Meningo Encephalitic Syndrome (infantile tremore syndrome) magnesium cum nutritional deficiency syndrome*)

By *B. C. Chhaparwal, Saroj Mehta***, *S. D. Singh*
Departement of Paediatrics, M.G.M. Medical College, Indore (M.P.), India

Zusammenfassung

Trotz vieler Hypothesen ist die Ätiologie des „infantilen Tremor-Syndroms", auch als „meningo-encephalitisches Syndrom" bezeichnet, unbekannt. Unter anderem wurden die Mg-Gehalte in Serum, Erythrozyten, Liquor und Urin bestimmt (Titangelb-Methode nach *Andreasen*, 1957). Die entsprechenden Kinder wiesen auf: Hypoproteinämie, Hypoalbuminämie und deutlich erniedrigte Mg-Gehalte in Serum, Liquor und Urin. Unter parenteraler Mg-Therapie kam es zu einem deutlich schnelleren Sistieren der Tremorerscheinungen. Das Krankheitsbild scheint demnach in Übereinstimmung mit früheren Beobachtungen ein „Magnesium-Mangel plus Malnutrition Syndrom" zu sein.

Summary

The aetiology of 'Infantile Tremor Syndrome' also referred to in literature as 'Meningo-Encephalitic Syndrome' is unknown, though many hypotheses have been put forward. Besides routine biochemical investigations, estimation of magnesium in serum, erythrocytes, cerebrospinal fluid and urine was determined by Titan-Yellow method as described by *Andreasen* (1957). These children had hypoproteinaemia, hypoalbuminaemia and markedly low levels of magnesium in serum, C.S.F. and urine. The tremors disappeared much earlier in children who received parenteral magnesium therapy. These findings bear out our previous suggestion that 'Infantile Tremor Syndrome' is a 'Magnesium cum Nutritional Deficiency Syndrome'.

Résumé

L'étiologie du «syndrome de tremblement infantile», rapporté également dans la littérature sous la dénomination de «syndrome méningo-encéphalique», est inconnue, bien que plusieurs hypothèses aient été avancées. Outre les recherches biochimiques habituelles, l'évaluation du Mg dans le sérum, les érythrocytes, le liquide céphalo-rachidien et l'urine a été déterminée par le procédé du jaune titan tel qu'il a été décrit par *Andreasen* (1957). Ces enfants ont présenté une hypoprotéinémie, une hypoalbuminémie, et des taux nettement faibles de Mg dans le sérum, le L.C.R. et l'urine. Les tremblements ont disparu beaucoup plus tôt chez les enfants qui ont reçu une thérapeutique magnésique parentérale. Ces constatations justifient une suggestion antérieure, selon laquelle le syndrome de tremblement infantile est un syndrome de déficit nutritionnel associé en Mg.

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**) Lecturer in Paediatrics, Institute of Medical Sciences, Banaras Hindu University, Varanasi (U.P.) India.

Introduction

The „Meningo Encephalitic Syndrome" also referred to in literature as „Infantile Tremor Syndrome" is characterised by a pale, apathetic, well contoured, plumpy infant, usually between the ages of 6 and 24 months. These children have sparse, light coloured hair over the scalp and eye brows and a vacant look and most commonly presenting with coarse tremors and tremulous cry. The skin over the thighs and shows a reticular or „honeycomb" pigmentation. Delayed mile stones and mental retardation are prominent features which is of varying duration. The aetiology of this syndrome is unknown though many hypotheses have been put forward. *Pohowalla* et al. (1960) suggested an infectious aetiology probably viral, *Jadhav* et al. (1962) suggested vitamin B_{12} deficiency as a contributory factor since they found low levels of serum vitamin B_{12} in their cases. *Kaul* et al. (1963) and *Bajpai* et al. (1966) did not find low levels of serum vitamin B_{12} in their cases and a therapeutic trial did not alter the course of the disease. *Sachdeva* et al. (1965) and *Mathur* et al. (1960) have suggested that the condition may be due to an imbalanced nutrition. *Mishra* et al. (1971) studied histopathologically the brain biopsies and could found encephalitic and meningeal inflammation in less than one-half of the cases studied and suggested viral infection as a probable cause of this syndrome. Recently, *Mahajan* et al. (1971) estimated sodium, potassium, chlorides, urea, sugar, transaminases in blood of these cases and did not observe any abnormality in their content. *Chhaparwal* et al. (1971) studied magnesium levels in serum and cerebrospinal fluid of these cases and found markedly low levels of magnesium in serum and CSF.

