

## Language Evaluation in Children with Infantile Tremor Syndrome and Pre ITS

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Conflict of interest: Nil

### Abstract:

**Background:** This study aimed to assess the language delay in 9 month to 3 years old children with ITS and pre ITS at the time of diagnosis and the effect of treatment on speech and language development after 6 months to one year.

**Methodology:** The study was conducted as a prospective longitudinal observational study on children of age 9 month to 3 year with diagnosis of ITS and PRE ITS admitted in Department of Pediatrics, Kamla Nehru Hospital and Hamidia Hospital Bhopal during the study period of 21 months. All the children were assessed for presence of development delay according to development quotient and assessment of language delay was done using Language Evaluation Scale Trivandrum (LEST 0-3 years).

**Results:** Mean age of children enrolled in our study was 12.91±4.66 months and males slightly outnumbered females in our study with male: female ratio of 1.15:1 in children with preITS as well as ITS. At baseline, i.e. before initiating treatment, no language delay was noted in only 5 (5.8%) cases, whereas majority of children had 2 item delay (53.5%), followed by 23.3% and 17.4% children with 3 items and 1 item delay respectively. At baseline 5 patients had no delay whereas at final follow up 6 of patients had no delay. The LEST positive at baseline were observed in 76.7% cases which at follow up was documented in significantly lower proportions of children with preITS and ITS (57%; p<0.05). After recovery from illness, the improvement was observed in 42 out of 86 children. The therapy was constituted of diet, medication, stimulation and on multivariate analysis, injection trineurosol and calorie addition with injection trineurosol were found to be independent factors associated with recovery.

**Conclusions:** ITS and PreITS are associated with language delay in as high as 76.7% cases. Early identification and management of ITS and preITS may improve the language development in such children. Further studies are warranted to explore the speech and language delay in children with ITS and preITS.

**Keywords:** LEST, Language Delay, ITS, Speech, Treatment.

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### Introduction

Infantile tremor syndrome is a clinical condition characterized by tetrad of pallor, skin pigmentation, delay or regression of development, and scanty brown hairs on scalp. This condition is called pre-ITS. With due course of illness, tremors or involuntary movements also develop in some children along with the above mentioned tetrad of features and the condition is termed as infantile tremor syndrome.[1]

The exact burden of Infantile tremor syndrome in India remains unknown, however, facility based incidence of ITS from pediatric ward have been reported to range from 0.77 to 2.5%.[2] As the syndrome is associated with developmental delay or regression of development, it is essential to assess the development of child with ITS.

Development assessment including Gross motor and fine motor development are routinely observed in infants. Assessment of language is also an important aspect of development assessment in ITS children. Language does not only mean speech but it also include understanding as well as processing of communication; i.e. it involve both the ability to understand the speech (receptive) and to express (expressive) with the help pf words and sentences.[3]

Infantile tremor syndrome is commonly observed in 6 months to 24 months of age[4] and this is also the critical period of speech development.[3] Speech delay is one of the most common neurodevelopmental condition observed in pediatric practice and its burden range from 2.3%

to 19%.[5] Language disorders differ from speech disorders. Voice, fluency or articulation disorders are component of speech disorder whereas dyslexia, specific language impairment, aphasia, auditory processing disorders or semantic pragmatic disorder are described as language disorders.[5]

Various tools have been in use for screening of speech and language delays but are usually a component of developmental assessment.[6-9] LEST scale (Language Evaluation Scale Trivandrum) is a 33 item screening tool used for assessment of Receptive-expressive emergent language scale (REELS).[10] This validated tool has a sensitivity of 95.8% and specificity of 77.5% for assessment of one item delays. However, its PPV, NPV positive and negative likelihood ratios have been documented as 14.2%, 99.8%, 0.05 and 0.05 respectively for one item delay. For two item delay, the sensitivity is 66.7% and specificity is 94.8%.[5]

Literature assessing the language and speech delay in infants and young children diagnosed with preITS and ITS is lacking. The present study is therefore an attempt to assess the language delay in 9 month to 3 years old children with ITS and pre ITS at the time of diagnosis and the effect of treatment on speech and language development after 6 months to one year.

