International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Platelet Serotonin Level: An Essential Role in Human Behavior, Stress Reaction and the Selection of Psychotropic Drugs

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Abstract: ***Platelet serotonin level in blood is pre - determined genetically &is grossly influenced by the individual's Stress reactions. This in turn inversely influences the level of Dopamine in blood. Serotonin and dopamine then both act together in the causation of different behavioral patterns after any stressful stimulus. The purpose of this study was to prove: i) Significance of Platelet serotonin level estimation as a prerequisite to diagnosis and treatment of Stress. ii) Importance of considering simultaneously symptoms of both Serotonin and Dopamine levels in blood for proper choice of medication. Some basic data and information collected from subjects having mental stress (Perceived Stress Scale score 27 - 40). Platelet serotonin levels were estimated. Subjects were then divided into two groups having a) Low Platelet Serotonin levels and b) High Platelet Serotonin levels. Fifteen case studies from each group were done. Treatments were started or modified accordingly and reviewed after 2 weeks. This study shows that both high and low values of Platelet serotonin may act as a biochemical stress marker. Subjects with high serotonin level also showed symptoms of low dopamine and vice versa. So it can be concluded that Platelet serotonin level in blood should be a routine test for any stress reaction. Symptoms of both Serotonin and Dopamine levels should be considered simultaneously, to help in the rational choice of medication. Empirical use of anti - depressants in high platelet serotonin cases may cause Serotonin syndrome.***

Keywords: Mental Stress; Platelet Serotonin; Dopamine; Stress bio - marker; Anti depressants, Serotonin syndrome

1. Introduction

Mental stress is a universal human state of mind with a widespread prevelance, regardless of age, sex, ethnicity and religion. Strangely only antidepressants, alone or in combination with long - term benzodiazepines / hypnotics, have been increasingly used in recent years around the world. (Parish, 1971; Knapp et al.2007; Chen et al.2008; Johnson et al.2014) though research shows antidepressants only reduce depression symptoms by 20% after 6 - 8 weeks when compared to placebo. (*Inform. Educ.*2006 - - , Depression: How effective are antidepressants). Serotonin (5HT), one of the neurotransmitters, having an immense role in some fundamental aspects of human physiology and behavior (Jacobs, 1994) is able to cross blood brain barrier under stressful conditions and the changes in central or neuronal 5HT corresponds highly to 5HT level in platelets (Cohen et al.1999; Huber et al.2001; Bianchi et al.2002; Oztas et al.2004) Again this serotonin system has been found to have an antagonistic action with dopamine system, according to anatomical and pharmacological studies. (Wong et al.1995; Daw et al.2002). So it would be prudent to measure platelet serotonin level from blood in all cases of mental stress and also to consider the symptoms of both Serotonin and Dopamine levels simultaneously for the proper choice of psychotropic drugs in it's management.

Platelet serotonin' has been recommended as an appropriate peripheral model of central neuronal activities (Sneddon, 1973;) because neurons and platelets have structural and functional similarities, share a similar serotonin uptake & release mechanism and platelets store more than 99% of serotonin in blood. (Camacho & Dimsdale, 2000; Barišić et al.2004; Newport et al.2004). The level of serotonin in the brain is both genetically predetermined within some range and may also be influenced by social interactions and experience. (Wright, 1995)

Platelet serotonin level in blood has an immense effect on the behavioral pattern of the person. Reduced platelet serotonin level has been shown to be associated with aggressive behavior, Impulsive behavior (Seo & Patrick, 2008), Non psychotic depression (Parsey et al.2006), Non paranoid schizophrenia (Muck - Seler, 1991), Panic disorder (Deakin & Graeff, 1991; Bell & Nutt, 1998) increased irritability, Self harm, (Dutta et al.2017), Suicidal tendency (Mann, 1990) OCD (Baumgarten & Grozdanovic, 1998), Autism spectrum disorder. (Spivak et al.2004; Oblak et al.2013; Daly et al.2014). Whereas increased Platelet Serotonin levels in blood has been shown to be associated with various behavioral disorders: Panic disorder (Iversen, 1984; Kahn et al.1988; Kahn et al.1988), severe aggression (Mann et al.1992), Psychosis, Paranoid schizophrenia, psychotic depression (Mück - Seler, 1991), bipolar (Shiah, 1999) inhibition of impulsive behavior (Miyazaki & Doya 2012)

Serotonin and dopamine are both antagonistic to each other. High levels of serotonin appears to inhibit dopamine production in some situations. Inversely low levels of serotonin will lead to an overproduction of Dopamine. (Seo et al.2008) Moreover, Serotonin (5 HT) 2 receptors inhibit Dopamine (DA) activity, and so 5 HT2 receptor antagonists counteract this inhibitory effect on the DA activity and may increase dopamine levels. (Sorensen et al.1993; Shi etal.1995; Milan et al.1998).