Keeping in view the studies of *Mahajan* et al. (1971) and *Chhaparwal* et al. (1971), a biochemical and therapeutic study of this syndrome was undertaken to provide chemical evidence for magnesium deficiency and for assessing the ther-

apeutic effect of parenteral magnesium therapy on the course of this syndrome.

Material and Methods

28 infants and children suffering from Infantile Tremor Syndrome were studied. Estimation of magnesium in serum, erythrocytes, cerebrospinal fluid and urine was determined by Titan Yellow method as described by *Andreasen* (1957). The results obtained were compared with those studied in normal children in this region. In each case, total proteins and its fractions were estimated, on admission. Other serum electrolytes like sodium, potassium, chloride and calcium were also determined in each case, on admission. All the children with this syndrome received a standard diet: Proteins 3 gm/kgm. of expected body weight in the form of milk, egg etc. with added multivitamin tablet and minerals like iron etc. The only difference in their therapy was that half of the cases received parenteral magnesium therapy in the dose of 2,0 to 4,0 mEq/kgm. parenterally per day as described by *Flink* (1969). The remaining half did selection. The results obtained were compared. Each case was followed every day and the clinical course of the disease was studied, especially the day of disappearance of Tremor was recorded, and magnesium levels in body fluids were again determined at the time of disappearance of tremors.

Results

As shown in table I these children varied in age from over 6 months to 18 months, the majority being below the age of 12 months. Sex distribution did not show any appreciable difference as there were 12 males and 16 females in this series.

Table II shows the magnesium levels in serum, R.B.C., CSF and urine in these children, the mean values for these body fluids being 1,764, 3,685, 1,864, 2,810 mEq/L. respectively. But for the values of magnesium in erythrocytes, these values were very low in serum, CSF and urine as compared to normal children in this region. It is observed from table III that these children suffer from hypoproteinaemia and hypoalbuminaemia.

Tab. I: Showing the age and sex distribution

Age group in months	SEX		Total
	Male	Female	
Up to 6	—	—	—
6 to 12	10	10	20
12 to 18	2	6	8
18 to 24	—	—	—
TOTAL	12	16	28

Tab. II: Showing the values of magnesium in serum, RBC, CSF and urine in 'Tremor Syndrome' cases with their statistical value on admission

	Magnesium in mEq/Litre			
	Serum	R.B.C.	C.S.F.	Urine
Mean	1,764	3,665	1,864	2,810
Range	1,3 to 2,2	2,0 to 5,2	1,2 to 2,4	1,2 to 5,0
Statistical significance 'P' value	Highly significant at 1 % level	Statistically insignificant	Highly significant at 1 % level	Highly significant at 1 % level

Tab. III: Showing the blood protein levels and its fraction in Tremor Syndrome cases on admission

	Proteins in gm %	
	Total	Albumin
Mean	5,821	2,685
Range	5,0 to 6,6	2,1 to 3,5

The mean values for total proteins and albumin were 5,821 and 2,695 gm% respectively. As is seen from table IV that values for other serum electrolytes like sodium, potassium, chloride and calcium were within normal limits. Table V shows the magnesium levels in various body fluids after the disappearance of tremors. Though the increase in magnesium levels were recorded in all the body fluids but the rise in CSF magnesium levels were not significant, as compared to the values observed on admission. Table VI

Tab. IV: Showing the serum electrolyte levels in 'Tremor Syndrome' cases on admission

	Electrolytes in mEq/L.			Calcium in mg%
	Sodium	Potassium	Chloride	
Mean	141,77	4,80	91,21	10,61
Range	125 to 155	3,5 to 5,0	80 to 110	5,5 to 13,0

Tab. V: Showing the values of magnesium in various body fluids after disappearance of tremors

	Magnesium in mEq/L.			
	Serum	R.B.C.	C.S.F.	Urine
Mean	1,947	3,543	2,08	6,0
Range	1,4 to 3,0	2,0 to 4,8	1,2 to 2,4	1,2 to 11,0

Tab. VI: Showing the duration of Tremors and its relationship to magnesium sulphate therapy

	Duration of tremors in days	
	Received magnesium sulphate therapy	Did not receive magnesium therapy
Mean	10	25
Range	6 to 18	18 to 36

shows that tremors disappeared much earlier in those cases who received parenteral magnesium therapy. The mean values of time taken in disappearance of tremors being 10 days in cases who received magnesium therapy and 25 days in those cases who did not receive parenteral magnesium therapy.