### Methodology

The present study was conducted as a prospective longitudinal observational study on children of age 9 month to 3 year with diagnosis of ITS and PRE ITS admitted in Department of Pediatrics, Kamla Nehru Hospital and Hamidia Hospital Bhopal during the study period of 21 months i.e. from 1st January 2019 to 30th September 2021.

Children with Hypothyroidism, known hearing impairment, underlying neurological disease, known genetic/metabolic disease, any congenital anomalies, family history of neurodegenerative disease/ speech impairment and whose parents not giving consent were excluded from the study.

Children fulfilling the inclusion criteria were enrolled during the period of 15 month- i.e. from 1st January 2019 to 31st March 2021. Thereafter children were followed up at 6 months after the enrolment in the study.

### Sample size calculation

Sample size was calculated using the formula  $n=4pq/d^2$ ,

Where  $p=2.5\%$  (prevalence of ITS), [2]

$q=100-p=97.5\%$ ,  $d=\text{allowable error}=5\%$

Using this formula, sample size was estimated to be 40.

Initially 47 cases with ITS and 45 cases with preITS were enrolled and of them, 2 cases with ITS and 4 cases with preITS lost to follow up and thus a total 45 cases of ITS and 41 cases of Pre ITS were included in our study. After obtaining ethical clearance from Institute's ethical committee, all the neonates fulfilling the inclusion criteria were enrolled. Detailed sociodemographic history regarding their age, gender, residence, Maternal and paternal information, etc. was obtained and entered in questionnaire. Date of admission, presenting features, and diagnosis was entered in questionnaire. All the children were assessed for presence of development delay according to development quotient. Further, all the children were subjected to detailed examination from head to toe, with special emphasis on features of ITS i.e. knuckle hyperpigmentation, hypopigmentation hair etc. All the children were subjected to anthropometric assessment which include weight, height/length, head circumference, mid upper arm circumference, chest circumference and were compared against standards. Assessment of IQ was also done. All the children were then subjected to systemic examinations and findings were documented in proforma. OAE was done for children at the baseline. Assessment of language delay was assessed using Language Evaluation Scale Trivandrum (LEST 0-3 years).[11]

The result of LEST scale was written

LEST delay scale	Interpretation
0 item delay	no delay
1 item delay	questionable delay
2 item delay	suspect delay
3 item delay	total delay
4 item delay	total delay

0 and 1 item delay was considered LEST negative and 2,3 and 4 item delay was considered LEST positive.

Depending upon the condition of the child, they were managed appropriately.

### Follow up

All the children were followed up after 6 month of enrollment in our study. Following parameters were observed at follow up. At follow up, LEST scale was used to assess the effect of treatment on Language development.

Treatment complete was considered when child received and continued treatment for more than 3 months whereas children who received treatment for less than 3 month or did not continue treatment due to any reason were considered as incomplete treatment.

**Statistical Analysis**

Data was compiled using MS Excel and analysed using IBM SPSS Software version 20. Categorical data was expressed as frequency and proportions

whereas numerical data was expressed as mean and Standard deviation. Children with ITS and PreITS were compared using chi square test. P value of less than 0.05 was considered statistically significant.

