A STUDY ON METABOLIC SEIZURES IN A TERTIARY CARE PAEDIATRIC HOSPITAL

Viveka Saravanan Raju¹, Leema Pauline Cornelius²

¹Assistant Professor, Department of Neurology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, Tamilnadu.

²Professor and HOD, Department of Paediatric Neurology, Institute of Child Health and Hospital for Children, Madras Medical College, Chennai, Tamilnadu.

ABSTRACT

BACKGROUND

This study is about the seizures caused by metabolic derangements in children. Metabolic seizures are important because many conditions are treatable and all of them have a risk for recurrence in the same family. Metabolic diseases can cause seizures by interfering with energy metabolism, changing osmolality or producing endogenous toxins. Long-term antiepileptic therapy may be needed in some metabolic seizures.

Aims and Objectives- To study the demography, the causes and the management of metabolic seizures.

MATERIALS AND METHODS

This was a descriptive study. Data on children with metabolic seizures who were admitted in Institute of Child Health and Hospital for Children, Madras Medical College, Chennai between January 1, 2014 and December 31, 2017 were included in this report.

Inclusion Criteria- Children up to 12 years including new-borns who were admitted with metabolic seizures in Institute of Child Health and Hospital for Children, Madras Medical College, Chennai between January 1, 2014 and December 31, 2017 were included in this report.

Exclusion Criteria- Children with perinatal asphyxia and structural brain abnormalities were excluded from this study.

RESULTS

Out of the 35 patients diagnosed to have metabolic seizures, 21 children had hypocalcaemia, 4 had hypoglycaemia, 3 had biotin deficiency and 2 had hyperglycaemia and 5 had pyridoxine responsive seizures.

CONCLUSION

1. In all children with refractory seizures, metabolic causes should be thought of.
2. Hypocalcaemia is the commonest cause of metabolic seizures in our study.

KEYWORDS

Hypoglycaemia, Hypocalcaemia, Hyperglycaemia.

HOW TO CITE THIS ARTICLE: Raju VS, Cornelius LP. A study on metabolic seizures in a tertiary care paediatric hospital. J. Evolution Med. Dent. Sci. 2018;7(15):1919-1922, DOI: 10.14260/jemds/2018/431

BACKGROUND

This study is about the seizures caused by metabolic derangements in children. Seizure in response to extracranial disease is called reactive seizures. Metabolic diseases can cause seizures by interfering with energy metabolism, changing osmolality or producing endogenous toxins. Reactive epilepsy may be eliminated if the underlying cause is detected and corrected. Metabolic disorders make up a special category of causes of neonatal and early infantile seizures. They are important because many conditions are treatable and all of them have a risk for recurrence in the same family.

Aim of Study

To study the demography, the causes and the management of metabolic seizures.

'Financial or Other Competing Interest': None.
Submission 19-02-2018, Peer Review 21-03-2018,
Acceptance 28-03-2018, Published 09-04-2018.

Corresponding Author:

Viveka Saravanan Raju,
Plot No. 8, 10th Cross Street,
Mangala Nagar, Porur,
Chennai-600116, Tamilnadu.
E-mail: drrvs1972@gmail.com
DOI: 10.14260/jemds/2018/431

MATERIALS AND METHODS

This was a descriptive study. Data on children with metabolic seizures who were admitted in Institute of Child Health and Hospital for Children, Madras Medical College, Chennai between January 1, 2014 and December 31, 2017 were included in this report.

Inclusion Criteria

Children up to 12 years including new-born who were admitted with metabolic seizures in Institute of Child Health and Hospital for Children, Madras Medical College, Chennai between January 1, 2014 and December 31, 2017 were included in this report.

Exclusion Criteria

Children with perinatal asphyxia and structural brain abnormalities were excluded from this study.

Statistical Methods

The descriptive data was analysed using SPSS version 16.0.

RESULTS

In our study, there were 20 male children and 15 female children (Figure 1).

