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Aggression as an independent entity even in psychosis- the role of inflammatory cytokines

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ABSTRACT

Background: Aggression is very common in psychosis (prevalence ranging from 34% to 70%) and is often the main or first symptom for which the patient receives medical attention. Studies have associated alteration in cytokine profiles among healthy persons with aggressive traits. We hypothesise that even among those with psychosis, aggression is an independent entity, irrespective of psychotic state and is associated with cytokine alterations. To our knowledge, this is the first study attempting to look at the inflammatory cytokines in aggressive psychotic patients.

Methods: Study included 80 participants divided into four groups viz. aggressive diseased, non aggressive diseased, aggressive non diseased and non aggressive non diseased depending upon presence or absence of aggression and psychosis. Interferon gamma(IFN-G), Interleukin 10(IL10) plasma concentrations and their ratio were measured using ELISA based assay kits read at absorbance of 450 nm wavelength using Double beam spectrophotometer. The four groups were compared on measures of aggression, psychosis, Interferon Gamma levels, Interleukin 10 levels, Proinflammatory: Antiinflammatory cytokine ratio using standard statistical instruments.

Results: In patients with psychosis, the cytokines IFN-G and IL10 were significantly lower compared to those without. The cytokines IFN-G and IL10 are both significantly associated both with aggression and psychosis. IL10, but not IFN-G is associated with aggression in absence of psychosis. The proinflammatory: antiinflammatory cytokine ratio, is more significantly associated with aggression, irrespective of psychosis. In fact, there is no significant relationship between the above ratio and psychosis. Strong correlation exists between the proinflammatory: antiinflammatory cytokine ratio and aggression scores, even after controlling for severity of psychosis.

Conclusions: It may be concluded from this study that in spite of a high prevalence of aggression in patients of psychosis, it is more likely to be an independent entity associated with individual cytokine changes and increased proinflammatory: antiinflammatory cytokine ratio as its hallmark.

1. Introduction

Aggression is very common in psychiatric disorders, particularly psychosis. Studies report the prevalence of aggression in patients with psychosis in the range of 34% to 70% (Spidel et al., 2010; Large and Nielssen, 2011; Huber et al., 2014). Most frequently, the members of the patient's family are the usual victims, followed by medical personnel, acquaintances and fellow patients (Mohr and Pecenak, 2005). Importantly, aggression is often the main or first symptom for which the patient receives medical attention or is admitted(Mohr and Pecenak, 2005). Presently, there is no approved treatment for aggression in patients with psychosis, and medications are used mostly on trial and error basis (Mauri et al., 2011). Previous aggressive episodes, presence of hostility/impulsivity, longer hospitalisation, involuntary hospitalisation, drug abuse, higher psychopathology scores, paranoid thoughts, acute psychosis are among the predictors of aggression (Cornaggia et al., 2011). Studies have been done to understand the cause of such aggression in patients with psychosis. Different perspectives like emotional recognition deficit, metacognition deficit have been explored for the same (Malone et al., 2012; Bo et al., 2014). A recent review article concluded that neuroinflammation is associated with white matter pathology in people with psychosis, even at first episode of presentation (Najjar and Pearlman, 2014). Growing evidence suggests that specific cytokines play a role in signalling the brain to produce neurochemical, neuroendocrine, neuroimmune and behavioural changes (Muller and Ackenheil, 1998; Kronfol and Remick, 2000). Inflammatory cytokines are secreted mostly from T Helper cells and depending upon cytokines secreted, its divided into two subsets- T Helper cell 1

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(Proinflammatory) secreting IL 2, IFN Gamma, TNF alpha, TGF beta, IL 1 beta and T Helper cell 2 (Antiinflammatory) secreting IL 4, IL 5 and IL 10 (Fauci et al., 2008). The ratio of TH 1 to TH 2 determines the inflammatory state of the body, and is usually measured indirectly by the ratio of proinflammatory to antiinflammatory cytokines (Fauci et al., 2008). Nonetheless, it's beyond doubt that there is complex, bi-directional communication between nervous, endocrine and immune systems (Blalock 1989). Specific cytokines are secreted in the brain from microgila, endothelium, and other non-neuronal cells in the brain (Kronfol and Remick, 2000; Vitkovic et al., 2001; Vallieres and Rivest, 1997; Quan et al., 1998). Studies have associated alteration in cytokine profiles among healthy persons with aggressive traits (Janicki-Deverts and Cohen, 2010; Suarez et al., 2002; Mommersteeg and Vermetten, 2008). These findings have also been replicated in animal models, where injection of proinflammatory cytokines in the key brain areas gave rise to aggressive behavior (Hassanain et al., 2003; Bhatt and Seigel, 2006; Bhatt and Bhatt, 2008).

We hypothesise that aggression, even among those with psychosis is associated with cytokine alterations similar to those who are not psychotic but with aggression. Psychosis is associated with neuroinflammation, which some how activates the pathway of aggression. Aggression is an independent entity, the resultant of a proinflammatory state, both in absence and presence of psychosis. We attempted to study the proinflammatory: antiinflammatory cytokine ratio in our study population which was divided into four subgroups, depending upon presence and absence of psychosis and aggression. We chose IFN-G as the proinflammatory cytokine and IL 10 as the antiinflammatory cytokine for the study as both of them have been regarded as the most relevant cytokines to study the antagonism between TH1 and TH2 like functions (Eckhoff and Kirchner, 1997). To our knowledge, this is the first study attempting to look at the inflammatory cytokines in aggressive psychotic patients.

2. Methods and materials

The current study was done in LGB Regional Institute of Mental Health, Tezpur, Assam, a tertiary care psychiatry centre under the Ministry of Health and Family Welfare, Govt. of India. The hospital being the 'Regional institute' of the entire North Eastern India, its catchment area includes seven North Eastern states of India and also West Bengal.