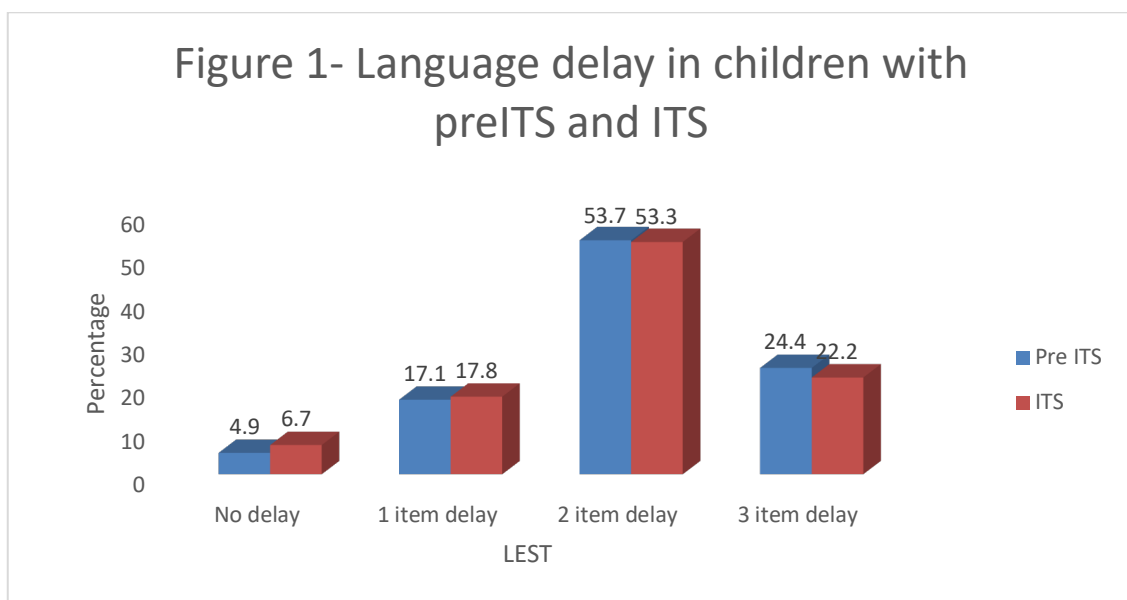
**Results**

This study was conducted on a total of 86 children, of them 45 (52.3%) had ITS whereas remaining 41 (47.7%) had pre ITS. The findings of present study are described as under-

**Table 1: Distribution of children with preITS and ITS according to sociodemographic variables**

Sociodemographic variables		Pre ITS (n=41) n (%)	ITS (n=45) n (%)	Total (n=86) n (%)	P value
Age (years)	9-12 months	26 (63.4%)	32 (71.1%)	58 (67.4%)	0.73
	>12-18 months	11 (26.8%)	9 (20%)	20 (23.3%)	
	>18-24 months	4 (9.8%)	4 (8.9%)	8 (9.3%)	
	Mean±SD	13.12±4.78	12.71±4.60	12.91±4.66	
Sex	Male	23 (56.1%)	23 (51.1%)	46 (53.5%)	0.21
	Female	18 (43.9%)	22 (48.9%)	40 (46.5%)	
Socio economic status	Upper middle	28 (68.3%)	27 (60%)	55 (64%)	0.18
	Lower middle	12 (29.3%)	12 (26.7%)	24 (27.9%)	
	Upper lower	1 (2.4%)	6 (13.3%)	7 (8.1%)	

Mean age of children enrolled in our study was 12.91±4.66 months whereas mean age of children with preITS and ITS was 13.12±4.78 and 12.71±4.60 months respectively. Males slightly outnumbered females in our study with male: female ratio of 1.15:1 in children with preITS as well as ITS. We observed no statistically significant difference in sociodemographic variables in children with preITS and ITS (p>0.05).



**Figure 1: Language delay in children with preITS and ITS**

At baseline, i.e. before initiating treatment, no language delay was noted in only 5 (5.8%) cases, whereas majority of children had 2 item delay (53.5%), followed by 23.3% and 17.4% children with 3 items and 1 item delay respectively. We documented no significant difference in language delay in children between preITS and ITS (p>0.05).

