

Auditory Evoked Potentials as Yardstick for Tinnitus

Paul N¹, Chatterjee I², Das I¹, Das R¹, Banerjee S^{*3} and Debnath S³

¹Department of Audiology, B.ASLP program, PKK College, West Bengal University of Health Sciences, India

²Department of Audiology, Senior Faculty, BASLP & MASLP, Ayjnihsd, West Bengal University of Health Sciences, India

³Clinical Audiologist and Speech-Language Pathologist, Decibel Hearing Clinic Pvt. Ltd, Kolkata, West Bengal, India

***Corresponding author:** Banerjee S, Clinical Audiologist and Speech-Language Pathologist, Decibel Hearing Clinic Pvt. Ltd, Kolkata, West Bengal, India, Tel: +91-9382922869, E-mail: Shrutinathbanerjee171097@gmail.com

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Abstract

Objective: Aiming to evaluate the recent theoretical postulates on tinnitus underscoring the role of thalamocortical neural tracts, the present study 1) explores Middle Latency Response (MLR) as a possible physiological measure of tinnitus: thus investigates the predicted exaggeration of Pa-Na, Na-Pb interpeak amplitudes in tinnitus patients and 2) explores MLR as a prognostic indicator of Tinnitus Retraining Therapy: thus evaluates possible decrease in Pa-Na & Na-Pb amplitude after 2weeks exposure to Tinnitus Retraining Therapy.

Method: An experimental group was constructed by randomly assigning 30 patients with mean age 38.5years and complain of debilitating tinnitus but with normal hearing for the study. MLR was administered on patients with normal ABR and OAE both pre- and post-tinnitus retraining therapy.

Results: Demonstrated no significant effect on Pa, Na & Nb absolute and interpeak latencies. However, significantly exaggerated Pa-Na and Na-Pb interpeak amplitudes between experimental and control groups as well as pre and post therapeutic groups were found.

Conclusion: This proves that MLR may adequately reflect thalamocortical hyperactivity in cases with distressing tinnitus and demonstrable improvement post TRT warrants the use of MLR as its prognostic indicator.

Keywords: Tinnitus; Normal Hearing; ABR; AMLR; OAE; THI; TRT

List of abbreviations: AYJNIHSD= Ali Yavar Jung National Institute of Speech and Hearing Disabilities; ERC=Eastern Regional Center; ISI= Indian Statistical Institute; RCI= Rehabilitation Council of India; MLR= Middle Latency Response; TRT= Tinnitus Retraining Therapy; GABA= Gamma-Aminobutyric Acid; TTT= Tinnitus Targeted Therapy; THI= Tinnitus Handicap Inventory; ABR= Auditory Brainstem Response; OAE= Otoacoustic Emission; PT= Pre therapy; PoT= Post Therapy; FCP= Final Common Pathway; fMRI= Functional Magnetic Resonance Imaging; ERP= Event Related Potential; SPECT= Single Photon Emission Tomography; LLR= Late Latency Response; C= Control Group; ISHA= Indian Speech & Hearing Association; BASLP= Bachelor of Audiology and speech-Language pathology; MASLP= Master of Audiology and Speech-Language Pathology

Introduction

Tinnitus is presently viewed as an abnormal, conscious, auditory percept reflecting multiple levels of neuronal dysfunction / dyssynchrony involving either or both the peripheral and central nervous system [1]. Most models and theories proposed for central, subjective tinnitus predict involvement of higher order auditory functions. The Neurophysiological model of Jasterboff [2] describes distressing tinnitus as reflecting four stage mechanism: generation of peripheral neuronal activity, detection, and perception in the subcortical and cortical auditory areas respectively, and a sustained activation of the auditory related limbic and autonomic nervous system. Shulman [3] proposed an algorithm-based Final Common Pathway model of tinnitus involving the neuroanatomical substrates of sensory, affect and psychomotor components of an aberrant auditory stimulus. It postulates the involvement of, and a complex interaction between, the brainstem, cochlear nucleus, olivocochlear bundle to the inferior colliculus, medial geniculate body, intralaminar-thalamic nuclei, parabrachial nucleus and also the primary ascending reticular activating formation of the lemniscal system to the thalamus. Hyper/depolarization of GABA-influenced thalamic activity results in thalamocortical oscillations in a synchronous signal at brain cortex. Reciprocal innervation from the thalamus to the medial temporal lobe system including the amygdala, hippocampus, etc. comprise an endogenous system which is hypothesized to result in the establishment of a “paradoxical memory” for the aberrant auditory sensation (tinnitus) with a reciprocal interaction with

the thalamus. These models also highlight the reduction in auditory masking and univocally reflect the importance of the auditory thalamo-cortical tract and its connections with the limbic and autonomic nervous system, in tinnitus percept [4].

