Clinical and Biochemical Spectrum of Pyridoxine Dependent seizures in India (P663)

JALAN A. B[1] , Kudalkar KV[1], Jalan RA[1], Shinde DH[1], Borugale MA[1], Joshi MM[1], Mahakal JM[1], ,Sonalkar ND[1]

NIRMAN: Div of Biochemical Genetics, Navi- Mumbai, India – 400705.

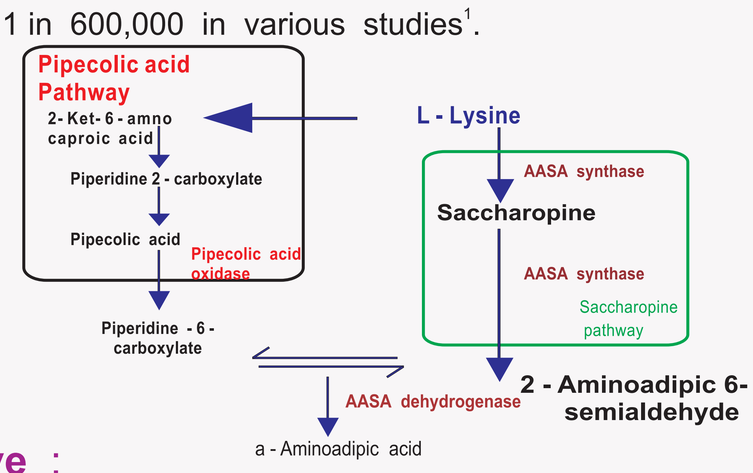
www.metabolicerrors.com

Abbreviations : -

PDE : Pyridoxine Dependent Epilepsy , NC : Non consanguineous, PIPA : Pipecolic Acid, AASA : Alfa Adipic Semialdehyde, GTC : Generalised Tonic Clonic Seizures.

Introduction :

Pyridoxine dependent epilepsy (PDE) (OMIM # 266100) is an autosomal recessive disorder characterized by a therapeutic response to pharmacological dosages of Pyridoxine (B6 Vitamin) and resistance to conventional antiepileptic drugs[1]. Hunt et al first described PDS in 1954 in a newborn with pharmaco - resitant seizures that were controlled immediately after parenteral admini - stration of a multivitamin cocktail containing vitamin B6[2]. PDE was mapped on 5q31 in 2000 and in the same year, was shown to be accompanied by increased levels of pipecolic acid in plasma and CSF[3]. Mills et al in 2006 confirmed that PDE was caused by ALDH7A1 gene (also known as Antiquitin gene) mutations, and the concentration of alpha-adipic semialdehyde (AASA) was increased in CSF, Plasma and Urine[4]. Incidence of PDE varies from 1in 20,000 to 1 in 600,000 in various studies[1].



Objective :

To analyze clinical and biochemical spectrum of PDS and develop a strategy to detect PDS at the earliest and treat. We hereby report our experience of 12 unrelated patients.

Materials & Methods :

We analysed 12 cases (6 males and 6 females) over last 2 years. These patients were evaluated clinically and biochemically including Ammonia, Lactate, Sugar, Free Fatty Acid, Beta Hydroxy butyrate Biotinidase enzyme, plasma and CSF – Aminoacids, Carnitine / Acyl carnitine profile, GC / MS of Urine for Organic acids, GC / MS – SIM of Urine, plasma and CSF for Pipecolic acid and AASA. Molecular studies are under progress. For estimation of Pipecolic acid and AASA EZfaast kit by Phenomenex was used. Calibration was set up for both Pipecolic acid and AASA every time the samples were run. Only Patients with elevated Pipecolic acid and / or AASA in CSF, Plasma or urine were included in this study. In 4 patients we did not receive any CSF sample and in 6 patients we did not receive urine sample. Transporting CSF or Urine in a frozen state (which is a must for reliable AASA analysis) is very difficult in India over long distances.

Results :

We found mildly elevated CSF Glycine in 6 / 8 cases (27.8±16.91 µmol/L), significantly elevated Pipecolic acid in 10/11 Plasma (14.55 ± 17.34 µmol/L) and 6/8 CSF (8.08 ± 10.27 µmol/L). Urine AASA was elevated in 3 out of 4 (34.08 ± 38.93). All the patients were treated with Pyridoxine or Pyridoxine + Folinic Acid with good response. One child also received Lysine restricted diet.