So it can be inferred that Serotonin and dopamine both may act together in the causation of different behavioral patterns

after any stressful stimulus. As an example. with Low Serotonin level, subjects may have one or more of the High Dopamine symptoms e. g.: Addiction, [Some studies show the use of dopaminergic antagonists in alcohol dependence] (Volkow et al.2007; Martinotti et al.2007; Kampman et al.2007; Bender et al.2007; Martinotti et al.2009), High Sexual drive (Sanna et al.2020), OCD (Denys et al.2004; Koo et al.2010), poor impulse control and aggression (Seo et al.2008), Gambling (Meyer etal.2004; Voon et al.2009), Improved ability to focus & learn, enhanced confidence & motivation, (Lou et al.2011) Mania, Difficulty in sleeping, Competitive attitude, Binge eating bouts, Hallucinations, Schizophrenia and Delusions (Laruelle & Abi - Dargham 1999; Howes et al.2009)

Similarly with High Serotonin level, subjects may have one or more of the Low dopamine symptoms: Low self esteem, trouble sleeping or disturbed sleep (Blum et al.2014), low energy, inability to focus, ADHD (Gold et al.2014), lack of drive & motivation, hopelessness, low mood (Diehl & gershon, 1992), anxiety, self harm (Breese et al.1989) suicidal (Roy et al.1992; Pitchot et al.2001), low sex drive (Graf et al.2019), hallucinations & delusions (Tost et al.2010), lack of insight/self - awareness. (Cadman 2018). These symptoms have been summarized in Table 1.

Moreover due to stigma and a lack of reliable diagnoses, they are frequently under diagnosed, undertreated, and can lead to self - medication with alcohol and narcotics and may even lead to violence and suicide in certain cases. (Shaler et al.2017; Sharma & Ressler 2019; Stein & Rothbaum 2018; Le - Niculescu et al.2020). Therefore measurement of Platelet serotonin and consideration of symptoms of both serotonin & dopamine are two essential steps towards rational choice of proper psychotrpic drug in cases of mental stress.

Table 1

LOW SEROTONIN LEVEL symptoms	**HIGH DOPAMINE LEVEL symptoms**
Impulsive behavior Aggression Increased irritability Non psychotic depression, Non paranoid schizophrenia Panic disorder DSH Suicidal tendency Autism spectrum disorder OCD	Poor impulse control Aggression Schizophrenia, Hallucinations, Delusions Improved ability to focus & learn Enhanced motivation, Competitive Mania, Difficulty in sleeping Addiction Gambling Binge eating, High Sexual drive OCD
HIGH SEROTONIN LEVEL symptoms	**LOW DOPAMINE LEVEL symptoms**
Severe aggression Panic disorder Inhibition of impulsive behavior Paranoid Schizophrenia Psychotic depression Bipolar Depression Psychosis	Low self esteem Lack of drive/motivation Hopelessness Low energy Inability to focus ADHD Disturbed Sleep Anxiety Low sex drive DSH, Suicidal Hallucinations Delusions Lack of insight/self - awareness

Objectives

Till date there are no proven biochemical markers to help the clinicians to understand a person's unique stress reactions and its treatment.

This study intends to establish:

1) Significance of Platelet serotonin level estimation as a prerequisite to the proper understanding and treatment of Stress reaction,
2) Importance of considering simultaneously symptoms of both Serotonin and Dopamine levels in blood.

2. Methodology

Self made questionnaires cum observation schedule were developed to collect basic data from 50 subjects having behavioral problems after one or more mental stressful events in their lives. All of them were administered 14 - item Perceived Stress Scale (Cohen et al.1983) for assessment rating of stress, average score of chosen subjects were in the range 27 - 40 indicating high perceived stress.

Serotonin ElisaKit (Demeditec Diagnostics, Germany) was used to measure Platelet serotonin level from blood and compared with normal subjects. Normal value in Pulse Diagnostic Lab. in Kolkata, India is 100 – 200 ng/ 10^9 platelets.

Then subjects were categorized into two groups having either High platelet serotonin level or Low platelet serotonin level. Fifteen case studies from each group were done and their symptoms or complaints were compared. Treatments were started/ altered according to platelet serotonin levels. Any improvements in symptoms were reviewed after 2 weeks.

3. Results

Estimation of random sampling of 50 subjects with mental stress (PSS score 27 - 40) were done. This study found that stress may even lead to low platelet serotonin levels though it is known that after any mental stressful stimuli, usually release of serotonin increased in plasma from activated platelets.1) Therefore we can infer that both high and low values of Platelet serotonin may act as a biochemical marker for Mental Stress.

Fifteen subjects from each group of high platelet serotonin and low platelet serotonin level, were chosen to study their behavioral symptoms. It was found that: i) Subjects having Low platelet serotonin level also showed of one or more symptoms of high dopamine level. ii) Similarly subjects having High platelet serotonin level showed one or more symptoms of low dopamine level.2) So it would be rational to consider the symptoms of both serotonin and dopamine levels together while taking proper history of any patient of mental stress.

From this study it was also found that: a) Subjects with low platelet serotonin level did not respond to SSRI alone. Drugs acting on high Dopamine levels were started along with SSRI. b) Subjects with high platelet serotonin, did not respond to SSRI (along with anti psyhotics in some cases). SSRIs were stopped and serotonin receptor antagonists were given along with dopamine receptor agonists for better control of symptoms. Improvement in symptoms or behavioral patterns were noted within a very short period of 2 weeks.3) Hence, this study did help in the choice/alteration of psychotropic drugs and improvements in symptoms were noticed within 2 weeks of treatment.

