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Original Research Article

Diphtheria pertussis tetanus vaccine induced convulsion: is hypocalcemia a triggering factor?

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ABSTRACT

Background: Active pertussis toxin in diphtheria pertussis tetanus (DPT) vaccine has been proposed to cause severe reactions. A convulsion following DPT vaccine is a known adverse reaction but hypocalcemia as a triggering factor is not reported. The aim of the study was to find the association between serum calcium and DPT vaccine induced convulsions and to study the clinical profile.
Methods: Retrospective observational and descriptive study was done at emergency ward of a tertiary care teaching hospital. 20 infants of DPT induced convulsions with previous normal neurodevelopment were included in the study. Main outcome measures were association between DPT vaccine induced convulsions and serum calcium levels.
Results: Out of 20 infants included in the study, male to female ratio was 1.8:1, all of them were less than 6 months of age, 17 (85%) were exclusively breast fed, hypocalcemia was seen in 17 cases (85%), 11 (55%) had fever. 16 (80%) had convulsions following third dose of DPT vaccine.
Conclusions: There is a significant association between hypocalcemia and DPT vaccine induced convulsion. Hence there is need for Calcium and Vitamin D3 supplementation in pregnant and lactating mothers and early detection and adequate treatment of rickets in infants.

Keywords: Calcium, Fever, Hypothalamus, Pertusiss toxin

INTRODUCTION

The pathophysiology of severe reactions to Diphtheria pertussis tetanus (DPT) vaccine is not well understood.[1] Active pertussis toxin in DPT vaccine has been proposed to cause severe reactions.[1]

Convulsions following DPT vaccine is a known adverse reaction but hypocalcemia as a triggering factor is not reported. Hence this study was conducted to evaluate the relationship between serum calcium and DPT vaccine induced convulsion and to study the clinical profile of the study population so that suitable preventive measures could be suggested.

METHODS

A retrospective observational and descriptive study conducted at children hospital attached to Medical College and Research Institute, Mysore, India. 20 infants admitted to pediatric emergency ward with neurological symptoms following DPT vaccine over a period of 3 years were included in the study. Infants with pre-existing seizures or neurodevelopmental abnormalities were excluded from the study. A detailed history, clinical examination findings, laboratory investigations including serum calcium, phosphorus and alkaline phosphatase, treatment modalities and outcome were recorded in a proforma. Institutional ethical committee clearance was obtained.

Statistical methods included mean, SD, chi-square test with Yate's correction and proportion test.

RESULTS

All the 20 infants included in the study were born at term and had normal growth and development. 13 (65%) were male, 7 (35%) were female with a male to female ratio of 1.8 is to 1. All infants were below 6 month of age,16 (80%) between 4 to 5 month of age. 17 (85%) infants were exclusively breastfed whereas 3 infants received additional cow's milk. 19 (95%) infants were up to date immunized, only-one infant had received first dose of DPT vaccine at 6 month.

As shown in Table 1, 16 (80%) infants had convulsions following third dose of DPT vaccine.

Table 1: Relation between DPT vaccine dose and number of infants with convulsion.

Dose of DPT	No of infants with convulsion	Percentage
I	2	10
II	2	10
III	16	80
Total	20	100

Table 2: Time interval between DPT vaccine and convulsion (mean 7.6 with SD 2.8 hour).

Time interval (hour)	No of cases	Percentage
<6	03	15
6-12	14	70
>12-24	03	15
Total	20	100

There was no history of fever or upper respiratory tract infection in any of the cases. There was family history of febrile seizure in one and epilepsy in one infant. One infant had similar seizures following previous dose of DPT vaccine. 11 (55%) infants had fever within 6 hours of vaccination.

Table 3: Correlation between serum calcium level and convulsion (P < 0.05 significant by proportion test).

Serum calcium (mg/dl)	No of cases with convulsion	Percentage
<7	6	30
7-8.8	11	55
>8.8	3	15
Total	20	100

All the cases had generalized tonic clonic seizures lasting for 5 minutes in 5 (25%) and between 5 to 10 minutes in 15 (75%). 7 (35%) cases had less than 5 episodes, 10 (50%) cases had between 5-10 episodes and 3 cases had more than 10 episodes of GTC's inter-ictal period was normal and active breastfeeding was present in 12 (60%) cases and post-ictal drowsiness varying from 5 to 45 minute was present in 8 (40%) cases. Excessive cry (8/20), altered sensorium (4/20) and irritability (11/20) were the other symptoms noted.

Table 4: Relation between serum calcium and fever.

Serum calcium (mg/dl)	No of cases with fever	No of cases without fever	Total no of case
<8,8	8 (40%)	9 (45%)	17 (85%)
≥8.8	3 (15%)	0	3 (15%)
Total	11 (55%)	9 (45%)	20 (100%)

Clinical features of rickets were present in all the 20 cases, included excessive sweating around the head in all, frontal bossing in 16 (80%), frontal and parietal bossing in 4 (20%), wrist widening in 6 (30%), rachitic rosary in 3 (15%) and wide open anterior fontanel in 17 (85%).