MLR is a class of auditory evoked potentials postulated to generate from both primary and non-primary auditory-thalamo-cortical pathways [5]; although Pa, Pb, Na, & Nb has slightly different generator sites, overall, they represent the temporoparietal auditory cortex. Studies have hypothesized MLR as a highly sensitive indicator of the central auditory function including the associated areas like the limbic system and the reticular formation [5].

Common approaches for tinnitus management include Tinnitus Retraining Therapy (TRT) [6], tinnitus masking paradigms [7] and the recently proposed medical-audiological approach of TTT [8], most of which, at least as a part of their regime, target reduction of the perception and interpretation of the aberrant auditory sensation at cortical level. Treatment efficacy has generally been assessed subjectively by such checklists as the THI [9].

Objective assessment of tinnitus severity, prognosis and the efficacy of various tinnitus treatment options were tried over the years [10]. However, several studies [11-13] found no consistent abnormalities of the ABR within the tinnitus population. A logical assumption is that MLR might provide objective information of the area most importantly involved in the percept of tinnitus, namely the thalamo-cortical tract. However, studies in this regard are sparse in literature. Promising outcome is provided by studies [14] whereby comparison between ABR, MLR and OAE in normal hearing patients with and without tinnitus was done and significantly enlarged Pa- Na amplitude was found. Extending the principle to hyperacusis, studies [15] suggest Pa latency at 2,000 Hz to be a promising objective indicator of hyperacusis treatment effects. A similar study on workers [16], found individuals with and without tinnitus and normal hearing thresholds exposed to occupational noise present altered MLR, suggesting impaired transmission of neuroelectrical impulses along the cortical and subcortical auditory pathways. Also, individuals with noise-induced tinnitus present more alterations (although not statistically significant) in MLR than individuals without tinnitus. The Na component of MLR receives contributions from subcortical regions of the auditory system, specifically the medial geniculate body of the thalamus [5,17] and perhaps portions of the inferior colliculus [5,18]. However, evidence from intracranial electrophysiologic recordings and magnetic responses in human suggests that generation of the Na component also involves the primary auditory cortex within the temporal lobe – Medial tip of Heschl's gyrus [19,20]. In the 1980s, studies of AMLR utilizing scalp electrodes in patients with cortical lesions confirmed the major role of the primary auditory cortex in generation of the Pa component [21]. Based on investigations in patients with temporal lesions, however, subcortical (e.g. thalamic) structures also appear to contribute to the Pa component [22]. The Pb component of the AMLR arises from the auditory cortex, perhaps the posterior region of the planum temporale [5,20].

Admittedly, objective parameterization of tinnitus is extremely important for accurate prognostic predictions as well as objective quantification of tinnitus symptoms. As shown above, theories posit hyperactivity in the thalamocortical tracts to be important in the perception of tinnitus. Concomitantly, several MLR components are hypothesized to be generated at the thalamocortical tract and the primary auditory cortex and thus suggest its utility in objectivization of tinnitus. However, the potential of AMLR for such a role is still not empirically proved. Studies are needed to explore the utility of AMLR in this regard.

Thus, striving to explore AMLR as a possible physiological measure of tinnitus, the present study aimed to investigate whether increased AMLR amplitude of Pa and Na is characteristic of individuals with severe tinnitus as opposed to individuals without tinnitus. The study thus, tested the hypothesis that individuals with severe tinnitus would have significantly high Pa- Nb and Na-Pb amplitudes compared to a control group. The present study further aimed to explore AMLR as a prognostic indicator, and in order to do so, it tested the hypothesis that there would be significant decrease in Pa- Nb and Na-Pb amplitudes after exposure to successful TRT in subjects with tinnitus.

