|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||

International Journal of Medical Science and Diagnosis Research (IJMSDR)

Available Online at www.ijmsdr.com

Volume 3, Issue 2; February: 2019; Page No. 232-235

EARLY-ONSET IDIOPATHIC INTRACTABLE SEIZURES AND AFFECTIVITY OF PYRIDOXINE TREATMENT IN CHILDREN

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Conflicts of Interest: Nil

ABSTRACT

INTRODUCTION: Pyridoxine dependent epilepsies (PDEs) are autosomal recessive disorders which are characterized by seizures at neonatal onset not responding to conventional antiepileptic drugs (CADs), and can only cease after parenteral pyridoxine administration. Diagnostic criteria for this condition are: cessation of clinical and electroencephalographic seizures following intravenous administration of 100 mg of pyridoxine, and no seizure recurrence while on long-term treatment. PDEs epidemiology with a considerable heterogeneity has been reported with birth incidences are 1:20,000 in Germany, 1:396,000 in Netherlands and 1:783,000 in the UK and Ireland. Mutations in the gene encoding for the alpha-aminoadipic-semialdehyde dehydrogenase (ALDH7A1) have been identified in the related enzyme deficiency. **MATERIAL AND METHODS**: All children attending the paediatric with intractable seizures, were enrolled in the study. Inclusion criteria was Intractable seizures, seizures had persisted for more than 6 months under regular administration of three or more appropriate antiepileptic drugs (AEDs), except pyridoxine; seizure frequency was more than once per day; and onset of epilepsy in the first 18 months of life. An **electroencephalogram (**EEG) was recorded for all patients. Those with abnormal EEG were given a pyridoxine trial, of an intravenous infusion of 100 mg of pyridoxine (vitamin B6 25 mg; vitamin B1 50 mg; vitamin B12 500 mg; D-panthenol 25 mg)which was diluted in saline and given over 10-min with a simultaneous EEG monitoring . This procedure was carried out in the EEG laboratory with all appropriate precautions. Follow up of the patients was done every 15 days. Those patients on pyridoxine therapy who remained seizure-free with previous AEDs were gradually tapered one by one over the next 3-months. **RESULTS**: A total of 27 patients with intractable epilepsy were included in the study. Of which 16 (59.3%) male and 11(40.7%) female were having intractable epilepsy. Of the total 5 patients with focal seizures 3(60%) were male and 2(40%) were female. out of 22 patients with generalized seizures 13 (59.1%) were male and 9(40.9%) were females. Mean age of onset of seizures in male was 5.3 months and in females was 5.1 months. EEG findings in all patients was abnormal. After pyridoxine treatment 2 patients with generalised seizures and receiving 3 antiepilectic drugs respond well to the treatment within 3 weeks of treatment. In another 4 patients seizure frequency decreased to 25% after treatment. **CONCLUSION**: Most of the patients responded well to the pyridoxine treatment, but the IV injections and risk of infection may be the problem and some patient may not continue the treatment.

KEYWORDS: alpha-aminoadipic-semialdehyde dehydrogenase, electroencephalogram**,** D-panthenol, seizures

Introduction

Childhood epilepsies are heterogeneous group of conditions that can differ in diagnostic criteria and management and have different outcomes. Researches on childhood epilepsy are more limited due to which many clinical questions remain unanswered. Pyridoxine dependent epilepsies (PDEs) are autosomal recessive disorders which are characterized by seizures at neonatal onset not responding to conventional antiepileptic drugs (CADs), and can only cease after parenteral pyridoxine administration[i]. Diagnostic criteria for this condition are: cessation of clinical and electroencephalographic seizures following intravenous administration of

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100 mg of pyridoxine, and no seizure recurrence while on long-term treatment[ii]. It has also been suggested that pyridoxine dependency is often under diagnosed, both because of occasional atypical presentation[iii]. PDEs epidemiology with a considerable heterogeneity has been reported with birth incidences are 1:20,000 in Germany, 1:396,000 in Netherlands and 1:783,000 in the UK and Ireland[iv]. Mutations in the gene encoding for the alpha-aminoadipic-semialdehyde dehydrogenase (ALDH7A1) have been identified in the related enzyme deficiency[v]. Some reports of initial response to phenobarbitone followed by later intractability, suggest that pyridoxine responsive seizures may not be identified in infancy. As this would likely lead to resistant/intractable seizure with or without developmental delay[vi].

MATERIAL AND METHODS

Present study was performed in the tertiary-care teaching hospital in ---------- at _____ .study was conducted over a periods of 12 months from _____ to _____

Written informed consent was obtained from the parents. All children attending the paediatric with intractable seizures, were enrolled in the study. Inclusion criteria was Intractable seizures, seizures had persisted for more than 6 months under regular administration of three or more appropriate antiepileptic drugs (AEDs), except pyridoxine; seizure frequency was more than once per day; and onset of epilepsy in the first 18 months of life. Patients with congenital malformations, chromosomal disorders, metabolic disorders and prior pyridoxine trial or use of vitamin B6 for management of seizures were excluded from the study.