#	ID	Age Months	Sex	Consang	Onset	Seizure
1	HM	1	M	3rd Con	1 day	GTC
2	BL	68	F	nc	1 day	GTC
3	VT	2	M	3rd Con	5 M	Focal + GTC
4	SP	2	F	NC	21 M	Multifocal
5	LP	5	F	NC	5 M	GTC + Myoclonic
6	BM	0.5	M	NC	4 M	Right Focal
7	YA	112	M	NC	1 M	GTC
8	RP	10	M	3rd Con	1 M	GTC
9	BN	3	F	NC	2.5 M	GTC + Myoclonic
10	BS	132	F	NC	2.5 M	GTC
11	BP	3	F	NC	0.5 M	Focal Seizures
12	KK	2	M	NC	1.5 M	Tonic + Myoclonic

ID	CSF Gly	Pls Gly	CSF PIPA	CSF AAS	Plas PIPA	Plas AAS	Ur PIPA	Ur AAS
NR	<20	<500	<1.25	<0.2	<2.5	<0.2	<1.54	<0.19
HM	20	500	5.2	-	5.2	-	-	-
BL	9.4	253	2.55	-	2.55	-	-	-
VT	8.0	361	13.71	-	7.81	-	-	-
SP	52	301	29.88	-	46.79	-	-	-
LP	-	225	-	-	4.89	-	13.91	-
BM	29	139	1.126	-	5.20	-	-	-
YA	-	126	-	-	5.0	-	1.46	6.84
RP	52	396	0.072	-	16.14	-	106.9	3.11
BN	30	304	0.047	5.27	5.27	-	11.94	-
BS	-	-	-	-	-	-	47.7	17.12
BP	-	-	-	-	-	-	22.6	0.44
KK	22	103	12.07	46.65	46.65	5.99	-	-
M	27.8	270.8	8.08	14.55	14.55	5.99	34.08	6.88
SD	16.91	127.9	10.27	17.34	17.34		38.93	7.31

Discussion : -

In our series of 12 patients we observed early onset seizures, within 24 hrs in 2 patients, within 1 month in 3 patients and rest were late onset. 5 patients had mainly clonic movements also associated with some tonic movements (GTC). Two patients had GTC with myoclonic jerks and one with only tonic spams + myoclonic jerks. 4 patients had focal or multifocal seizures. Hence the type of seizure probably will not give any indication to PDE. It may be early or late onset. Only 25 % babies were born out of consanguineous marriage. Clinical features were described by Belene Perez et al in a series of 12 genetically confirmed cases[5] . These were seizures of neonatal onset, intra uterine convulsions, perinatal hypoxic ischemic encephalopathy, family background of lethal epileptic encephalopathy, consanguinity, status epilepticus in 3 patients etc. Seizure types were focal, multifocal, clonic, or myoclonic[5]. **Clue to the suspicion was normal metabolic studies including ammonia, lactate, sugar, blood gases, normal carnitine / acyl carnitine profile and GC / MS of urine for organic acids. Resistant seizures with near normal biochemistry suggest a strong possibility of PDE.**

Folinic acid responsive seizures are genetically identical to Antiquitin gene defect[1]. Stoeckler et al has found improvement in seizures upon Folinic acid administration (3-5 mgm/kg/day)[1]. Hence all our patients received a combination of Pyridoxine 15- 30 mgm/kg/day + Folinic acid 3-5 mgm / kg / day. Recently an observational study showed that adjunct treatment with a lysine restricted diet is safe, results in partial normalization of lysine intermediates in body fluids, and may have beneficial effects in seizure control and psychomotor development[6]. Based on this report we suggested Lysine restricted diet to one patient who showed partial response, but this child was lost for follow-up. The diet was started as Lysine restricted aminoacid mix (GAc-A - amino acid mix).

Conclusion :

PDS is a treatable disorder which is not easily detected unless specific tests are performed. We propose screening in plasma PIPA and if positive, either CSF – PIPA or Urine AASA should be studied. All such suspected patients may be given a trial of Pyridoxine and /or Folinic acid, pending the results of biochemical or molecular studies. Lysine restricted has also been recommended and advised.

Conflict of Interest : None.

References :

1. S. Stockler et al, Pyridoxine dependent epilepsy and Antiquitin deficiency. Mol Genet. Metab. (2011) doi : 10.1016 / j.ymgme. 2011.05.014
2. Clara D M van Karnebeek, Sravan Jaggumantri, Current treatment and Management of Pyridoxine-dependent Epilepsy, Curr Treat Options Neurol (2015) 17:7, DOI 10.1007/sl11940-014-0335-0
3. Zhixian Yang et al, Clinical Diagnosis, Treatment and ALDH7A1 Mutations in Pyridoxine - Dependent Epilepsy in Three Chinese Infants, PLOS, March 2014, Vol9, Issue 3, e92803; 1-6 , www.plosone.org
4. Mills PB, Struys, Jacobs C, Plecko B, Baxter P et al (2006) Mutations in Antiquitin in individuals with pyridoxine dependent seizures, Mat Med 12:307-309.
5. Belen Perez, Jalan A et al, Clinical, biochemical and molecular studies in pyridoxine dependent epilepsy : Antisense therapy as possible new therapeutic option., Epilepsia, 54 (2), 239-248, 2013.
6. Clara D M van Karnebeek and Sylvia Stoeckler et al, Lysine restricted Diet as Adjunct therapy for Pyridoxine Dependent Epilepsy; The PDE Consortium Consensus Recommendations, JIMD Reports, DOI 10.1007/8904_2014_296

Poster Presented at SSIEM Conference in Lyon (France) (1st – 4th Sept 2015) – Poster # P663.