EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 11
371-375
Year: 2018

CLINICAL SIGNIFICANCE OF BLOOD TRANSTHYRETIN LEVEL AS A NON-INVASIVE PROGNOSTIC INDICATOR FOR PATIENTS OF DEPRESSION – A PILOT STUDY

***Dr. Vanita Lal, MBBS(Hons) MD,DNB and Garima Gupta**

Professor and Head, Department of Biochemistry, Chief Medical Superintendent, GIMS, Gautam Buddha Nagar, Kasna, NCR, GNoida PIN 201310.
Assistant Professor, State Medical College, Barmer, Rajasthan.

***Corresponding Author: Dr. Vanita Lal**
Professor and Head, Department of Biochemistry, Chief Medical Superintendent, GIMS, Gautam Buddha Nagar, Kasna, NCR, GNoida PIN 201310.

Article Received on 02/09/2018 **Article Revised on 23/09/2018** **Article Accepted on 13/10/2018**

ABSTRACT

Introduction: Transthyretin (TTR) is a major transporter of thyroxine hormone. Alterations in TTR have been found to be associated with neurogenerative disorders. Thus the current study aimed to evaluate the clinical significance of serum transthyretin levels among cases of depression and healthy control subjects. ***Materials & Methods*:** Total 100 euthyroid cases with depression and 50 healthy subjects were included in the study. Degree of depression was evaluated using 17-item Hamilton Depression Scale. Present study analysed the level of Serum transthyretin, and other thyroid binding globulin, albumin, globulin, thyroid hormone, thyroid stimulating hormone were measured. ***Result:*** According to the Hamilton Depression Scale, 37 (37%), 37 (37%) and 26 (26%) patients were found to have mild, moderate and severe depression respectively. In cases of depression TTR was found to be 22.84 mg/dl however, in healthy control subjects 28.43mg/dl was observed was found to be significant ($p<0.0001$). Cases of depression with degree of depression such as mild, moderate and severe, TTR was 25.14mg/dl, 22.28mg/dl and 20.39mg/dl respectively ($p<0.0001$). Increase level of TSH level was observed in cases of depression (3.75 mIU/L) however, in healthy control subjects 2.34 mIU/L was observed and differences was found to be significant ($p=0.02$). Distribution of Serum Albumin Level (SAL) among cases of depression was 34.70 mg/dl while in healthy subjects 30.90 mg/dl was observed and difference was found to be significant ($p=0.0009$). Degree of depression such as mild, moderate and severe had 11.84, 15.08 and 19.46 HDRS score ($p<0.0001$). Significant negative correlation (r -0.74, $p<0.0001$) was observed of TTR with HDRS score among cases of depression. ***Conclusions:*** The present study suggests that serum TTR could be good noninvasive predictive indicator for depression and could help to access the severity of disease and its prognosis.

KEYWORDS: Transthyretin, Degree of Depression, Hamilton Depression Scale.

INTRODUCTION

Depression is common mood disorder, not only affects the quality of life[1] but also reduces efficient ability,[2], worsens rehabilitation outcomes[3], and increases mortality after stroke.[4] Factors associated with post stroke depression include history of depression before stroke, history of a previous stroke, stroke severity, and disability after stroke.[1] Patients with depression are incapable to participate in the rehabilitation process or to engage in necessary behavioural changes and cognitive therapies, leading to a vicious cycle between depression and functional impairment.[5] Transthyretin (TTR) is a 54-kDa protein that is mainly synthesized by the liver and choroid plexus and participates in the transport of thyroxin and retinol. Serum transthyretin level is decreased in various conditions such as inflammation, protein malnutrition, end-stage liver disease, or malignancy.[6] It also known as pre-albumin is a protein synthesized in the liver and the choroid plexus of the brain.[7] Depression has been well documented in hyper and hypothyroidism, with varying explanation. Depression in euthyroid individuals still remains an enigma. In the peripheral tissues, transthyretin, thyroid binding globulin (TBG) and albumin are the carrier proteins for Thyroxine, T_4[8] whereas in the brain tissue, TTR is the only carrier protein. Studies have documented the correlation of the severity and frequency of depressive episodes with CSF transthyretin.[9] TTR was considered to be essential for delivering its ligands to target tissues, particularly to the CNS.[10] However, studies in TTR null mice have questioned whether TTR is indeed essential for thyroid hormone transfer into the brain.[11] TTR-null mice display significantly reduced levels of thyroid hormones in the choroid plexus and no