Materials and Methods

Instrumentation

Tinnitus Handicap Inventory (THI [9]); Pure tone Audiometer : Madsen Itera II Diagnostics (Otometrics), Immittance Audiometer: Madsen Zodiac 901 ; Auditory evoked potential instrument: Biologic Navigator Pro Auditory Evoked Potentials Systems.

Subjects

An experimental group was constructed by randomly assigning 30 patients (Age-range from 20 to 50 years with Mean Age: 38.5 years) with complaint of “debilitating / highly distressing” tinnitus but with no complaint of hearing loss for the study. A Control group of 30 age-matched normal subjects were also taken. Hearing loss, of any degree, and kind, and middle ear pathology, were identified as extraneous variables and were controlled. Pure tone audiometry (extended high frequency upto 12 KHz) and immittance audiometry was done for each prospective subject to rule out hearing loss (even high frequency hearing loss) and conductive pathology if any. Distortion Product OAE was done to rule out any subtle or early outer hair cell dysfunction unreflected in pure tone audiometry. Single channel ABR using 100µs clicks were performed to rule out any abnormality in terms of latency &/or amplitude of ABR peak I, III, V. Further, only patients with unilateral tinnitus were considered for the experimental group. Patients who were found to have secondary tinnitus during tinnitus assessment were excluded from the experimental group.

Procedure

- 1) All the patients coming to the institute clinic with complaint of significantly loud and distressing tinnitus that is severe enough to hamper their daily living were subjected to the Tinnitus Handicap Inventory [9] whereby the severity of tinnitus was assessed and scaled. Only the patients having an overall score of > 38, i.e moderate upto > 78, i.e catastrophic tinnitus of subjective, central type was taken up for the study.
- 2) Tinnitus pitch matching followed by loudness matching was done using conventional psychoacoustical balancing procedures [23]. Following Jasterboff's recommendation, continuous pure-tones, pulsed pure-tones, as well as narrowband noise and white noise were used for matching [6]. Likewise, the other recommendations on assessment parameters and methods were adhered to [7]
- 3) Each patient was assessed for maskability using Feldmann's original test of maskability [24]. Only subjects falling under type I and type III curves i.e good candidates for sound masking were selected.
- 4) Minimum Suppression Levels and the "mixing point" of tinnitus for each patient were determined; as per recommendations of the TRT regime.
- 5) The selected subjects were then administered the ABR using E.A.R-3A insert earphones using standard single-channel test protocol using 500Hz Tone-Burst.
- 6) Middle Latency Response (MLR) using E.A.R-3A insert earphones using the following test protocol: (Appendix: A)

Stimuli type: 500Hz tone burst (for Pb enhancement), Stimuli rate: 5.1/sec at 70dBnHL.

No. of sweeps: 200; Presentation: monaural presentation; Electrode montage: single channel, noninverting: Fpz; inverting: Cz1; Ground: Cz2.; filter settings: 10Hz-100Hz (Hall,2015).

Data acquisition

- a) Absolute latencies (in ms) of peak Pa, Na, and Pb were recorded. Nb was excluded from the study as in most tracing it was of very poor morphology and often indistinguishable.
- b) Amplitude (in μV) of Pa-Na, Na-Pb. Peak to peak amplitude measurement was done.
- c) The means of all the above parameters were elicited from the raw data (pre therapeutic group: PT).
- d) Similarly, MLR was administered on the subjects of the control (C) group and the means of the study parameters were recorded and documented.
- e) Each patient underwent Tinnitus Retraining Therapy (TRT) regime consisting of regular sound therapy sessions [25] and counseling sessions with home management strategies for 2 weeks or until subjective perception of tinnitus reduced to 10-20 % of pre therapy status with THI scores reduced to 0-36, i.e no or slight symptoms.
- f) Entire audiological test regime including MLR was repeated post-therapeutically. The means of Pa, Na, Pb absolute latencies and Pa-Na & Na -Pb amplitude ratios were documented (Post-therapeutic group: PoT).

Statistical analysis

The means between pre- and post-therapeutic groups were compared for significant differences using one-tailed directional hypothesis testing (t-test) with Null hypothesis1: there is no significant difference of means between PT& PoT at 95% confidence interval ($\mu_{PT} - \mu_{POT} \neq 0$).