The study was done on 80 participants, in whom, 58 were patients of psychosis, whereas, 22 were healthy volunteers selected by advertising in the hospital campus. Due clearance was taken from the institutional ethics committee before initiating the study.

During the period of three months, all the patients advised inpatient admission by the consultant psychiatrist of the day ($n = 421$) were approached. Only those who were admitted with a diagnosis of 'Psychosis' according to ICD 10 Diagnostic Criteria by the consultant.

psychiatrist ($n = 328$) and scored above 75 in PANSS (for establishing psychosis of 'moderate severity' or above) (Mortimer, 2007) were included for application of the inclusion exclusion criteria. Those within the age group of 18–60 years who gave written informed consent for the study were included. The exclusion criteria included those with primary/comorbid substance use disorder (other than tobacco use), mental retardation/autism/dementia/axis II diagnosis, regular 2nd generation antipsychotic or antidepressant use in last 3 months, electro convulsive therapy in last 3 months, depot antipsychotic inj. Use In last 6 m. or with physical examination suggestive of any infection or chronic disease or h/o infection/fever in last 3 months or any h/o chronic cardiac, pulmonary, hepatic, rheumatic, neurologic or kidney, h/o hormonal medications/immunosuppressant in last 3 month or with altered blood routine investigation parameters after admission. Finally, those who didn't read or understand English were excluded. The exclusion criteria were made stringent so as to remove any condition that alters the inflammatory cytokines as far as practicable.

Similar inclusion exclusion criteria were applied for the volunteers (except PANSS score). Lifetime History of Aggression Scale (LHAS) was applied to divide the patients as well as volunteers into aggressive and non aggressive (trait aggression) based on cut off score of 12 (Coccaro and Berman, 1997). Since the catchment area of the study site included people from multiple states, with multiple mother tongues and local dialects, only those who were comfortable in English were included in the study and the original version of the LHAS was used. In most states of India, English is still used as the common language for communication between individuals of different native tongues. Using LHAS, the 58 patients were divided into 36 aggressive patients with psychosis (Aggressive diseased, AD) and 22 non aggressive patients with psychosis (Non Aggressive Diseased, NAD). Similarly, 22 volunteers were divided into 11 aggressives without psychosis (Aggressive Non Diseased, AND) and 11 non aggressives without psychosis (Non Aggressive Non Diseased, NAND).

On the next day following admission (Day 1), within 15 min after waking up of the patient, 3c.c. of Fasting Blood was collected with aseptic precautions for cytokine assessment. Similarly, fasting blood was drawn from the volunteers (controls) as well. Cytokines were assessed using IFN-G assay kit [Human interferon gamma ELISA kit from thermo scientific, model no. EHIFNG, with Sensitivity: < 2 pg/ml, assay range: 25.6–1000 pg/ml, reproducibility: intra-assay CV: < 10%, inter-assay CV: < 10%, 100% specificity for human IFN-G] and human interleukin 10 ELISA kit from thermo scientific, model no. EHIL 10, 96 well kit [Sensitivity: < 3 pg/ml, assay range: 15.36–600 pg/ml, reproducibility: intraassay CV: < 10%, inter-assay CV: < 10%, 100% specificity for human IL 10]. The kit instructions were followed in toto (EHIFNG and EHIL10 kit manual from Piercenet) including using samples in duplicate for quantification https://tools.thermofisher.com/content/sfs/manuals/MAN0011423_Human_IFNgamma_ELISA_UG.pdf; https://tools.thermofisher.com/content/sfs/manuals/MAN0011454_Human_IL10_ELISA_UG.pdf. The ELISA kit were read at absorbance of 450 nm wavelength using double beam spectrophotometer (multiskan spectrum, model no.- 51118650, sl no- 1500-a16) from Thermo Scientific.

The results were compared between the four groups- AD, NAD, AND and NAND, and statistical analysis were done using appropriate tools like Mean, Standard Deviation, Standard Error of Mean, Unpaired t- test, one way ANOVA, Pearson Correlation, Partial Correlation as and when appropriate using SPSS v.16.0 for Windows.

3. Results

Among the patients ($n = 58$), 35 were diagnosed with schizophrenia, 11 were diagnosed with acute and transient psychosis while 12 were diagnosed with psychosis Not Otherwise specified. The mean duration of psychosis of the patients was 36.4 months (s.d. 27.88, S.E.M. 3.66). There was significant difference ($p < 0.001$) between the LHAS score among the aggressive group and non aggressive group, both among patients/diseased ($t = 19.768$, $df = 56$, $p < 0.001$) and controls/volunteers ($t = 11.567$, $df = 20$, $p < 0.001$) (two tailed independent t-test). The description of the groups and their relevant statistics are given in Table 1.

On comparing IFN-G, IL 10 levels and IFN-G/IL10 ratio between aggressive and non aggressive subgroups (irrespective of psychosis), independent sample t-test revealed small but significant difference for IFN-G and proinflammatory: antiinflammatory cytokine ratio ($P = 0.017$, d.f. 78, $t = 2.439$ and $P < 0.001$, d.f. 78, $t = 10.665$) with higher levels in aggressive subgroup (Fig. 1a). The difference is even more marked for the IFN-G/IL10 ratio than for IFN-G independently.

On comparing IFN-G, IL 10 levels and IFN-G/IL10 ratio between diseased and non diseased subgroups (irrespective of aggression), independent sample t-test revealed significant difference of cytokines independently with higher levels in non diseased subgroup ($P < 0.001$, d.f. 78, $t = 9.134$, and $P < 0.001$, d.f. 78, $t = 10.836$) (Fig. 1b).