Figure 1

Age Group	No. of Patients
New-borns	7
1-3 Months	17
More than 3 Months	11

Table 1. Age Distribution

Causes	No. of Patients
Hypocalcaemia	21
Hypoglycaemia	4
Biotin Deficiency	3
Hyperglycaemia	2
Pyridoxine deficiency	5

Table 2. Aetiology

Out of 35 patients diagnosed to have metabolic seizures 21 children had hypocalcaemia, 4 had hypoglycaemia, 3 had biotin deficiency and 2 had hyperglycaemia (Figure 6) and 5 had pyridoxine responsive seizures (Table 2).

Figure 2

In our study, a 4 months old baby had refractory seizures and found to have hypoglycaemia and on evaluation had decreased serum cortisol (0.1 mg/L), diagnosed as Addison's disease and started on hydrocortisone. Anti-epileptics were tapered and stopped, since seizures were controlled.

In another case a seven-year-old boy who developed refractory seizures, his blood sugar was low on multiple occasions. On evaluation, serum insulin was elevated 2 times the normal and C-peptide level was normal. Endoscopic ultrasound showed no insulinoma. Genetic causes are to be ruled out in this case.

Another 5-year-old boy with refractory seizure was found to have hypoglycaemia with decreased insulin levels (0.11)

on multiple occasions. C-peptide normal. Urine ketones negative. Diagnosed to have FAO defect.

Figure 3

A child presented with refractory left focal seizures. Investigations revealed Sr. calcium- 7.6 mg. Ionised Ca- 0.8 mg. Serum PTH- 292 microgram/mL (normal 10 - 65), serum phosphorus- 6, serum ALP- 613 IU/L (normal < 449). Vit D- 18.7, diagnosed to have Vit D deficiency.

A 2-year-old child had seizures since 11 months of age. On evaluation serum calcium- 6.3 and serum parathormone- 2 (normal 10 - 65). Serum ALP- 28. Vit D level was normal. Case of primary hypoparathyroidism.

DISCUSSION

Disturbances of internal homeostasis that affect the cell function will cause seizures. This includes a lack of oxygen as in hypoxic-ischaemic injury, electrolyte abnormalities such as hypocalcaemia,¹ hypoglycaemia,² hyperammonaemia and metabolic disturbances like organic acidurias and maple syrup urine disease.³

Broad screening of electrolytes, glucose, ammonia, plasma or serum amino acids and urine organic acids should be obtained.⁴

Non-ketotic hyperglycaemia is due to deficient glycine cleavage enzyme activity and characterised by elevated glycine in body fluids. Neonates with classic non-ketotic hyperglycaemia present in the first days of life with hypotonia,⁵ feeding difficulties, lethargy progressing to coma, seizures and apnoea requiring ventilation in many of the cases. They often have a burst suppression pattern on electroencephalogram, which later evolves into hypersarrhythmia and multifocal epilepsy. On magnetic resonance imaging, many neonatally presenting patients have increased signal on diffusion weighted images in the areas that are myelinated at birth, most often in the posterior limb of the internal capsule and sometimes in the long tracts in the brain stem. One-third of patients present in early-to-mid infancy with seizures, hypotonia and developmental delay. On follow-up, many have a very poor outcome. These patients have developmental delay and signs of spasticity at less than 6 months of age. They develop brain atrophy and multifocal seizures. But a subset of patients (1/6 of patients presenting neonatally and 1/2 of patients presenting in infancy) have a better outcome. Though these patients make developmental progress, they remain moderately-to-severely mentally retarded (IQ 20 - 60). They can learn to sit and grasp, and develop choreatic movements. Their seizures are milder and is often easily treated with a single anticonvulsant.