Further, a 2-WAY ANOVA was performed to find if there is no significant difference of means between PT, PoT& C at 95% confidence interval. (null hypotheses: there is no significant difference in means of PT; there is no significant difference in means of PoT; there is no significant difference in means of C; There is no interaction between PT and C).

The above null hypotheses were constructed separately for Pa, Na, Pb, latencies and Pa-Na and Na -Pb

Results

Mean Absolute latency values of the significant MLR peaks in pre-therapeutic and post therapeutic experimental group and control group were elicited and given in table

1. These values are closely comparable with the normatives as given in literature [5,26,27] across the three groups, and there was no significant difference between the 3 groups. As pointed out by Hall [5], because of the dearth of high frequency components in MLR response, even large variability in latency values are relatively insignificant. Moreover, it is a common assumption that

lesions higher up in the central auditory pathway would have greater impact on response amplitudes rather than latency. The latency outcomes thus are as expected from literature (Figures 1 and 2).

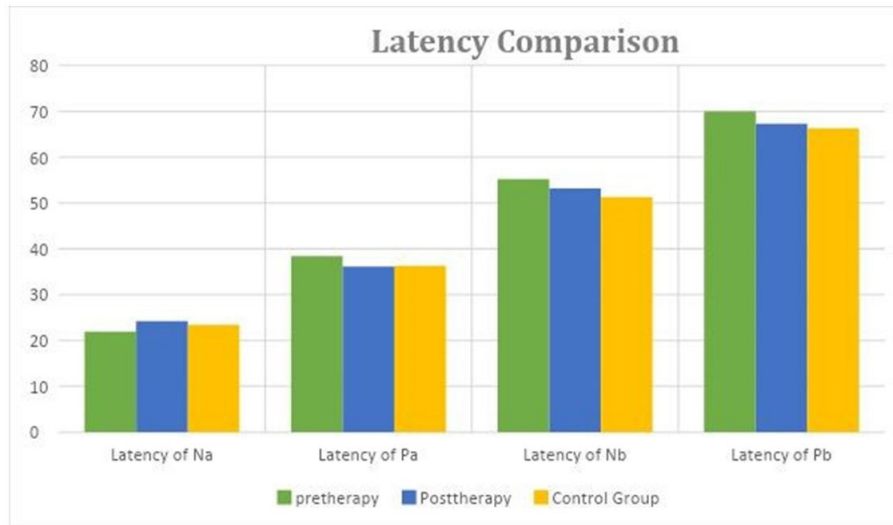


Figure 1: Latency Comparison of MLR peak's

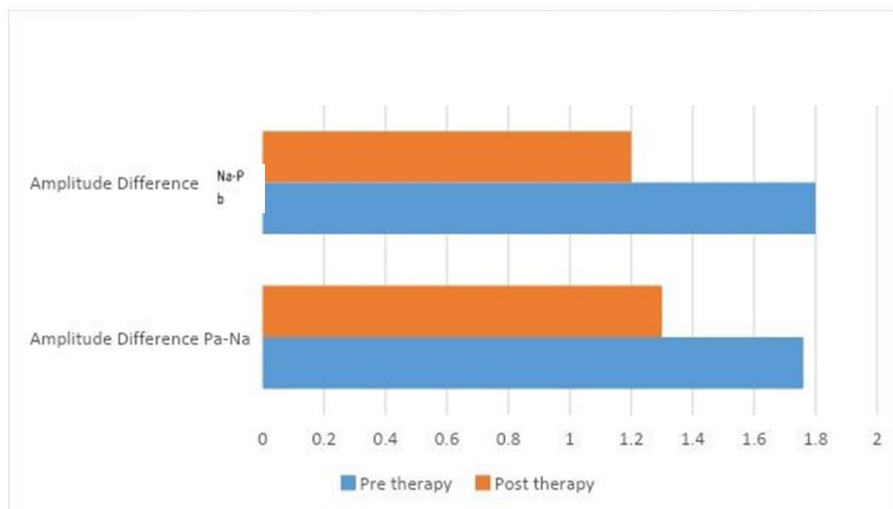


Figure 2: Interpeak Latency Difference between Pre and Post Therapy MLR

2. Exaggerated mean NaPb amplitude was found in the pre-therapeutic experimental group (PT) as compared to literature normative [5,27,28], as well as when compared with the C group. 2-way ANOVA for NaPb was performed to find out the relation between the PT, PoT, and C group. There was a significant effect of NaPb amplitude between the PT, PoT & C groups $F(8,7)=0.705, P=0.684$. Tukey post-hoc analysis of multiple comparisons gives greater difference between the PT and C groups than the PoT and C group (Table 1).