**Table 2: Treatment received in past by study participants**

Treatment received	Pre ITS (n=41) n (%)	ITS (n=45) n (%)	Total (n=86) n (%)
Calories addition	10(24.4%)	6(13.3%)	16(18.6%)
Stimulation	5(1.2%)	7(15.6%)	12(14%)
Inj. Trineurosol	9(19.5%)	11(24.4%)	19(22.1%)
Calorie and stimulation	11(26.8%)	8(17.8%)	19(22.1%)
Calorie and Inj. Trineurosol	5(12.2%)	7(15.6%)	12(14%)
Stimulation with inj. Trineurosol	2(4.9%)	3(6.7%)	5(5.8%)
Inj. Trineurosol with propranolol	0(0%)	2(4.4%)	2(2.3%)
Stimulation with Inj. Trineurosol and propranolol	0(0%)	1(2.2%)	1(1.2%)
P value	0.582		

The present study documented no significant difference in treatment received in children with pre ITS and ITS ( $p>0.05$ ).

**Table 3: Comparison of LEST at baseline and final follow up in children with ITS and preITS**

LEST		Pre ITS (n=41) n (%)	ITS (n=45) n (%)	Total (n=86) n (%)
Negative	Baseline	9 (22%)	11 (24.4%)	20 (23.3%)
	Follow up	18 (43.9%)	19 (42.2%)	37 (43%)
Positive	Baseline	32 (78%)	34 (75.6%)	66 (76.7%)
	Follow up	23 (56.1%)	26 (57.8%)	49 (57%)
P value		0.03	0.02	0.009

The LEST positive at baseline were observed in 76.7% cases which at follow up was documented in significantly lower proportions of children with preITS and ITS (57%;  $p<0.05$ ).

**Table 4: Status on LEST scale before and after treatment**

Language delay as per LEST		Baseline n (%)	Follow up n (%)	P value
All	No delay	5 (5.8%)	6 (6.98%)	<b>0.0004</b>
	1 item delay	15 (17.4%)	34 (39.5%)	
	2 item delay	46 (53.5%)	42 (48.8%)	
	3 item delay	20 (23.3%)	4 (4.7%)	
PreITS	No delay	2 (4.9%)	3 (7.3%)	<b>0.01</b>
	1 item delay	7 (17.1%)	16 (39.02%)	
	2 item delay	22 (53.7%)	21 (51.2%)	
	3 item delay	10 (24.4%)	1 (2.4%)	
ITS	No delay	3 (6.7%)	3 (6.7%)	<b>0.049</b>
	1 item delay	8 (17.8%)	18 (40%)	
	2 item delay	24 (53.3%)	21 (46.7%)	
	3 item delay	10 (22.2%)	3 (6.7%)	

At baseline 5 patients had no delay whereas at final follow up 6.98% cases had no delay. Initially 1 item delay was noted in 17.4% at baseline but at final follow up 1 item delay was noted in 39.5% cases. Similarly 53.5% and 23.3% cases had 2 and 3 item delay at baseline which at follow up was in 48.8% and 4.7% cases respectively. We observed significant improvement in LEST score in all the children ( $p<0.05$ ).

**Table 5: Multivariate analysis of treatment received with LEST score at follow up in children with preITS and ITS**

Treatment received	Pre ITS (n=41)			ITS (n=45)		
	OR	95% CI	P value	OR	95% CI	P value
Calories addition	Ref			Ref		
Stimulation	0.28	0.03-2.69	1.0	0.08	0.005-1.19	0.07
Inj. Trineurosol	0.26	0.04-1.84	0.18	<b>3.26</b>	<b>1.33-7.59</b>	<b>0.03</b>
Calorie and stimulation	0.24	0.04-1.5	0.13	1.31	0.24-4.61	0.22
Calorie and Inj. Trineurosol	0.643	0.07-6.06	0.699	<b>4.27</b>	<b>1.19-19.6</b>	<b>0.001</b>
Stimulation with inj. Trineurosol	0.62	0.06-6.2	0.66	3.16	0.49-7.62	0.33
Inj. Trineurosol with propranolol±stimulation	-	-	-	1.17	0.39-3.34	0.45

On multivariate analysis, we reported that injection trineurosol and calorie addition with injection trineurosol had significantly higher odds of improvement of language delay in ITS children as compared to only calorie addition ( $p < 0.05$ ).