The glycine cleavage enzyme system consists of 4 subunits named P, T, H and L. Non-ketotic hyperglycaemia is

diagnosed by finding elevated glycine in serum and cerebrospinal fluid (CSF) with an increased ratio of CSF: plasma glycine (NO. 06 with normal ≤ 0.02).⁶ The diagnosis is confirmed by enzyme activity assay in a liver biopsy or by mutation analysis. Mutations have been found in the AMT gene encoding the T-protein in 25% of patients and in the GLDC gene encoding the P-protein in 75% of patients.⁷ The condition is usually treated with benzoate to reduce the glycine levels and with NMDA receptor blockers such as dextromethorphan.⁸ Early myoclonic seizures respond to benzodiazepines, but seizure control becomes more difficult in severely affected patients during the first year of life, often requiring multiple anticonvulsants by 1 year of age.

In biotinidase deficiency, biotin is not recycled from biocytin to biotin. This causes a deficiency of the biotin cofactor with subsequent deficient enzyme activities of the carboxylases: pyruvate carboxylase, propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase and the acetyl-CoA carboxylases. The clinical presentation is in infancy on average starting around 7 weeks of age. Patients present with seizures, often GTCS or myoclonic. They have hypotonia, lethargy and ataxia.⁹ They develop a skin rash which is usually eczematoid, alopecia and keratoconjunctivitis untreated. They develop psychomotor retardation, hearing loss and can develop irreversible optic atrophy. Some patients have initially presented with severe infantile seizures such as Ohtahara syndrome. The biochemical presentation mimics holocarboxylase synthetase deficiency. Clinical diagnosis is suspected from elevated lactate and from metabolites of the carboxylases on urine organic acids such as elevated 3-hydroxyisovaleric acid, 3-methylcrotonylglycine, lactic acid, methylcitric acid, 3-hydroxypropionate or from an abnormal plasma acylcarnitine profile (elevated C3- and hydroxy-C5-acylcarnitines). The diagnosis is confirmed by assaying the biotinidase enzyme activity in serum, in which patients with severe deficiency have less than 10% residual activity and by mutation analysis. Treatment with biotin 10 mg/day results in good outcome. This utterly treatable condition should not be missed as an aetiology of infantile seizures and physicians should not rely solely on the results.

The vast majority of patients with pyridoxine-dependent epilepsy have a deficiency in α -aminoadipic semialdehyde dehydrogenase. Alpha-aminoadipic semialdehyde is derived from the catabolism of lysine through pipecolic acid and is in equilibrium with Δ^1 -piperidine-6-carboxylate (6-PC), which reacts with pyridoxal-5'-phosphate. These patients have elevated α -aminoadipic semialdehyde and 6-PC in urine and serum and a secondary elevation of pipecolic acid in serum. They present with seizures in the neonatal period or early infancy. They usually have encephalopathy with irritability and temperature instability. As neonates, they usually have a burst suppression pattern on EEG. Later they develop hypsarrhythmia and often develop multifocal seizures. Most patients have developmental delay and some have white matter abnormalities.

Diagnosis is made by treatment with intravenous pyridoxine 100 mg under EEG monitoring followed with oral pyridoxine 30 mg/kg/day for at least 3 days.¹⁰ The response to intravenous pyridoxine alone lacks sensitivity and

specificity. A direct diagnosis is by demonstration of α -aminoadipic semialdehyde or 6-PC in urine or serum and confirmation by sequencing analysis of the ALDH7A1 gene.¹¹ Treatment is with oral pyridoxine 15 to 30 mg/kg/day and monitoring for neuropathy in those patients when treated at high doses. Most patients have seizure control, but still have developmental delay. A few rare patients have been reported who present with West syndrome with hypsarrhythmia, whose seizures respond to pyridoxine. These patients do not have α -aminoadipic semialdehyde dehydrogenase deficiency and represent a separate disorder, the cause of which is currently not yet known. The outcome in these patients seems to be favourable with treatment. This treatable condition warrants a three-day trial with pyridoxine in all patients with West syndrome, regardless of biochemical findings.