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	.075 ^a	22	.003	.801	.680	.716
Intercept	45.495	1	45.495	10702.922	.000	.999
POST	.016	8	.002	.480	.838	.354
CONTROL	.018	6	.003	.723	.646	.383
POST * CONTROL	.024	8	.003	.705	.684	.446
Error	.030	7	.004			
Total	75.155	30				
Corrected Total	.105	29				

Table 1: Dependent Variable: PRE

3. Exaggerated mean PaNa amplitude was found in the pre-therapeutic experimental group (PT) as compared to literature normative [5,27,28] as well as when compared with the C group. 2-way ANOVA for PaNa was performed to find out the relation between the PT, PoT, and C group. There was a significant effect of PaNa amplitude between the PT, PoT& C groups $F(6,2)= 1.499$, $P=0.453$. Tukey post -hoc analysis of multiple comparisons gives greater difference between the PT and C groups than the PoT and C group (Table 2).

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	.060 ^a	27	.002	1.713	.435	.959
Intercept	61.265	1	61.265	47127.011	.000	1.000
POST	.020	11	.002	1.384	.493	.884
CONTROL	.023	10	.002	1.747	.418	.897
POST *CONTROL	.012	6	.002	1.499	.453	.818
Error	.003	2	.001			
Total	76.639	30				
Corrected Total	.063	29				

a. R Squared = .959 (Adjusted R Squared = .399)

Table 2: Dependent Variable: PRE

4. There was significant average difference between PaNa amplitude of PT and PoT ($t_{29}=11.436$, $p> 0.005$) (Table 3) and on average the PoT group is 0.16400 lower than the PT group. This implies a significant reduction of PaNa amplitude after 3 months of tinnitus retraining therapy including sound therapy and is concomitant with reduction in tinnitus distress and intensity of tinnitus as reflected in THI and post therapeutic matching (Table 4).

	t	df	Sig. (2-tailed)
Pair 1 pre - post	11.436	29	.000

Table 3: Paired Samples Test

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference	
				Lower	Upper
Pair 1 pre - post	.16400	.07855	.01434	.13467	.19333

Table 4: Paired Samples Test Paired Differences

5. Similarly, there was also significant average difference between NaPb amplitude of PT and PoT ($t_{29}=23.857$, $p> 0.005$) (Table 5) and on average the PoT group is 0.27833 lower than the PT group. This implies an even greater reduction of NaPb amplitude after 3 months of TRT. However, in interpreting this data, it must be borne in mind that the PT group NaPb amplitude was found to be excessively exaggerated in the first place (Tables 6,7 and 8).

	t	df	Sig. (2-tailed)
Pair 1 PRE - POST	23.857	29	.000

Table 5: Paired Samples Test

	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference	
				Lower	Upper
Pair 1 PRE - POST	.27833	.06390	.01167	.25447	.30219

Table 6: Paired Samples Test Paired Differences

		Levene Statistic	df1	df2	Sig.
PRE	Based on Mean	.001	1	7	.981
	Based on Median	.003	1	7	.961
	Based on Median and with adjusted df	.003	1	6.451	.961
	Based on trimmed mean	.000	1	7	.986

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.a,b

^aDependent variable: PRE

^bDesign: Intercept + POST + CONTROL + POST * CONTROL

Table 7: Dependent variable and Design

		Levene Statistic	df1	df2	Sig.
PRE	Based on Mean	8112963841460	1	2	.000
		8630000000000			
		00.000			
	Based on Median	8112963841460	1	2	.000
		8630000000000			
		00.000			
	Based on Median and with adjusted df	8112963841460	1	1.000	.000
		8630000000000			
		00.000			
	Based on trimmed mean	1622592768292	1	2	.000
		1725000000000			
		00.000			

Tests the null hypothesis that the error variance of the dependent variable is equal across groups.a,b

^aDependent variable: PRE

^bDesign: Intercept + POST + CONTROL + POST * CONTROL

Table 8: Tests the null hypothesis that the error variance of the dependent variable is equal across groups

Discussion

Theodoroff *et al.* [29] in their study to examine the potentiality of AMLR as diagnostic measure of tinnitus, could not find adequate specificity to detect neurophysiological changes associated with tinnitus but attributed this to the test protocol used. None-the-less, it is in direct contrast to the present findings.