None of the mothers were on either calcium and vitamin D3 rich diet or the supplements. There is statistically significant correlation between serum calcium and convulsion, P being <0.05 by proportion test.

As per table 4 there was no statistically significant correlation between fever and serum calcium P being >0.05 by chi-square test with Yate's correction

Treatment modalities included intravenous administration of calcium gluconate, mannitol, anticonvulsants and inotropes as emergency measures. Inj vitamin D3 6 lakh IU IM followed by calcium, phosphorus and oral Vitamin D3 400 IU per day were given to17 (85%) cases with hypocalcemia. Mothers were given calcium, phosphorus a vitamin D3 supplements.

DISCUSSION

This hospital-based study of 20 infants less than 6 month of age, born at term ,with no previous history of seizures, with normal growth and development ,most of them being exclusively breastfed, mothers not on any calcium and Vitamin D3 rich food or supplements, presented with fever(11 cases)within 6 hour and GTCs within 24hour of receiving DPT vaccine. 17 (85%) cases had hypocalcemia (serum calcium < 8.8 mg /dl) which was statistically significant. Similar observation has not been found in the search of literature for association between DPT vaccine induced convulsion and hypocalcemia. Hence an attempt is made to understand the pathophysiology of DPT vaccine induced convulsion considering hypocalcemia as a triggering factor in addition to pertussis toxin and fever.

Seizures associated with DPT vaccine have similar characteristics as febrile seizures. Pertussis component of DPT vaccine is responsible for much of the

reactogenicity.[1] Neurological events following in close temporal proximity to the administration of DPT vaccine have often raised questions of causal association.[2] Febrile seizures induced by petussis toxin are more severe and the cause for this is unknown.[3] Whether pertussis vaccine causes or is only coincidentally related to such an illness or reveals an inevitable event has been difficult to determine conclusively for the following reasons

- Serious neurologic illness manifests in first year of life irrespective of vaccination
- No specific clinical sign, pathologic finding or laboratory test to say caused by DPT vaccine
- Difficult to assess whether infant less than 6 month was neurologically normal before vaccination and
- Because of rarity, appropriately designed large studies are needed.[2]

A causal relationship between pertussis whole cell vaccine and neuronal responses has been demonstrated in animal model. Pertussis toxin causes neurologic damage; by affecting cellular signalling, catecholaminergic and GABAergic systems and defect in blood brain barrier due to endotoxin mediated endothelial damage. Whole cell pertussis vaccine induces increased IL-1B production in the hippocampus and hypothalamus of vaccinated animals. This leads to decrease in release of inhibitory neurotransmitters GABA and adenosine in the hippocampus and induce convulsive activity. Acellular pertussis vaccine does not produce such IL-1B induced responses.[4]

This increased IL-1B production is also responsible for elevation of body temperature within 2 to 4 hour after injection of whole cell pertussis vaccine, thus demonstrating the temporal relationship.[4] The rate of febrile seizures occurring within 3 days of DTwP vaccination in clinical studies is consistently 60 per 100,000 doses and are common in children with personal or family history of seizures and are considered benign.[5] Febrile seizures are often associated with hypocalcemia (unpublished) or actually hypocalcemic seizures. Fever is the purposeful elevation of body temperature specifically to release stored calcium from bone reserves.[6]

Hypocalcemia as a triggering factor for DPT vaccine can be explained on the basis of increased neuroexcitability. Low ionized calcium levels in the extra cellular fluid, by binding to exterior surface of sodium channel protein molecule in the plasma membrane of nerve cells, increase the permeability of neuronal membranes to sodium ions, causing a progressive depolarization which increases the possibility of action potentials. When calcium ions are absent the voltage level required to open voltage gated sodium channels is significantly altered (less excitation is required), with hypocalcemia action potentials may be spontaneously generated causing contraction of peripheral skeletal muscles resulting in clinical seizures.[7] With this understanding, it may be concluded that pertussis toxin produces seizure and fever by acting on central nervous system which are triggered or potentiated by hypocalcemia. As there are no publication to interrelate pertussis toxin, hypocalcemia and fever in causing DPT vaccine induced convulsion, more animal experiments or large scale clinical studies are warranted.

CONCLUSION

Hypocalcemia is a triggering factor for DPT vaccine induced convulsions. There is need for case control as well as animal studies. Adequate Vitamin D3 and calcium supplements to pregnant and lactating mothers is rewarding. Early detection and adequate treatment of Rickets in infants is essential. Preventing DPT vaccine induced convulsion can alleviate parental apprehension and positively impact immunization programme.

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