**Table 6: Association of LEST status with treatment completion**

Treatment	LEST	Pre ITS (n=41) n (%)	ITS (n=45) n (%)	Total (n=86) n (%)
Complete	Not improved	3 (7.3%)	0 (0%)	5 (5.8%)
	Improved	20 (48.8%)	20 (44.4%)	40 (46.5%)
Incomplete	Not improved	17 (41.5%)	24 (53.3%)	39 (45.3%)
	Improved	1 (2.4%)	1 (2.2%)	2 (2.3%)
P value		<b>0.0001</b>	<b>0.0001</b>	<b>0.0001</b>

In present study, non-completion of treatment was associated with no improvement in LEST score in preITS as well as ITS children ( $p < 0.05$ ).

### Discussions

Children with infantile tremor syndrome show normal growth and development from birth until 4 to 6 months of age, thereafter mental sluggishness sets in, which is followed by development regression.[12,13] Gradually the infant becomes less active, shows less interaction with parents and lose interest in the surroundings.[13]

Developmental delay have been documented in as high as 85% of the children with ITS and regression of milestones may be noticed in 58% to 100% of the patients with ITS.[12-14] As the ITS is usually observed in 6 months to 24 months of age[4], which is a critical period for development of speech, assessment of language development is essential in these children.[3]

We thus conducted this study on 80 children with ITS and preITS seeking care at our Hospital during the study period to assess the language delay and the effect of treatment on speech and language development after 6 months to one year.

Mean age of children was  $12.91 \pm 4.66$  months and slight male predominance for ITS was noted in our study. A validated tool i.e. LEST scale (Language Evaluation Scale Trivandrum) was used in our study for assessment of language delay. This is a 33 item screening tool which helps in assessment of Receptive-expressive emergent language scale (REELS).[10]

The reported sensitivity and specificity of this tool is 95.8% and 77.5% respectively.[5] We reported one item, two item and three item delay on LEST scale in 16.25%, 55% and 22.5% cases respectively. Based upon the features of children, treatment was provided to them in the form of addition of calories, stimulation, Injection trineurosol and propranolol alone or in combination.

The treatment was given for 6 to 9 months and the effect of treatment was noted at final follow up,

which revealed slight improvement in the language development along with significant difference was noted between the language delay at baseline and follow up ( $p < 0.05$ ).

To best of our knowledge, none of the previous studies have exclusively explored the language delay in children with ITS and preITS, rather developmental delay have been assessed previously.

Though Goraya et al in their review did not mention regarding any scale, but they described language delay in few children with ITS.[2] John et al documented the developmental delay and milestone regression in 85% and 33.3% cases with ITS.[14] Few children who showed no delay at baseline, later deteriorated at final follow up. Overall, improvement was observed in 42 out of 86 children. Nutritional deficiency, particularly Vitamin B12 deficiency have been linked to developmental delay in such children.[15]

In our study, treatment was given in the form of stimulation, calorie addition, Injection Trineurosol and propranolol alone or in combination. Incomplete treatment was significant determinant of non-improvement in LEST scale ( $p < 0.05$ ). Makwana et al also reported developmental delay in children with ITS but not specifically language delay.[15] Jain et al reported regression of milestones in 65% cases in their study.[16]

The exact etiology and mechanism of language delay in these children is not known but have been linked to deficiencies of nutritional elements such as Vitamin B12, zinc, copper etc. which helps in neurodevelopment.[14]

We reported that injection trineurosol and calorie addition with injection trineurosol helps in improvement of language development in ITS children.

### Conclusions

ITS and PreITS are associated with language delay in as high as 90% cases. Early identification and management of ITS and preITS may improve the language development in such children. Further

studies are warranted to explore the speech and language delay in children with ITS and preITS.

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