other protein appears to replace TTR in the transport of T4 in the CSF.[12] TTR protein involved in the transport of thyroxin across the blood-brain barrier has been found to be reduced in CSF from patients with depression.[13] It has been shown that levels of transthyretin (TTR, formerly prealbumin), a thyroid hormone binding protein secreted into the cerebrospinal fluid (CSF) from the choroid plexus, are lower in depressed patients than in controls.[14] Thus the present study aimed to investigate the clinical importance of serum transthyretin in Depression patients.

MATERIALS AND METHODS

Patients Selection and Sample Collection

The study was commenced after obtaining approval from the Institutional Ethics Committee and informed written consent from the patients. It was carried out in the department of Biochemistry and the Psychiatry outpatient clinic of a tertiary-care hospital and medical college in North-Western India. The study included 100 patients diagnosed with depression. The diagnosis was confirmed by Psychiatry Consultant using Mini International Neuropsychiatric Interview (MINI) by concerned clinician.[15] Hamilton Depression Rating Scale (HDRS) was used to assess severity of depression.[16] All the patients with depressive disorder were included except patients with bipolar depression, psychotic depression, and any other co morbid psychiatric or chronic physical disorders were excluded from the study.

All the patient's blood samples were collected in plain vial and serum were separated by centrifugation method (2000rpm for 5 minutes) and stored at -20^{0}c till the analysis.

Statistical analysis: All the statistical analysis was done using SPSS and graph Pad prism software. All the quantitative data were presented as mean with standard deviation. Parametric and non parametric tests were used for comparison of different groups. P value < 0.05 was considered to be significant.

RESULTS

Demographics: In present study total 100 cases and 50 controls were included in study.

Among cases 55% were males and 45% were females however, in control subjects 70% were males and 30% were females (**Table 1**).

Table 1: Distribution of selected characteristics of patients and healthy controls.

Variables	Patients n (%)	Healthy controls n (%)
Total no.	100 (100%)	50 (50%)
Gender		
Males	55 (55%)	35 (70%)
Females	45 (45%)	15 (30%)
Degree of Depression		
Mild	37 (37%)	
Moderate	37 (37%)	
Severe	26 (26%)	

Prognostic importance of TTR among Cases of Depression and Healthy controls

Significant (p<0.0001) difference was observed in TTR among cases and controls. In cases of depression TTR was found to be 22.84 mg/dl however, in healthy control subjects 28.43mg/dl was observed (Figure 1). When it was compared among cases of depression with degree of depression was found to be significant (p<0.0001). Cases of depression with degree of depression such as mild, moderate and severe, TTR was 25.14mg/dl, 22.28mg/dl and 20.39mg/dl respectively (Figure 2).

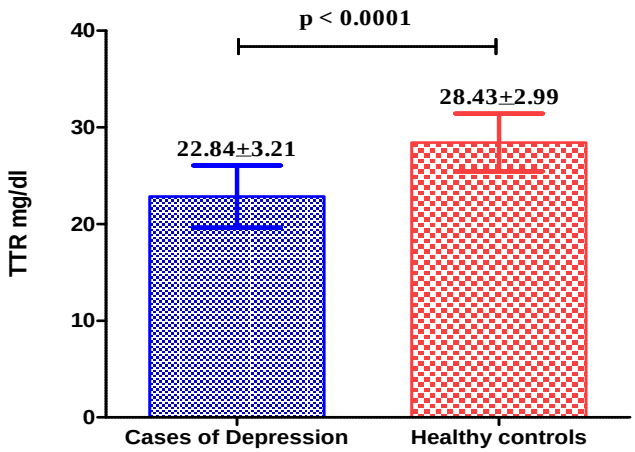

Figure 1: Distribution of TTR level among cases of depression and healthy controls.