An **electroencephalogram (**EEG) was recorded for all patients. Those with abnormal EEG were given a pyridoxine trial, of an intravenous infusion of 100 mg of pyridoxine (vitamin B6 25 mg; vitamin B1 50 mg; vitamin B12 500 mg; D-panthenol 25 mg)which was diluted in saline and given over 10-min with a simultaneous EEG monitoring . This procedure was carried out in the EEG laboratory with all appropriate precautions including resuscitation equipment and trained personnel. Continuous EEG monitoring was done throughout the infusion and till 20 min later, to look for correction of EEG abnormalities. All patients were then prescribed oral pyridoxine, 10-15 mg/kg/day for 6 weeks with current anticonvulsant therapy.

CT scan or MRI of brain, EEG, serum electrolytes, blood gases, carried out for all resistant epilepsy patients.

Follow up of the patients was done every 15 days. Those patients on pyridoxine therapy who remained seizure-free with previous AEDs were gradually tapered one by one over the next 3-months.

RESULTS

A total of 27 patients with intractable epilepsy were included in the study. Of which 16 (59.3%) male and 11(40.7%) female were having intractable epilepsy. Focal seizures were observed in 5 patients generalized in 22 patients

Characteristics	Male	female
Focal seizures	3(60%)	2(40%)
Generalized seizures	13 (59.1%)	9(40.9%)
Total	16 (59.3%)	11(40.7%)
Mean age of onset of seizures	5.3 months	5.1 months

Of the total 5 patients with focal seizures 3(60%) were male and 2(40%) were female. out of 22 patients with generalized seizures13 (59.1%) were male and 9(40.9%) were females. Mean age of onset of seizures in male was 5.3 months and in females was 5.1 months. An EEG finding in all patients was abnormal.

After pyridoxine treatment 2 patients with generalised seizures and receiving 3 antiepileptic drugs respond well to the treatment within 3 weeks of treatment. In another 4 patients seizure frequency decreased to 25% after treatment. Moreover the oral dose of pyridoxine at 50 mg/Kg twice a day for two days has been found as effective as the iv dose. 3 patients stopped treatment after 15 days but seizures reverted back and well controlled when again pyridoxine treatment was restarted. Various additional clinical features have been described in

patients with classical PDE including abnormal foetal movements, features suggestive of birth asphyxia or hypoxic ischemic encephalopathy, irritability, abnormal cry, exaggerated startle response, dystonic movements, respiratory distress, abdominal distension, bilious vomiting, hepatomegaly, hypothermia, shock and acidosis. Seizures may be of almost any type but generalized tonic-clonic seizures predominate

DISCUSSION AND CONCLUSION

Pyridoxine-dependent epilepsy (PDE) was first described in 1954[vii]. It is generally resistant to antiepileptic drugs but can be controlled within an hour by 50–100 mg of pyridoxine, usually given intravenously. The epilepsy remains controlled by 5–10 mg/kg/day of oral pyridoxine, seizures may restart within days when pyridoxine is stopped but are rapidly controlled again when treatment is restarted[viii].Various clinical features have been described in patients with classical PDE which includes abnormal foetal movements, features suggestive of birth asphyxia or hypoxic ischemic encephalopathy, irritability, abnormal cry, dystonic movements, exaggerated startle response, respiratory distress, abdominal distension, hepatomegaly, bilious vomiting, hypothermia, shock and acidosis. Seizures may be of almost any type but generalized tonic-clonic seizures predominate. Similar results were shown in our study about 21(77.8%) patients out of 27 were having generalized seizures. In our study all patients EEG was abnormal. Nabbout et al also suggested that EEG is usually abnormal in PDE patients[ix]. Jiao, et al. tried intravenous pyridoxine for seizure in his study on children and found it to be effective and safe for treatment of recurrent seizures[x].

Research shows that elevated serum and CSF pipecolic acid levels, and elevated amino adipicsemi aldehyde levels in various body fluids have been shown to be associated with PDE[xi]. 2 patients with generalised seizures and receiving 3 antiepilectic drugs respond well to the treatment within 3 weeks of treatment, but their EEG was not normal even after 3 weeks of the treatment. This delayed normalization of EEG was suggested in the Study Gupta VK et al[xii].

In conclusion most of the patients responded well to the pyridoxine treatment, but the IV injections adherence to the treatment and risk of infection may be the problem and some patient may not continue the treatment. Further larger studies are required to confirm the findings.

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