On the other hand, our results were in consonance with the existing models of tinnitus (*viz.* the neurophysiological model [1,3] and more importantly, the FCP [3] model, as already described above), which highlight the role of thalamo-cortical tracts and associated areas in tinnitus percept. These theories and models commonly posit that while in most types of tinnitus, there is an aberrant peripheral auditory sensation at the onset, a subsequent cascade of neural reorganization in the central auditory system is imperative for chronicity of the condition. In literature [30], the existing tinnitus models has been summarized into the following groups: peripheral models; neural synchrony models; Filling in models; Global workplace models and most importantly, the subcortical hyperactivity models, which includes central gating, frontostriatal gating and thalamocortical gating. The role of thalamocortical gating has also been overwhelmingly supported by studies in literature. A study [31] on “Tinnitus-related dissociation between cortical and subcortical neural activity in humans with mild to moderate sensorineural hearing loss” using fMRI and ERP points out a selective elevation of medial geniculate body and cochlear nucleus activity in tinnitus patients which they interpreted as indicative of failure of thalamic gating. The findings are in consonance with the holistic concept of Final Common Pathway of tinnitus as hypothesized by Shulman [3,32], which provides an explanation of the neuroanatomical substrate of both the aspects of tinnitus percept, *viz* auditory sensory component and its reciprocal affect or emotional-behavioral component. The FCP hypothesis even provides a logical basis of the neurophysiological model, explains a synchrony-dyssynchrony hypothesis and is well supported by fMRI [33,34] and SPECT studies. However, such imaging studies are not easily replicable in clinical settings and neither do they provide any functional information on tinnitus. Functional electrophysiological studies may, on the other hand, fill this gap.

Middle latency responses have been shown to be affected by induced lesions in the superior olivary complex, Lateral Lemniscus and Inferior Colliculus in animal studies [35] and hyperexcitability of MLR was demonstrated after tetanic stimulation of auditory cortex in rats [36]. Applying logic of deductive reasoning, thus MLR may well be used for objective quantification of distressing, central tinnitus. There is, but scanty studies in literature in this regard. Review of literature extracted none but a single study [37], which reported detailed neurophysiological assessment in patients with tinnitus and demonstrated significantly exaggerated MLR peaks amplitudes. Such exaggeration of different MLR components were demonstrated, albeit sporadically in few other studies also [38]. Such sporadic effects on MLR have also been demonstrated in noise-induced tinnitus [39]. The present study replicates these findings in our subjects with tinnitus using the present set of acquisition protocols. Comparison between the pre and post therapeutic data and between tinnitus and control group in the present study clearly demonstrates that NaPb and PaNa peak amplitudes of MLR may be exaggerated in distressing tinnitus and further, is directly correlated to the degree of tinnitus percept. If replicable, at least NaPb can be used in objective quantification of tinnitus as well as to objectively quantify prognosis.

Conclusion and Future direction

This demonstrates the compatibility of the present neurophysiological models in defining the tinnitus percept with the Thalamo-cortical tract playing an important role, and highlights the utility of MLR in objectively defining tinnitus. In future, clinical protocols can be developed using AMLR to monitor tinnitus management. Comparable utility of LLR and ERPs may also be studied.

Conflict of interest

There is no conflict of interest whatsoever.

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Data Availability Statement

Raw data were generated at the clinical service wing of PKK College of Education, Pratibandhi Kalyan Kendra; Keota, Latbagan, Sahagunj, Hooghly, West Bengal, India, 712104 and are available on request from the Director, PKK at the above mentioned institutional address; email id: pkkorg@yahoo.co.in; Derived data supporting the findings of this study are available from the corresponding author [Nilanjan Paul; paulnilanjan2@gmail.com] on request.

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