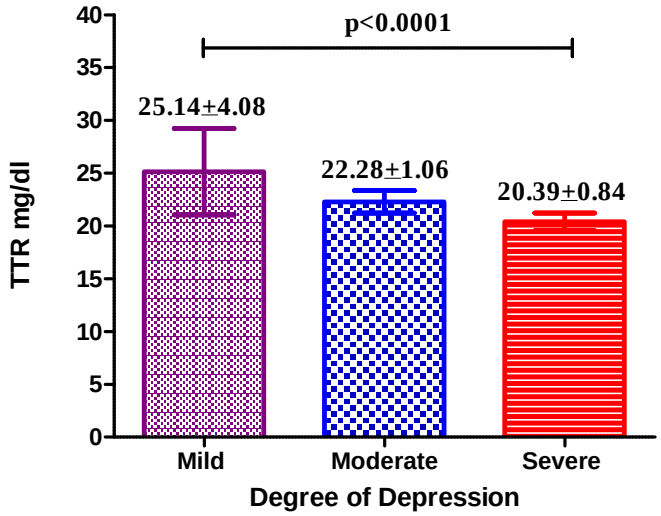

Figure 2: Distribution of TTR level among cases of depression with respect to degree of depression.

Distribution of biochemical outcome among Cases of Depression and Healthy controls

Several biochemical parameters were compared among cases of depression and healthy control subjects. Significant difference was observed in distribution of TSH and SAL among cases of depression and healthy cases. Increase level of TSH level was observed in cases of depression (3.75 mIU/L) while in healthy control subjects 2.34 mIU/L was observed and differences was found to be significant (p=0.02). Distribution of Serum Albumin Level (SAL) among cases of depression was 34.70 mg/dl while in healthy subjects 30.90 mg/dl was observed and difference was found to be significant (p=0.0009). No significant difference was found in T3, T4 and TBG level among cases of depression and healthy control subjects (**Table 2**).

Table 2: Distribution of Biochemical parameters among cases of depression and healthy subjects.

Parameters	Cases of Depression	Healthy controls	p value
FREE T3pg/ml	2.65±0.95	2.71±0.84	0.78
FREE T4 ng/dl	1.48±0.80	1.52±0.69	0.60
TSH mIU/L	3.75±7.11	2.34±0.86	0.02
TBG mg/dl	1.68±0.64	3.48±13.80	0.21
SAL (Serum Albumin Level) g/l	34.70±9.71	30.90±4.16	0.009

Association of Hormones outcome with degree of depression among cases of depression

Significant impact of degree of depression was observed on HDRS score, degree of depression such as mild, moderate and severe had 11.84, 15.08 and 19.46 HDRS score (p<0.0001). No significant impact of degree of depression was observed on biochemical parameters (**Table 3**).

Table 3: Distribution of Biochemical parameters among cases of depression with respect to degree of depression.

Degree of depression	Mild	Moderate	Severe	p value
FREE T3pg/ml	2.47+0.83	2.70+1.03	2.85+0.97	0.13
FREE T4 ng/dl	1.45+0.61	1.58+1.0	1.39+0.72	0.97
TSH mIU/L	3.44+2.52	4.33+10.93	3.36+4.32	0.35
TBG mg/dl	1.79+0.65	1.69+0.69	1.53+0.54	0.33
SAL (Serum Albumin Level) g/l	34.07+8.08	35.49+11.61	34.48+9.16	0.79
SGL(Serum Globulin Level) GM/DL	2.37+0.68	2.15+0.60	2.28+0.67	0.45
HDRS score	11.84+1.09	15.08+1.16	19.46+1.96	<0.0001

Correlations of TTR with different hormonal parameters among cases of depression

Significant negative correlation (r -0.74, p<0.0001) was observed of TTR with HDRS score among cases of depression. No such significant correlation was observed of TTR with biochemical parameters (**Table 4**).

