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Unconjugated Bilirubin in Patients with Schizophrenia in Acute episode

Thesis

Submitted for Partial Fullfilment of Master Degree in ***Neurpsychiatry***

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Maha Sabry Mohamed Abdellatif Omar

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Abb.	Full term
5-HT	*5-hydroxytryptamine*
6-GP	*P-glycoprotein*
ABOi	*ABO incompatibility*
AChR	*Alpha 7 acetylcholine receptor*
AMPAR	*α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor*
B+A complex	*Bilirubin albumin complex*
BBB	*Blood–brain barrier*
BE	*Bilirubin encephalopathy*
BMI	*Body mass index*
BPRS	*Brief Psychiatric Rating Scale*
CB2	*Cannabinoid receptor 2*
CBC	*Complete blood count*
CDSS	*Calgary Depression Scale for Schizophrenia*
CGI-SCH	*Clinical Global Impression-Schizophrenia*
CNS	*Central nervous system*
CO	*Carbon monoxide*
CSF	*Cerebrospinal fluid*
D	*Diagnostic*
DA	*Dopamine*
DARPP-32	*DA- and cAMP-regulated neuronal phosphoprotein of 32 kDa*
DEFα4	*Defensin α4*
EAAT	*Excitatory amino acid transporter;*
ECT	*Electro-convulsive therapy*
EEG	*Electroencephalogram*
G6PD def	*Glucose-6- phosphate dehydrogenase deficiency*
GABA	*γ-aminobutyric acid*
GAD	*Glutamic acid decarboxylase*

List of Abbreviations (Cont...)

Abb.	Full term
GAF	*Global Assessment of Functioning*
GSK3α	*Glycogen synthase kinase 3α*
HVA	*Homovanillic acid*
IFN-γ	*Interferon-γ*
IL	*Interleukins*
IL-1β	*Interleukin-1β*
IL-2	*Interleukin-2*
IL2Rα	*Interleukin-2 receptor-α*
IL-6	*Interleukin-6*
IL-8	*Interleukin-8*
KainateR	*Kainate receptor*
mC	*Methylated deoxycytidine*
MRP-1	*Multidrug resistant protein-1*
NADP+	*Nicotinamide adenine dinucleotide phosphate;*
NADPH	*Reduced form of NADP+*
NE	*Norepinephrine*
NMDA	*Glutamate and N-methyl-D-aspartate*
NMDA	*N-methyl-D-aspartate*
NMDAR	*N-methyl-D-aspartate receptor;*
NS	*Nonspecific*
PANSS	*Positive and Negative Syndrome Scale*
PBMC	*Peripheral blood mononuclear cells*
RBCs	*Red blood cells;*
Rhi	*Rh Rhesus blood group incompatibility*
S100A12	*S100 calcium binding protein A12*
SANS	*Scale for the Assessment of Negative Symptoms*
SAPS	*Scale for the Assessment of Positive Symptoms*

List of Abbreviations (Cont...)

Abb.	Full term
SCID-I	*Structured Clinical Interview for DSM-IV™ Axis I Disorders*
SELENBP1	*Selenium-binding protein 1*
TH	*Tyrosine hydroxylase*
TMT	*Trail Making Test*
TNF	*Tumor necrosis factor*
TR	*Treatment response*
UDP	*Uridine diphosphate*
UGT1A1	*Uridine diphosphate-glucuronyl transferase 1A1*
VCAM-1	*Vascular cell adhesion molecule 1*

INTRODUCTION

Unconjugated bilirubin is the water insoluble fraction of total bilirubin in serum that crosses the blood brain barrier. Having antioxidant effects**,** it increases in response to the in situ neurotoxic psychotic episode ***(Dore et al., 1999; Rund, 2014)***. On the other hand, it has both direct and indirect toxic effects on central nervous system and brain tissue connectivity, even in healthy human subjects without bilirubin metabolism dysfunction, making neurons more susceptible to further inflammatory damage which is believed to underlie the clinical and cognitive symptoms of schizophrenia ***(Glimore et al., 2004; Brites, 2012; Gama Marques et al., 2019).*** Hence, it may be consequence or cause of a psychotic state.

Evidence supporting a correlation between unconjugated bilirubin and schizophrenia is considerable and most previous studies have managed to report a statistically relevant link between the two variables ***(Dornelles et al., 2019)***.

In animal studies, chronic microglial activation in Gunn rats by toxic levels of unconjugated bilirubin (due to genetic deficiency in glucuronyl transferase) has been found to contribute to behavioural and neuropsychological changes in these rats that might be attenuated by antipsychotics, as in human patients with schizophrenia ***(Liaury et al., 2012; Tsuchie et al., 2013)***. This rat has already been used as schizophrenia animal model ***(Rice & Shapiro, 2008)***.

In human studies, infants with neonatal unconjugated hyperbilirubinemia (due to decreased erythrocytes survival and deficient hepatic clearance) have presented with later diagnoses of mental disorders and shown a higher risk for schizophrenia when compared to a control group ***(Jones, 1994; Dalman & Cullberg, 1999)***.

Gilbert's syndrome (idiopathic chronic mild unconjugated hyperbilirubinemia due to genetic deficiency in UDP-glucuronosyltransferase-1 enzyme) is found in up to 10% of general population but reaches the double of that prevalence among patients with schizophrenia ***(Bosma et al., 1995)***.

Patients with schizophrenia especially during acute episode showed significantly higher frequency of elevated unconjugated bilirubin mean levels when compared with patients in remission phase**,** other psychiatric patients and general populations ***(Muller et al., 1991; Bach et al. 2010)***. They also showed a positive correlation between these higher levels and positive and negative syndrome scale (PANSS) score in addition to a poor outcome ***(Powell & Hansen, 2007; Gama Marques and Arantes-Gonçalves, 2018).***

The interest of this literature lies in the possibility of finding an objective, measurable, and potentially influenceable parameter which could help complement the still somewhat subjective approach to the diagnosis, management, and even