As a sample, detailed complaints, history and treatment of only 5 case studies in each category of Low Platelet Serotonin and High Platelet Serotonin, are given below, in Table 2.

Table 2: Low Serotonin – High Dopamine Cases

Age/ Sex	Presenting Complaint	Other clinical features	Duration of illness & Stressful Factor	Past Psychiatric treatment	Platelet serotonin level ng/10^9	Treatment given	Improvement within 2 weeks
30M	Anxiety	Impulsive aggression Cannabis Addiction	>4 years Dominating Mother Disturbed distance Relationship	SSRI only	45.92	Added Flupenthixol 0.5 mg	Marked improvement in aggression, Anxiety Reduced urge for cannabis
42F	Aggression Anxiety	Impulsive Competitive	>3 years Disharmony relationship Stressed about younger daughter	None	1.14	SSRI + Flupenthixol	Improvement noticed within 2 weeks
42M	Phobia	Social Anxiety, depression, paranoia	>2 years Abusive parents	SSRI	0.02	Added Flupenthixol 0.5 mg	Marked improvement within 2 weeks
23M	Social anxiety, Irritability	Impulsively aggressive,	>2 years Stressed about career	Prodep (SSRI)	12.43	Added Amisulpride	Marked improvement
28F	Depression, Anxiety	Paranoid delusion about a vaginal rash, PCOS	>6 months	SSRI	0.02	Added Amisulpride	Improved

High Serotonin – Low Dopamine Cases

Age/ Sex	Presenting Complaint	Other clinical features	Duration of illness & Stressful Factor	Past Psychiatric treatment	Platelet serotonin level ng/10^9	Treatment Given	Improvement within 2 weeks
46F	Severe aggression Irrelevant talk	Lack of motivation Decreased libido	>3 years Death of Father in childhood Over - possessive dominating mother	Olanzepine 10 mg daily once only	685.98	Valproic acid 500 mg BD added	Marked improvement in Aggression, no more irrelevant talking, Motivation to work improved, libido improved.
44M	Auditory hallucination	Aggression decreased libido	>6 months Stressed with local residents bad & irrartional behavior	SSRI	304.69	Stopped SSRI, started *Olanzepine & Levecitaram	Responded well within 2 weeks
48M	Lack of motivation Decreased libido	Lack of concentration having low self esteem disturbed sleep	>2 years Stressed about mother's death	SSRI	815.68	Stopped SSRI Started *Amisulpride *Lamitrogine	Improved well within 2 weeks
24F	Aggression, Sibling jealousy Suicidal	Paranoid, lack of motivation. obsessed with her hair	Stressed about Mathematics from Class V - - VIII	SSRI + aripiprazol	845.8	SSRI stopped Started on Lamitrogine & Rispiradone	Improved well within 2 weeks
60F	Aggression, Hallucination	Disturbed sleep, low libido	>3 years Stressed about sons	SSRI+ Antipsychotics	560.8	SSRI stopped Valproic acid added	Improved markedly within 2 weeks

4. Discussion & Implications

Platelet serotonin level estimation test may be done in any patient suffering from mental stress showing behavioral abnormalities. This test also may help to remove stigma of treatment in mental health in non - willing subjects.

While observing and treating patients with high and low serotonin levels, it is indicative that they may have low and high dopamine levels respectively. These results have been supported by several previous research studies (Wong et al.1995; Daw et al.2002; Seo et al.2008).

Therefore it is important to consider the symptoms of both serotonin and dopamine levels together while taking proper history of any patient of mental stress and treat accordingly, e. g. non psychotic depression with addiction and high sexual drive, where the platelet serotonin is found very low, may not respond to SSRI only. The other symptoms may be due to the accompanied high dopamine level which needs to be treated at the same time.

Similarly, patient having severe aggression with lack of drive or motivation, where serotonin level is found high, low dopamine level factor has to be taken also into consideration and treat accordingly.

In patients, where the platelet serotonin is already high, empirical use of anti - depressants as the drug of first choice in mental stress may further raise serotonin level which may be more detrimental and may cause 'Serotonin Syndrome' in a some cases.

5. Conclusion

This study proves the importance of measuring platelet serotonin level in blood, for proper understanding of abnormal human behavior in mental stress, the relevance of considering simultaneously symptoms of both Serotonin and Dopamine levels, for rational choice of psychotropic drugs. This study may help to reduce the empirical use of anti - depressants as the drug of first choice in any stress reaction as this may lead to potentially fatal 'Serotonin syndrome' logically in high serotonin level cases. Whether this platelet serotonin test will be accepted as a routine blood test is a separate discussion but the evidence suggests that by doing so could lead to a future where stress reactions and other abnormal human behavioral patterns can be treated more efficiently and rationally.

Acknowledgement
No financial support was taken for this study. Informed consent was taken from each and every subject taking part in this study.

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