Correlation Coefficient (TTR)	T3	T4	TSH	TBG	SAL	SGL	HDRS
	-0.125	0.008	0.061	0.102	0.092	0.129	-0.743**
Sig. (2-tailed)	.215	.939	.547	.311	.361	.202	<.0001

DISCUSSION

Transthyretin (TTR) is a protein mainly synthesized in liver and choroid plexus and participates in the transport of several hormones such as thyroxin and retinol. Serum transthyretin level have been found to be decreased in various conditions such as inflammation, protein malnutrition, end-stage liver disease, or malignancy.[6] TTR was rapidly recognized as the third specific binding protein (BP) ensuring the transport of thyroid hormones; the other 2 are serum albumin (ALB) and thyroxine binding globulin (TBG). It has been reporter that thyroid hormone transporter function of TTR has been emphasized, as reduced levels of TTR have been found in CSF from patients with major depressive disorder, which could potentially lead to lower levels of thyroid hormone in the brain.[17] It has previously been shown that TTR levels are reduced in depressed patients compared to healthy controls.[18] It was postulated that the low levels of TTR resulted in reduced levels of thyroid hormones being distributed throughout the brain and CSF, which could lead to thyroid hormone- related depression.[17]

Present study found the significant difference in distribution of TTR among cases and healthy controls. It was also observed that degree of depression have impact on reduction on TTR, reduction of TTR in patients was observed with the severity of disease among patients. TSH and SAL was found to be decreased in patients when compared with control. This suggested decrease in TTR level in patients associated with decreased level of TSH and SAL level among patients. It was observed that HDRS score linked with degree of depression such as severity of disease. The most important finding, correlation of TTR with HDRS score was found to be negative suggested inverse correlation. Study conducted in an animal model revealed decreased prealbumin production correlates with serotonergic hypofunction[18], which is involved in the pathophysiology of depressive disorder and showed basis for a correlation between prealbumin and depression.[19] Study conducted by Fleming et al in 2007 found that TTR enhances nerve regeneration and may cause depression[20] (Fleming et al., 2007). Joo Y et al in 2006 demonstrated that Transthyretin mRNA expression and protein expression was found to be decreased in a chronic stress-specific manner.[21] Serum prealbumin was significantly lower in patients when compared with post-stroke depression, Baseline serum prealbumin level was associated with post-stroke depression at 1 month, suggesting that prealbumin might be a useful biomarker for post-stroke depression.[22]

CONCLUSION

Present study concluded, serum TTR could be good noninvasive predictive indicator to access the severity of disease and its prognosis. Patients with depression had low serum levels of TTR compared to control. Patients with depression should be evaluated and followed up by a simple blood test as serum transthyretin.

