrospectively by 2 child and adolescent psychiatrists (MA, MLS) in a retrospective manner (Shon et al., 2014).

2.4. Statistical analysis

We used SPSS for Windows ver. 21 (IBM Inc., Chicago, IL) for statistical analysis. Descriptive statistics are expressed as mean ± SD for continuous variables and rates (%) for categorical variables. We compared 2 groups of patients: psychotic versus non-psychotic adolescent inpatients. For univariate analyses, we used two-tailed Student's *t*-tests, Paired *t*-test, Mann-Whitney *U* test or Chi-square test, as appropriate. Correlation between NLR and CGI-S values was conducted using Spearman correlation test. Multivariate analysis was performed using binary logistic regression analyses with psychosis as a dependent variable controlling for age, sex and BMI as covariates. A p-value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Elevated NLR in non-affective psychotic adolescents compared to non-psychotic controls

Clinical and demographic data of non-affective adolescent inpatients is detailed in Table 1. Psychotic patients (n = 81), were comprised of adolescents diagnosed with acute psychosis at admission (CGI-S = 5.5 ± 0.9), most patients were diagnosed with schizophrenia spectrum disorders as their major diagnosis at discharge (71/81, 87.7% of psychotic patients). Non psychotic patients (n = 285) were composed mainly of adolescents hospitalized due to disruptive symptoms with the major diagnoses of conduct/ODD/ADHD (136/285, 47.7% of non-psychotic patients), or patients hospitalized due to non-specific behavioral symptoms following typical adolescent life events, consequently diagnosed with adjustment or cluster B personality disorders (70/285, 24.6% of non-psychotic patients), or with serious neurodevelopmental disorders (autism spectrum disorder, intellectual disability) hospitalized due to a non-psychotic behavioral deterioration (43/285, 15.1% of non-psychotic patients).

The psychotic patients were significantly younger and had longer hospitalizations compared to non-psychotic patients (Table 1). No differences were found in terms of sex distribution, smoking status, BMI or the use of antipsychotic medication at admission (Table 1). Analysis of blood count parameters revealed that psychotic patients had significantly elevated total leukocytes count with no difference in platelet count. The NLR was higher by 56% in psychotic compared to non-psychotic patients (2.51 ± 1.8 versus 1.91 ± 1, respectively, p = 0.001, Fig. 1). No significant correlation was found between the psychotic patients' CGI-S score and the NLR (r = 0.08, p = 0.484).

Multivariate analysis was performed to assess the effect of covariates on the association between NLR and psychosis. A binary logistic regression with psychosis as the dependent variable was applied. The model contained NLR, age, sex and BMI as independent variables. The