Glucose is the main fuel of the brain. It is transported across the blood-brain-barrier and into astrocytes by the glucose transporter (GLUT1, also called SLC2A1). Patients are haploinsufficient due to a mutation in the GLUT1 gene¹² and have a partial deficiency of the transporter function. Most (76%) patients present in the first 6 months of life. They have a variety of seizures including complex seizures, generalised seizures and myoclonic seizures.¹³ Early absence seizures have also been reported. The seizures, which are often therapy resistant, sometimes improve with feeding and worsen with barbiturates such as phenobarbital which partially inhibits this transporter. The EEG often shows a 2.5 to 4 Hz spike wave pattern. Other symptoms include ataxia which is sometimes intermittent, language delay, developmental delay, spasticity, choreoathetosis and dystonia. They can develop microcephaly. Hypometabolism in the thalami and temporal lobes has been demonstrated on PET scanning. Untreated patients have substantial developmental delay.

The diagnosis is suspected by the finding of hypoglycorrhachia 45 mg/dL in CSF and a CSF: plasma glucose ratio 0.4 (normal 0.6), in the absence of other causes of hypoglycorrhachia. The diagnosis can be confirmed by mutation analysis of the GLUT-1 gene or by an uptake assay of labelled 3-O-methylglucose into red blood cells. Treatment consists of feeding the brain with an alternative fuel, specifically ketones using a ketogenic diet. The aim is to keep the serum ketones above 3 mm. Inhibitors of the GLUT-1 transporter such as barbiturates and caffeine should be avoided. Seizure control is improved with treatment, but residual developmental delays often persist.

CONCLUSION

In all children with refractory seizures, metabolic causes should be thought of. Hypocalcaemia is the commonest cause of metabolic seizures in our study.

Limitations

In this study sample size was small, because of short study period and extensive genetic analysis could not be done.

REFERENCES

- [1] Papetti L, Parisi P, Leuzzi V, et al. Metabolic epilepsy: an update. *Brain Dev* 2013;35(9):827-41.

- [2] Arzimanoglou A. Epilepsy in children. 3rd edn. UK: Lippincott Williams & Wilkins Press 2004:81-7.
- [3] Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. *Neurology* 1987;37(12):1837-44.
- [4] Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. *Semin Fetal Neonatal Med* 2013;18(4):185-91.
- [5] Volpe JJ. Neonatal seizures. In: Volpe JJ, ed. *Neurology of the newborn*. 4th edn. Philadelphia: Saunders 2001:178-214.
- [6] Korman SH, Gutman A. Pitfalls in the diagnosis of glycine encephalopathy (non-ketotic hyperglycinemia). *Dev Med Child Neurol* 2002;44(10):712-20.
- [7] Hamosh A, Scharer G, VanHove J. Glycine encephalopathy. In: Pagon RA, Bird TD, Dolan CR, et al, eds. *Gene Reviews* [Internet]. Seattle (WA): University of Washington, Seattle 2009:1993-2002.
- [8] Hyland K, Gibson K, Sharma R, et al. Neurotransmitter disorders. In: Sarafoglou K, Hoffman G, Rothman K, eds. *Pediatric endocrinology and inborn errors of metabolism*. McGraw-Hill 2009:789-892.
- [9] Collins JE, Nicholson NS, Dalton N, et al. Biotinidase deficiency: early neurological presentation. *Dev Med Child Neurol* 1994;36(3):268-70.
- [10] Gospe SM. Pyridoxine-dependent seizures: new genetic and biochemical clues to help with diagnosis and treatment. *Curr Opin Neurol* 2006;19(2):148-53.
- [11] Mills PB, Struys E, Jakobs C, et al. Mutations in antiquitin in individuals with pyridoxine-dependent seizures. *Nat Med* 2006;12(3):307-9.
- [12] Plouin P, Kaminska A. Neonatal seizures. *Handb Clin Neurol* 2013;111:467-76.
- [13] Hunt AD, Stokes J, McCrory WW, et al. Pyridoxine dependency: report of a case of intractable convulsions in an infant controlled by pyridoxine. *Pediatrics* 1954;13(2):140-5.