REFERENCES

1. Ayerbe, L., Ayis, S., Wolfe, C.D., Rudd, A.G., 2013. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br. J. Psychiatry, 202: 14–21.
2. Linden, T., Blomstrand, C., Skoog, I., 2007. Depressive disorders after 20 months in elderly stroke patients: a case-control study. Stroke, 38: 1860–1863.
3. Masskulpan, P., Riewthong, K., Dajpratham, P., Kuptniratsaikul, V., 2008. Anxiety and depressive symptoms after stroke in 9 rehabilitation centers. J. Med Assoc. Thai., 91: 1595–1602.
4. Whyte, E.M., Mulsant, B.H., 2002. Post stroke depression: epidemiology, pathophysiology, and biological treatment. Biol. Psychiatry, 52: 253–264.
5. Hama, S., Yamashita, H., Yamawaki, S., Kurisu, K., 2011. Post-stroke depression and apathy: Interactions between functional recovery, lesion location, and emotional response. Psychogeriatrics, 11: 68–76.
6. Ingenbleek, Y., Young, V., 1994. Transthyretin (prealbumin) in health and disease: nutritional implications. Annu Rev. Nutr., 14: 495–533.
7. Dickson PW, Aldred AR, Marley PD et al. Rat Choroid plexus specializes in the synthesis and secretion of transthyretin (prealbumin) J Biol Chem, 1986; 261: 3475-3478.
8. Palha JA, EpiskopouV, Maeda S et al. Thyroid hormone metabolism in a transthyretin–null mouse strain. JBiol Chem., 1994; 269: 33135-33139.
9. Palha JA, FernandesR, deEscobar GM et al. Transthyretin regulates thyroid hormone level in the choroid plexus but not in brain parenchyma: a study in transthyretin–null mouse model. Endocrinology, 2000; 141: 3267-3272.
10. Schreiber G., Southwell B. R. and Richardson S. J. (1995) Hormone delivery systems to the brain transthyretin. Exp. Clin. Endocrinol., 103: 75–80.
11. Palha J. A. (2002) Transthyretin as a thyroid hormone carrier: a function revisited. Clin. Chem. Lab. Med., 40: 1292–1300.
12. Palha J. A., Fernandes R., Morreale de Escobar G., Episkopou V., Gottesman M. and Saraiva M. J. (2000) Transthyretin regulates thyroid hormone levels in the choroid plexus but not in the brain

parenchyma: study in a transthyretin-null mouse model. Endocrinology, 141: 3267–3272.
13. Merched A, Serot JM, Visvikis S, Aguillon D, Faure G, Siest G. Apolipoprotein E, transthyretin and actin in the CSF of Alzheimer_s patients: relation with the senile plaques and cytoskeleton biochemistry. FEBS Lett, 1998; 425: 225–228.
14. Sullivan, G.M., Mann, J.J., Oquendo, M.A., Lo, E.S., Cooper, T.B., Gorman, J.M., 2006. Low cerebrospinal fluid transthyretin levels in depression: correlations with suicidal ideation and low serotonin function. Biol. Psychiatry, 60: 500–506.
15. Lecrubier Y, Sheehan D, Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (M.I.N.I.) a short diagnostic structured interview: reliability and validity according to the CIDI. Eur Psychiatry, 1997; 12: 224–31.
16. Hamilton M. Hamilton Psychiatric Rating Scale for primary depressive illness. Br J Soc Clin Psychol., 1967; 6: 278–96.
17. Hatterer JA, Herbert J, Hidaka C, Roose SP, Gorman JM. CSF transthyretin in patients with depression. Am J Psychiatry, 1993; 150: 813–815.
18. Sullivan GM, Mann JJ, Oquendo MA, Lo ES, Cooper TB, Gorman JM. Low cerebrospinal fluid transthyretin levels in depression: correlations with suicidal ideation and low serotonin function. Biol Psychiatry, 2006; 60: 500– 506.
19. Mann, J.J., 2013. The serotonergic system in mood disorders and suicidal behaviour. Philos Trans. R. Soc. Lond. B Biol. Sci., 368: 20120537.
20. Fleming, Carolina E, Saraiva Maria J, Sousa Mónica M, 2007. Transthyretinen- hances nerveregeneration. J. Neurochem., 103: 831–839.
21. Joo Y, Choi KM, Lee YH, Kim G, Lee DH, Roh GS et al. Chronic immobilization stress induces anxiety- and depression-like behaviors and decreases transthyretin in the mouse cortex. Neurosci Lett., 2009 Sep 18; 461(2): 121-5.
22. Wang L, Xu H, Ren W, Zhu L, Chang Y, Gu Y et al. Low serum prealbumin levels in post-stroke depression. Psychiatry Res., 2016 Dec 30; 246: 149-153.