Discussion

28 cases of Infantile Tremor Syndrome were studied. The mean values for magnesium in serum, erythrocyte, cerebrospinal fluid and urine were 1,764, 3,685, 1,864 and 2,810 mEq/L. respectively. Thus it was seen that there was significant fall in magnesium levels in serum, CSF and urine. All these children were investigated at a time when tremors were distinctly manifest. It is evident from statistical analysis that as compared to normal children in this region, the difference in magnesium content in body fluids was highly significant, but for levels in erythrocytes, in „Infantile Tremor Syndrome" cases. The magnesium levels in body were determined again after the disappearance of tremors in 23 of these 28 cases, since 2 cases left against medical advice, two cases died and one case absconded from the ward. The rise in magnesium levels were observed in serum, CSF and urine after the initial determination. No significant change was found in cases of erythrocyte levels on follow-up. Experimental magnesium deficiency is known to produce plasma, erythrocyte, soft tissue and bone magnesium depletion (*Mc Intyre* and *Davidson*, 1958; *Tufts* and *Greenberg*, 1938). Magnesium deficiency results in hyper irritability, tetany and convulsions which can lead to death (*Kruse* et al., 1932). Experimental magnesium deficiency produced in young growing rats a decrease in brain magnesium and an increase in brain calcium. These changes were associated with retarded brain growth and convulsion with a high mortality rate (*Hunt*, 1973). The CSF magnesium concentration in rats weighing 90—100 gms. fell by 48 % from control values, this was observed in the experimental magnesium deficiency produced in young rats (*Chutkow*, 1968). *Hunt* (1973) observed that the effect of magnesium deficiency on brain growth is directly dependent upon the rate of growth of an individual organ at the start of the deficiency period. This is in direct agreement with Winick's statement (1966), that timing is the critical element in determining the outcome of nutritional deprivation. He and his colleagues have shown that permanent reduction in brain size, in the number of brain cells, the DNA, RNA and protein content, and prominent intellectual impairment occurs in both rats (*Winick* and *Noble*, 1965) and humans (*Winick* and *Rosso*, 1969) who experienced severe nutritional deprivation during the first few weeks (rats) or months (human infants) of life. Magnesium deficiency must be classed as severe nutritional deprivation, not only because of the obvious weight retardation which is characteristic of the syndrom but also because magnesium deficiency is known to decrease exogenous protein utilisation (*Colby* and *Fryo, 1951; Bunce* et al., 1963) and inhibits endogenous protein synthesis (*Menakes*, 1954) with all the possible consequences this entails.

In this study of tremor syndrome cases, the other electrolytes estimated were sodium, potassium, chloride and calcium and the mean values for these being 141,77, 4,8, 91,210 mEq/L. and 10,61 mg% respectively. The values for these electrolytes did not differ significantly from those reported for normal children in this region. Similar observations have been made by *Mahajan* et al. (1971). These cases were also studied for their blood protein content. The values for total proteins and albumin were 5,821, 2,685 gm% respectively. Thus hypoproteinaemia and hypoalbuminaemia was also recorded in "Infantile Tremor Syndrome" cases.

Of the 28 cases, 14 infants (50 %) received parenteral magnesium therapy and 14 (50 %) were

without magnesium therapy. In children receiving magnesium therapy, the tremors disappeared after 10 days and in those who did not receive magnesium therapy, the tremors persisted for 25 days. Hence it is evident that magnesium supplemented therapy was superior to therapy without supplements. These findings bear out our previous suggestion that magnesium deficiency with malnutrition seems to be of definite importance in the aetiology of this syndrome and parenteral magnesium therapy is beneficial as compared to therapy without magnesium supplements.

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(For the authors: Dr. B. C. Chhaparwal, 157, Radio Colony, Indore, 452001, India)